FORM 7A

THE PATENTS ACT, 1970
(39 of 1970)

And

THE PATENT RULES, 2003
[Section 25(1) and Rule 55]

REPRESENTATION FOR OPPOSITION TO GRANT OF PATENT

1. I Dr. Kanchan Kohli an Indian national of the address: E-156, First Floor, East of Kailash, New Delhi, India -110065, hereby submit representation by way of opposition to the grant of patent in respect of application No. **4412/DELNP/2007** dated 08 June 2007 for the invention titled "PHARMACEUTICAL COMBINATIONS OF AN ANGIOTENSIN RECEPTOR ANTAGONIST AND AN NEP INHIBITOR" in the name of **NOVARTIS AG.** of the address Lichtstrasse 35, CH-4056, Basel, Switzerland.

2. **ON THE GROUNDS**:

   I. **Section 25(1) (e)** *that the invention so far as claimed in any claim of the complete specification is obvious and clearly does not involve any inventive step, having regard to the matter published as mentioned in clause (b) or having regard to what was used in India before the priority date of the applicant's claim*;

   II. **Section 25(1) (f)** *that the subject of any claim of the complete specification is not an invention within the meaning of this Act, or is not patentable under this Act*;

   III. **Section 25(1) (g)** *that the complete specification does not sufficiently and clearly describe the invention or the method by which it is to be performed*;

3. Our address for service in India is : **BLI Consultancy Pvt. Ltd. R-9, Eknath Puram, Amravati, Maharashtra- 444607, India,**
Email: patentconsult.ashu@gmail.com

Agent for the Opponent
Adv. Swapnil J Gawande (IN/PA 1587)

To,
The Controller of Patents
Patent Office
At Delhi

FORM 7A

THE PATENTS ACT, 1970
(39 of 1970)

And

THE PATENT RULES, 2003
[Section 25(1) and Rule 55]

REPRESENTATION FOR OPPOSITION TO GRANT OF PATENT

1. I Dr. Kanchan Kohli an Indian national of the address: E-156, First Floor, East of Kailash, New Delhi, India -110065, hereby submit representation by way of opposition to the grant of patent in respect of application No. **4412/DELNP/2007** dated 08 June 2007 for the invention titled "PHARMACEUTICAL COMBINATIONS OF AN ANGIOTENSIN RECEPTOR ANTAGONIST AND AN NEP INHIBITOR" in the name of **NOVARTIS AG.** of the address Lichtstrasse 35, CH-4056, Basel, Switzerland.

2. **ON THE GROUNDS**:

   I. **Section 25(1) (e)** *that the invention so far as claimed in any claim of the complete specification is obvious and clearly does not involve any inventive step, having regard to the matter published as mentioned in clause (b) or having regard to what was used in India before the priority date of the applicant's claim*;

   II. **Section 25(1) (f)** *that the subject of any claim of the complete specification is not an invention within the meaning of this Act, or is not patentable under this Act*;

   III. **Section 25(1) (g)** *that the complete specification does not sufficiently and clearly describe the invention or the method by which it is to be performed*;

STATEMENT IN SUPPORT OF THE REPRESENTATION

i. **PARTICULARS OF THE IMPUGNED APPLICATION**

a) The Indian Patent Application No. **4412/DELNP/2007** entitled "PHARMACEUTICAL COMBINATIONS OF AN ANGIOTENSIN RECEPTOR ANTAGONIST AND AN NEP INHIBITOR" has been filed by **NOVARTIS AG.** on 08 June 2007. The Indian Patent Application No. 4412/DELNP/2007 is hereafter referred as "Impugned Patent Application" or "Impugned Application" (**Exhibit 02)**.

b) The impugned application is national phase application for PCT International Application No. PCT/US2006/043710 filed on 08 November 2006.

c) The impugned application claims earliest priority of a US Patent Application No. 60/735,093 dated 09 November 2005 along with three other US Patent Application Nos. 60/735,541 dated 10 November 2005, 60/789,332 dated 04 April 2006, and 60/822,086 dated 11 August 2006.

ii. The opposition under Section 25(1) of The Patents Act, 1970 (hereinafter referred to as 'the Act') can be made by "any person". Therefore, Dr. Kanchan Kohli hereafter referred as "the opponent" is thus competent to make the representation for opposition to grant of patent under Section 25(1) of the Act. Although it is not necessary but, for the purpose of full disclosure, it may be noted that opponent has a reputable credentials in the field of pharmaceutical drugs and have an experience of around 37 years with more than 243 publications in referred journals. Thus, opponent is engaged in and researching in the same field to which the impugned Patent Application relates. Curriculum vitae of the opponent is annexed herewith as **Exhibit 1**.

iii. As on the date of filing this opposition, the status of the said application shown on the online records of the IPO is "Application in Hearing". The said application was examined by the IPO and the First Examination Report (FER) was issued on 30 January 2015. A reply to the FER was submitted by the applicant with the IPO on 27 November 2015.

iv. The opponent herewith submits opposition along with supporting facts and documentary evidence to oppose the grant of patent for impugned Patent Application.

v. **EVIDENCE RELIED UPON BY THE OPPONENT**:

S.No.	Details of Documents	Exhibit No.
01	Impugned application as filed as national phase application in India and published during international phase as WO/2007/056546	**Exhibit 02**
02	Amended claim set dated 06, June 2020	**Exhibit 03**
03	**D1: WO 03/059345** (Jul 24, 2003)	**Exhibit 04**
04	**D2: WO200206253** (Jan 24, 2002)	**Exhibit 05**
05	**D3: WO2004078163** (Sep 16, 2004)	**Exhibit 06**
06	**D4: European Patent No. 0443983** (Feb 28, 1996)	**Exhibit 07**
07	**D5: US 5217996** (Jun 8, 1993)	**Exhibit 08**
08	**D6: Christer B. Aakeröy *et al,* "**Building co-crystals with molecular sense and supramolecular sensibility"; CrystEngComm, 2005, 7(72), 439–448 (June 2005)	**Exhibit 09**
09	**D7**: **Page 252** of the Chapter 16- Identical and Non-identical twin drugs in the book titled **"The Practice of Medicinal Chemistry"** edited by Camille Georges Wermuth (Jun 11, 2003)	**Exhibit 10**

Claims 1 to 8 of the impugned application, as filed on June 6, 2020, upon which the present representation for opposition is filed are as follows:

AMENDED CLAIMS (CLEAN COPY)

We claim:

1. A compound comprising the Angiotensin Receptor Antagonist valsartan and the NEP Inhibitor (2R,4S)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2- methyl-pentanoic acid ethyl ester having the formula [((S)-N-valeryl-N-{[2'-(1 H-tetrazole-5-yl)-biphenyl-4-yl]-methyl}-valine) ((2R,4S)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester)]Na_3 • x H_2O, wherein x is 0 to 3.

2. The compound as claimed in claim 1, wherein x is 2.5.

3. The compound as claimed in claim 2, which is trisodium [3-((1S,3R)-1- biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(S)-3'- methyl-2'-(pentanoyl{2''-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate] hemipentahydrate.

4. The compound as claimed in claim 1-3, wherein the compound is in crystalline form.

5. The compound as claimed in any one of claims 1 to 4 as and when used in a preparation of pharmaceutical composition or medicament.

6. A method of preparing the compound as claimed in any of claims 1 to 4, said method comprising the steps of:

(i) dissolving (S)-N-valeryl-N-{[2'-(1H-tetrazole-5-yl)-biphenyl-4-yl]-methyl}-valine or a salt thereof and (2R,4S)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2- methylpentanoic acid ethyl ester or a salt thereof in a suitable solvent;
(ii) dissolving a basic Na compound in a suitable solvent;
(iii) combining the solutions obtained in steps (i) and (ii);
(iv) precipitation of the solid, and drying same to obtain the dual-acting compound; or alternatively
obtaining the compound by exchanging the solvent(s) employed in steps (i) and (ii) by
(iva) evaporating the resulting solution to dryness; (va) re-dissolving the solid in a suitable solvent;
(via) precipitation of the solid and drying same to obtain the compound

7. The method as claimed in claim 6 wherein the suitable solvent in steps (i) and/or (iva) is acetone.

8. The method as claimed in claims 6 or 7, wherein the basic Na compound is NaOH, Na_2CO_3, $NaHCO_3$, NaOMe, NaOAc or NaOCHO.

SUPPORT AND BASIS FOR ESTABLISHING GROUNDS OF OPPOSITION:

vi. **Ground I: Section 25(1) (e) [Lack of Inventive Step]**: That the invention so far as claimed in any claim of the complete specification is obvious and clearly does not involve any inventive step, having regard to the matter published as mentioned in clause (b) *i.e*. published before the priority date of the claim in India or elsewhere in any document, or having regard to what was used in India before the priority date of the Applicant's claim.

There are several prior art documents which individually or in combination disclose the technical features of claims of impugned application. Teachings and suggestions of close prior art documents clearly establishing obviousness of impugned application are summarized and explained herein below:

Lack of inventive step over WO2003059345 (D1):

Teachings and suggestions of art(s) **D1** (**Exhibit 04**) alone or in combination with any of the prior art documents **D2** – **D7**, indisputably leads to a compound comprising the Angiotensin Receptor Antagonist valsartan and the NEP Inhibitor (2R,4S)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methylpentanoic acid ethyl ester having the formula [((S)-N-valeryl-N-{[2'-(1H-tetrazole-5-yl)-biphenyl-4-yl]methyl}valine) ((2R,4S)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methylpentanoic acid ethyl ester)]Na_3 • x H_2O, wherein x is 0 to 3 and method for preparation of said compound as claimed in the impugned Application.

The claims lack inventive step over **D1** which discloses **a combination of pharmaceutical composition comprising Valsartan and NEP inhibitor**. D1 also discloses that preferred NEP inhibitor is sacubitril as its sodium salt. Further the combination disclosed in D1 has greater therapeutic effect than monotherapy and promotes less angioedema and is effective for the treatment of antihypertensive therapy and useful in the treatment or prevention of heart failure.

D1 on page on page 7 disclose:

It has surprisingly been found that, a combination of valsartan and a NEP inhibitor achieves greater therapeutic effect than the administration of valsartan, ACE inhibitors or NEP inhibitors alone and promotes less angioedema than is seen with the administration of a vasopeptidase inhibitor alone. Greater efficacy can also be documented as a prolonged duration of action. The duration of action can be monitored as either the time to return to baseline prior to the next dose or as the area under the curve (AUC) and is expressed as the product of the change in blood pressure in millimeters of mercury (change in mmHg) and the duration of the effect (minutes, hours or days).

Further benefits are that lower doses of the individual drugs to be combined according to the present invention can be used to reduce the dosage, for example, that the dosages need not only often be smaller but are also applied less frequently, or can be used

D1 on page on page 8 further disclose:

It can be shown that combination therapy with valsartan and a NEP inhibitor results in a more effective antihypertensive therapy (whether for malignant, essential, reno-vascular, diabetic, isolated systolic, or other secondary type of hypertension) through improved efficacy as well as a greater responder rate. The combination is also useful in the treatment or prevention of heart failure such as (acute and chronic) congestive heart failure, left ventricular dysfunction and hypertrophic cardiomyopathy, diabetic cardiac myopathy, supraventricular and ventricular arrhythmias, atrial fibrillation, atrial flutter or detrimental vascular remodeling. It can further be shown that a valsartan and NEP inhibitor therapy proves to be beneficial in the treatment and prevention of myocardial infarction and its sequelae. A valsartan plus NEP inhibitor combination is also useful in treating

Thus, the mechanism of action of these two active drugs and their metabolism were already known from D1 at the time of the invention and the applicant merely combined the actives to form a supramolecular complex.

D2: **WO200206253** (**Exhibit 05**) discloses salt of valsartan which are highly stable, non-hygroscopic, and have high degree of dissociation in water, and thus have increased biological availability. D2 teaches valsartan, especially its various salt forms selected from the group consisting of the monosodium salt, the monopotassium salt, the disodium salt, the dipotassium salt, the magnesium salt,

the calcium salt, the bis-diethylammonium salt, the bisdipropylammonium salt, the bis- dibutylammonium salt, the mono-L arginine salt, the bis-L-arginine salt, the mono-L-lysine salt and the bis-L-lysine salt, as well as salt mixtures thereof, which specifically forms hydrates such as di and tri hydrates. D2 specifically disclosed the disodium salt of valsartan, hydrates and process for its preparation.

D2 on page on page 3 disclose:

Preferred salts are for example selected from the
mono-sodium salt in amorphous form;
di-sodium salt of valsartan in amorphous or crystalline form, especially in hydrate form, thereof.
Mono-potassium salt of valsartan in amorphous form;
di-potassium salt of valsartan in amorphous or crystalline form, especially in hydrate form, thereof.
calcium salt of valsartan in crystalline form, especially in hydrate form, primarily the tetrahydrate thereof;
magnesium salt of valsartan in crystalline form, especially in hydrate form, primarily the hexahydrate thereof;
calcium/magnesium mixed salt of valsartan in crystalline form, especially in hydrate form;
bis-diethylammonium salt of valsartan in crystalline form, especially in hydrate form;
bis-dipropylammonium salt of valsartan in crystalline form, especially in hydrate form;
bis-dibutylammonium salt of valsartan in crystalline form, especially in hydrate form, primarily the hemihydrate thereof;
mono-L-arginine salt of valsartan in amorphous form;
bis-L-arginine salt of valsartan in amorphous form;
mono-L-lysine salt of valsartan in amorphous form;
bis-L-lysine salt of valsartan in amorphous form.

D2 on page on page 4 disclose:

have unexpectedly advantageous properties. Under given conditions, the crystalline salts and crystalline salt hydrates have a clear melting point which is linked with a marked, endothermic melting enthalpy. The crystalline salts according to the invention are stable and are of better quality than valsartan also during storage and distribution. The amorphous or partially amorphous salts have limited stability, i.e. as the solid, they have a restricted stability range. To be stabilised, they require certain measures which can be achieved for example by galenic formulations.

In addition, both the crystalline and the amorphous salts according to the invention have a high degree of dissociation in water and thus substantially improved water solubility. These

D2 apart from teaching valsartan salts in hydrated form, specifically in hemipentahydrate form, exhibiting desirable pharmaceutical and therapeutic efficacy against hypertension; D2 also teaches the effectiveness of combination therapy along with other ACE/NEP inhibitor for treating hypertension and cardiovascular diseases.

Therefore, the hydrated forms of valsartan, particularly the hemipentahydrates also with their benefits in combination therapy was known in the art at the date of the invention. Thus, D1 and D2 provide a clear motivation to a person skilled in the art to formulate complexes of valsartan and an NEP inhibitor in order to

achieve improved anti-hypertensive effect. Further, as taught in D2 the valsartan disodium salts in hemipentahydrate forms were known at the time of the alleged invention. Thus, D1, and D2 would motivate a person skilled in the art to combine the valsartan disodium salts in hemipentahydrate form with NEP inhibitors in an expectation to achieve improved efficacy.

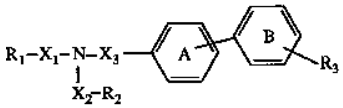
D3: **WO2004078163** (**Exhibit 06**) discloses a pharmaceutical composition comprising a co-crystal of an API and a co-crystal former. The API and co-crystal former has at least one functional group selected from secondary amide, N-heterocyclic ring (among other functional groups) which are responsible for hydrogen bonds in the cocrystal. D3 further discloses Valsartan as a API (among the list of API) for the formation of cocrystal. D3 also discloses a process for the production of a pharmaceutical composition comprising a co-crystal of an API and a co-crystal former which comprises grinding, heating or contacting in solution the API with the co-crystal former under crystallization conditions. Further, D3 teaches that cocrystal would improve the dissolution, bioavailability, and stability and helps in crystallization of amorphous compounds.

D3 on page on page 17 disclose:

> In each process according to the invention, there is a need to contact the API with the co-crystal former. This may involve grinding or milling the two solids together or melting one or both components and allowing them to recrystallize. The use of a granulating liquid may improve or may impede co-crystal formation. Non-limiting examples of tools useful for the formation of co-crystals may include, for example, an extruder or a mortar and pestle. Further, contacting the API with the co-crystal former may also involve either solubilizing the API and adding the co-crystal former, or solubilizing the co-crystal former and adding the API. Crystallization conditions are applied to the API and co-crystal former. This may entail altering a property of the solution, such as pH or temperature and may require concentration of the solute, usually by removal of the solvent, typically by drying the solution. Solvent removal results in the concentration of both API and co-crystal former increasing over time so as to facilitate crystallization. For example, evaporation, cooling, co-sublimation, or the addition of an antisolvent may be used to crystallize co-crystals. In another embodiment, a slurry comprising an API and a co-crystal former is used to form co-crystals. Once the solid phase comprising any crystals is formed, this may be tested as described herein.

D4: **European Patent No. 0443983** (**Exhibit 07**) discloses and claims valsartan for the first time. It is submitted that the compound valsartan as disclosed in the present prior art has the IUPAC name (S)-N-valeryl-N-{[2'-(1H-tetrazole-5-yl)-

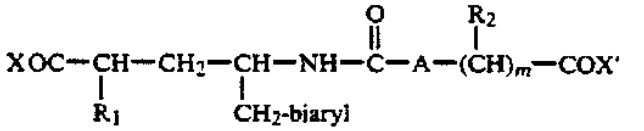
biphenyl-4-yl]methyl}valine) and the present application relates to the compound having general structure:



(I),

Also, D4 discloses the method of manufacture of the claimed compounds and specifically, valsartan.

D5: US 5217996 (**Exhibit 08**) teaches NEP inhibitor, which are useful antihypertensive or saluretic agents. These compounds are biaryl substituted 4-amino-butyric acid amide derivatives of formula I:



(I)

which prolong and potentate the diuretic, natriuretic and vasodilator properties of ANF in mammals, by inhibiting the degradation thereof to less active metabolites. D5 in examples 7 and 8 and claim 6, it particularly teaches the sodium salt of the sacubitril [N-(3-Carboxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl)-4-amino-2R-methyl butanoic acid, ethyl ester]. Therefore, admittedly NEP inhibitors like (2R,4S)-5-biphenyl4-yl~5-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester (Sacubitril) and its salts were known to be useful as anti-hypertensive agents. Reference directed to page 2; col 1; para 2 of D5.

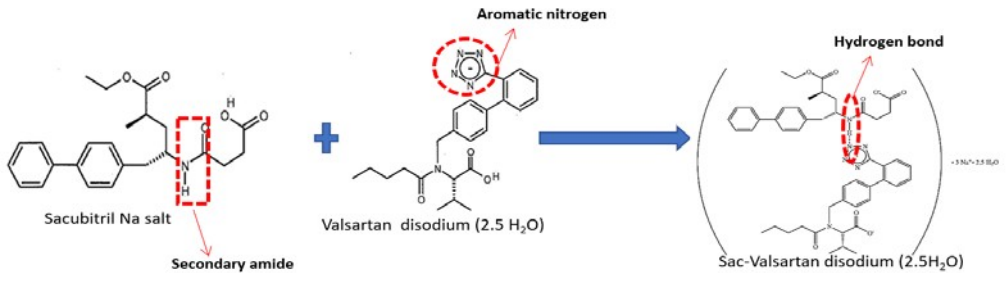
D6: Christer B. Aakeröy *et al* (**Exhibit 09**) discloses co crystallization is a deliberate attempt at bringing together different molecular species within one periodic crystalline lattice without making or breaking covalent bonds. Recrystallization and cocrystallization processes are, in essence, only distinguishable by their intents. The goal of the former is chromomeric product. The document also discloses that the most widely used synthons for the directed assembly of binary co-crystals contains a carboxylic acid in combination with a suitable N-containing heterocycle.

D7: **The Practice of Medicinal Chemistry** edited by Camille Georges Wermuth, (**Exhibit 10**) on page 252 of the Chapter 16- Identical and Non-identical twin

drugs teaches that administration of twin drugs can be favourable compared with the two separated drugs. The new entity will have its own pharmacokinetic property and thus possible improved efficacy *in vivo*.

Thus, considering teachings and suggestions of art(s) **D1** alone or in combination with any of the prior art documents **D2** – **D7**, indisputably leads a person skilled in the art to a compound comprising the Angiotensin Receptor Antagonist valsartan and the NEP Inhibitor (2R,4S)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methylpentanoic acid ethyl ester having the formula [((S)-N-valeryl-N-{[2'-(1H-tetrazole-5-yl)biphenyl-4-yl]methyl}valine) ((2R,4S)-5-biphenyl-4-yl-4-(3-carboxypropionylamino)-2-methylpentanoic acid ethyl ester)]Na_3 • x H_2O, wherein x is 0 to 3 and method for preparation of said compound as claimed in the impugned application.

Particularly as D1 discloses combination of Sacubitril or its salt + Valsartan or a salt for heart failure with preferred sacubitril salt being its sodium salt and that D2 discloses salt of Valsartan having improved physical properties which include disodium salt as its 2.5 hydrate and that D3 teaches cocrystal formation by combining API and cocrystal former. API and cocrystal former containing **secondary amide** and **aromatic Nitrogen** groups **can form hydrogen bond in the cocrystal**, and motivations provided by D4 – D7, a person skilled in the art have a clear motivation to formulate complex with cocrystalization through hydrogen bond formation of sacubitril containing secondary amide as NEP inhibitor and valsartan containing aromatic Nitrogen groups and to achieve improved effect. Thus, claims 1 – 8 of the impugned application, are clearly suggested or are easily attainable to a person skilled in the art without any ingenuity required for experimentation and thus lack inventive step.



Therefore, pending claims of the impugned application are clearly obvious in view of the prior art(s) and does not involve any inventive step. Therefore, the ground of lack of Inventive Step under **Section 25(1) (e)** is evidently established and the impugned application is liable to be rejected / refused on this ground alone.

vii. **Ground IV: Section 25(1) (f) [Not an invention or non-patentable invention]**: Without prejudice to the submissions made hereinbefore, the subject of any claim of the complete specification is neither an invention within the meaning of this Act nor it is patentable under this Act.

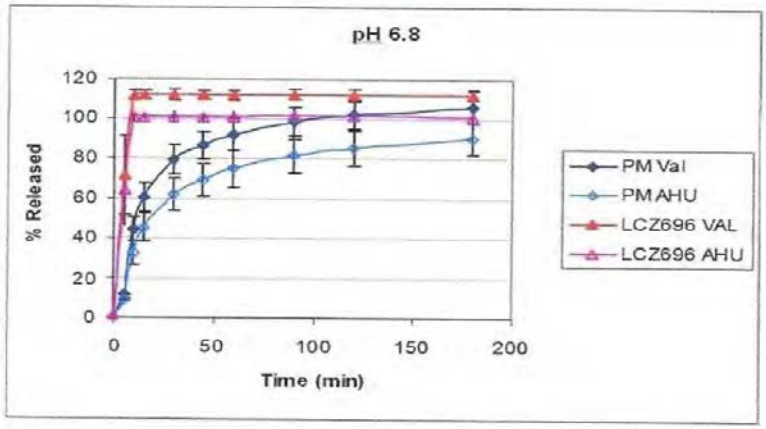
A. Claims 1 to 8 of the impugned application are obvious to a person skilled in the art as established in the preceding paragraphs and hence do not meet the requirements of **Section 2(1) (j)** and **Section 2(1) (ja)** of the Patents Act, 1970. Thus, the impugned application with its claims 1 to 8 is not an invention under Section 2(1) (j) and Section 2(1) (ja) of the Patents Act, 1970.

B. It is most respectfully submitted that the impugned patent application does not constitute an invention and is not patentable in view of the Section 3(d) of the Act. It is submitted that the compounds claimed in the impugned patent application fall within the purview of Section 3(d) of the Act as the same are nothing but derivatives of previously known angiotensin receptor inhibitors and NEP inhibitors.

As per **Section 3 (d)** of the Patents Act, 1970: "*the mere discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of that substance or the mere discovery of any new property or new use for a known substance or of the mere use of a known process, machine or apparatus unless such known process results in a new product or employs at least one new reactant.*

*Explanation: — **For the purposes of this clause**, salts, esters, ethers, polymorphs, metabolites, pure form, particle size, isomers, mixtures of isomers, complexes, **combinations and other derivatives of known substance shall be considered to be the same substance, unless they differ significantly in properties with regard to efficacy***".

The claims of impugned application relate to a supramolecular complex of Valsartan and Sacubitril and D1-WO2003059345, discloses a physical mixture of Valsartan and Sacubitril and thus is closest prior art. Thus, to show any enhancement in efficacy, a comparison of results obtained by using mixture disclosed in D1 should be shown. However, the applicant has deliberately not shown any enhanced efficacy over D1 and is trying to mislead the prosecution. A careful observation of the graph presented by the applicant in an affidavit of Dr. Michael Motto submitted along with filing written submissions dated June 6, 2020, would illustrate that the similar time of about 180 minutes is taken for dissolution of entire quantity of the physical mixture and of the supramolecular complex, and the percentage of the drug released (at pH 6.8) is also same. To elaborate, at pH 6.8, the amount of valsartan released is same as LCZ696 VAL. Relevant excerpt of submissions are reproduced herein.



PM Val = valsartan released from a physical mixture
PM AHU = sacubitril released from a physical mixture
LCZ696 VAL = valsartan released from LCZ696
LCZ696 AHU = sacubitril released from LCZ696

This means that the efficacy of both is equivalent. Also, in the dissolution graphs at pH 4.5 and 6.8, the release of valsartan is shown to be more than 100%, which is not possible. It is well known that mere bioavailability does not amount to therapeutic effect (Novartis Vs. Union of India, para 189). Accordingly, claims 1-5 of impugned application are not patentable under

Section 3(d) of the Act and liable to be rejected for lack of therapeutic efficacy.

Further, D4 discloses and claims valsartan with the IUPAC name (S)-N-valeryl-N-{[2'-(1H-tetrazole-5-yl)biphenyl-4-yl]methyl}valine). D4 also discloses a method of manufacture of the claimed compounds and specifically valsartan. While D5 discloses the compound which acts as NEP inhibitor, and which can be used as antihypertensive or saluretic agents. D5 in examples 7 and 8 and claim 6, particularly teaches the sodium salt of the sacubitril [N-(3-Carboxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl)-4-amino-2R-methyl butanoic acid, ethyl ester]. The Applicant has taken a stand before the Hon'ble Indian Patent Office that Section 3(d) is not applicable to combinations/compositions /complexes of two active agents since combinations /complexes of two active agents cannot be considered as simple derivatives of either of the active agent. It is submitted that as per Section 3(d), the combinations and other derivatives of known substance shall be considered to be the same substance, unless they differ significantly in properties with regard to efficacy. Thus, compound claimed in the impugned application is a "known substance" or "mere new form" of valsartan as known in D4 and sacubitril as known in D5. It is pertinent to appreciate that compound claimed in impugned application is a complex of two known actives in co-crystal forms, which is held together via noncovalent bonds, thus retaining their individual structural identities with known properties. Such a dual-acting complex comprising two known drugs complexed as a "co-crystal" is merely a new form of a known substance, especially in view of that D1, which discloses the physical combination of valsartan and (2R, 4S)-5-biphenyl-4-yl-4-(3-carboxypropionylamino)-2-methylpentanoic acid ethyl ester.

There is absolutely nothing in the description or otherwise in favour of impugned patent application that would show that the "known efficacy" of the "known substance" has been enhanced. The omission to acknowledge the closest prior art, *i.e.* D1, which incidentally belongs to the applicant is clearly a deliberate suppression with the ulterior motive of

evergreening. Claim of impugned application are nothing but an attempt to evergreen the already existing and patented formulation comprising the same actives as claimed in claim of the impugned application. Thus, claims 1 - 8 of the impugned application fall within the scope of Section 3(d) of the Patents Act, 1970 and make them non-patentable and liable for rejection/refusal on this ground alone.

viii. **Ground V: Section 25(1) (g) [Lack of Sufficiency, Clarity and Enablement]**:

The description of the impugned application does not sufficiently and fairly describe the invention and the method by which it is to be performed. The description of the method or the instructions for the working of the invention as disclosed in the complete specification is not sufficient in itself to enable a person with average skill and average knowledge of the art to which the invention relates, to work the invention.

Section 10(4) of the Act states that "*Every complete specification shall—*

(a) fully and particularly describe the invention and its operation or use and the method by which it is to be performed;

(b) disclose the best method of performing the invention which is known to the applicant and for which he is entitled to claim protection; and

(c) end with a claim or claims defining the scope of the invention for which protection is claimed.

(d) be accompanied by an abstract to provide technical information on the invention."

However, the applicant has failed to sufficiently describe in the complete specification:

- The best methods of developing the preferred embodiments of the compounds as claimed in claims 1 - 5;

- The synthesis of the compounds as claimed in Claim 6 - 8 is too vague and does not teach a person skilled in the art to undoubtedly arrive at the claimed supramolecular structure; and

- No clarity as regard to how the water molecules are associated to the complex of valsartan and sacubitril.

The complete specification should sufficiently and clearly describe the invention and not leave a person skill in the art in a state where he has to conduct undue experimentation to perform the invention. There is no data and examples in the complete specification of the impugned application to show the best mode of working of the invention. Accordingly, it is not known as to what is, the exact and actual workable method for arriving at the compounds as claimed in the impugned application. Thus, as the impugned application lacks sufficiency and support, ground under Section 25(1)(g) of the Act is established and makes the impugned application liable to be refused at the outset.

ix. In the light of above-mentioned averments made for opposition to the impugned application, it is sincerely submitted that this application should be refused grant on the basis of the provisions of Sections **25(1)(e); 25(1)(f); and 25(1)(g)**.

x. **RELIEF SOUGHT**

In view of the representation presented above, the opponent states that it has established and made out a case on each of the aforesaid grounds of opposition and respectfully pray to the Learned Controller that:

1) the Indian Patent Application No. **4412/DELNP/2007** be rejected, and no patent be granted for said application;

2) the opponent may be allowed to submit further submissions and evidence in case the claims on record are amended;

3) the opponent may be allowed to file further documents if necessary to support the averments;

4) any other relief as the Learned Controller may deem fit to be awarded in favour of the opponent.

xi. The opponent also formally requests under Rule 55 (1) for providing a hearing before any final decision on the impugned application.

3. Our address for service in India is : **BLI Consultancy Pvt. Ltd. R-9, Eknath Puram, Amravati, Maharashtra- 444607, India,**
Email: patentconsult.ashu@gmail.com

Agent for the Opponent

Adv. Swapnil J Gawande (IN/PA 1587)

To,
The Controller of Patents
Patent Office
At Delhi

Annexure 01

A CURRICULUM VITAE OF QUALIFICATIONS AND EXPERIENCE

DR. KANCHAN KOHLI

M. PHARM, Ph.D.

Ex Professor and Head

Department of Pharmaceutics

Jamia Hamdard, New Delhi-110062

I. PERSONAL PARTICULARS

Name:	Dr. Kanchan Kohli
Email ID:	kanchankohli@gmail.com
Academic Qualification:	M. Pharma, Ph.D.
Position:	Ex professor and Head Department of Pharmaceutics, Jamia Hamdard New Delhi-110062
Nature of job:	Teaching and Research
Total Teaching/ Research:	37 years
Specialization:	Pharmaceutics
Administrative Experience:	6 years
Research Guidance:	Guided 40 Ph.D. (**Out of which 4 were Inspire fellow**) & M. Pharm students

RESEARCH INDEX

- **Total number of papers published in referred journals = 243**
- **Total publications: 236**
- **H index = 45 (Source= Google Scholar)**
- **Total number of citations = 8830 (Source= Google Scholar)**
- **I10 index** = 139 (Source= Google Scholar)

I. PUBLICATIONS

1. Gupta Priya, Singh Archu, Shafi Sadat, Ralli Tanya, Pottoo Hyder Faheem and Kohli Kanchan*, Cannabis sativa in Phytotherapy: Reappraisal of therapeutic potential and regulatory aspects, Current Pharmaceutical Biotechnology 2023.
2. Zafar Khan, Mohammed A.S. Abourehab, Neha Parveen, Kanchan Kohli & Prashant Kesharwani (2022) Recent advances in microbeads-based drug delivery system for achieving controlled drug release, Journal of Biomaterials Science, Polymer Edition
3. Ralli, Tanya, et al. "Silymarin as a Phyto-pharmaceutical: Isolation, simultaneous quantification of four biomarkers and in-silico anti-inflammatory activity." *Chinese Journal of Analytical Chemistry* (2022): 100174
4. Abulsalam Alhalmi, Saima Amin, Zafar Khan, Sarwar Beg, Omkulthom Al Kamaly, Asmaa Saleh, Kanchan Kohli, Nanostructured Lipid Carriers based co-delivery of Raloxifene and Naringin: Formulation, Optimization, *In-vitro, Ex-vivo, In vivo* assessment, and acute toxicity studies, *Pharmaceutics*, 2022.
5. Abulsalam Alhalmi, Saima Amin, Kanchan Kohli, Spectrophotometric simultaneous estimation of Raloxifene and naringin by Vierordt's method, *Research Journal of pharmacy and technology*, 2022
6. Gupta, Priya, et al. "Combinatorial Chemosensitive Nanomedicine Approach for the Treatment of Breast Cancer." *Current Molecular Medicine* (2022).
7. Abdulsalam Alhalmi, Sarwar Beg, Waleed H. Almalki, Saad Alghamdi, and Kanchan Kohli. "Recent Advances in Nanotechnology-Based Targeted Therapeutics for Breast Cancer Management." *Current drug metabolism*.
8. Abdulsalam Alhalmi, Dr Beg, Dr Mir, R. Showkat, Prof Kohli, Dr Al-Salahi, and Saima Amin. "Formulation and Optimization of Naringin Loaded Nanostructured Lipid Carriers Using Box-Behnken Based Design: In Vitro and Ex Vivo Evaluation." *JDDST-D-22-00042*.
9. Kanchan Kohli, Ali Mujtaba, Rozina Malik, Saima Amin, Md Sarfaraz Alam, Abuzer Ali, Md Abul Barkat, and Mohammad Javed Ansari. "Development of Natural Polysaccharide–Based Nanoparticles of Berberine to Enhance Oral Bioavailability: Formulation, Optimization, Ex Vivo, and In Vivo Assessment." *Polymers* 13, no. 21 (2021): 3833.
10. Bharti Mangla, Shamama Javed, Muhammad Hadi Sultan, Pankaj Kumar,

Kanchan Kohli, Asim Najmi, Hassan A. Alhazmi, Mohammed Al Bratty, and Waquar Ahsan. "Sulforaphane: A review of its therapeutic potentials, advances in its nanodelivery, recent patents, and clinical trials." *Phytotherapy Research* 35, no. 10 (2021): 5440-5458.

11. Bharti Mangla, Kanchan Kohli, and Saifu Rabiu. "Review of medicinal uses, phytochemistry, pharmacological properties, extraction methods and toxicology of Lannea microcarpa (African Grapes)." *Current Traditional Medicine* 7, no. 1 (2021): 125-137.

12. Foziyah Zakir, Adil Ahmad, Mohd Amir Mirza, Kanchan Kohli, and Farhan J. Ahmad. "Exploration of a transdermal nanoemulgel as an alternative therapy for postmenopausal osteoporosis." *Journal of Drug Delivery Science and Technology* 65 (2021): 102745.

13. Reshal Suri, Yub Raj Neupane, Nikita Mehra, Md Nematullah, Farah Khan, Ozair Alam, Ashif Iqubal, Gaurav Kumar Jain, and Kanchan Kohli. "Sirolimus loaded chitosan functionalized poly (lactic-co-glycolic acid) (PLGA) nanoparticles for potential treatment of age-related macular degeneration." *International Journal ofBiological Macromolecules* 191 (2021): 548-559.

14. Ralli, Tanya, et al. "Clinical and Regulatory Status of Silymarin." *Applied Drug Research, Clinical Trials and Regulatory Affairs: Formerly Applied Clinical Research, Clinical Trials and Regulatory Affairs* 8.2 (2021): 104-111.
15. Priya Gupta, Yub Raj Neupane, Suhel Parvez, and Kanchan Kohli. "Recent advances in targeted nanotherapeutic approaches for breast cancer management." *Nanomedicine* 16, no. 29 (2021): 2605-2631.

16. Bharti Mangla, Shamama Javed, Muhammad Hadi Sultan, Pankaj Kumar, Kanchan Kohli,Waquar Ahsan. Sulforaphane: A review of its therapeutic potentials, advances in its nanodelivery, recent patents, and clinical trials. Phytotherapy Research. 2021.

17. Tanya Ralli, Yub Raj Neupane, Zoya Saifi, Kanchan Kohli. Gut microbiota as an emerging therapeutic avenue for the treatment of non-alcoholic fatty liver disease. Current Pharmaceutical Design. 2021.

18. Abdulsalam Alhalmi, Sarwar Beg, Kanchan Kohli, Md Waris, Tanuja Singh. Nanotechnology Based Approach for Hepatocellular Carcinoma Targeting.

CurrentDrug Targets. 2020. 22 (7), 779-792

19. Vaidehi Garg, Gaurav Kumar Jain, Nirmal Jayabalan, Yassine Riadi, Prashant Kesharwani, Kanchan Kohli. Amelioration of endotoxin-induced uveitis in rabbit by topical administration of tacrolimus proglycosome nano-vesicles. Journal of Pharmaceutical Sciences. 2020, 110(2):871-875.

20. Bharti Mangla, Yub Raj Neupane, Archu Singh, Pankaj Kumar, Sadat Shafi, Kanchan Kohli. Lipid-nanopotentiated combinatorial delivery of tamoxifen and sulforaphane: ex vivo, in vivo and toxicity studies. Nanomedicine. 2020, 15 (26): 2563-2583.

21. Bharti Mangla, Sarwar Beg, Ozair Alam, Waquar Ahsan, Anzarul Haque, Kuldeep Singh Patel, Waleed Hassan Almalki, Majed Alrobaian, Kanchan Kohli.Systematic development and validation of RP-HPLC method for simultaneous estimation of tamoxifen and sulphoraphane with specific application for nanolipidic formulations. Arabian Journal of Chemistry. 2020, 13(11), 7909:1878-5352

22. Md Shoaib Alam, Mohammed S Algahtani, Javed Ahmad, Kanchan Kohli, Sheikh Shafiq-Un-Nabi, Musarrat Husain Warsi, Mohammad Zaki Ahmad. Formulation design and evaluation of aceclofenac nanogel for topical application. Therapeutic Delivery. 2020, 11 (!2):767-778.

23. Nimrit Kaur Soni, LJ Sonali, Archu Singh, Bharti Mangla, Yub Raj Neupane, Kanchan Kohli. Nanostructured Lipid Carriers potentiated oral delivery of Raloxifene for breast cancer treatment. Nanotechnology. 2020, 31 (47): 475101.

24. Reshal Suri, Yub Raj Neupane, Gaurav K Jain, Kanchan Kohli. Recent theranostic paradigms for the management of Age-related macular degeneration. European Journal of Pharmaceutical sciences. 2020, 153, 105489.

25. Archu Singh, Yub Raj Neupane, Bharti Mangla, Sadat Shafi, Kanchan Kohli. PEGylated nanoliposomes potentiated oral combination therapy for effective cancer treatment. Current Drug Delivery. 2020, 17 (9): 728-735.

26. Bharti Mangla, Ozair Alam, Rehan Abdur Rub, Muzaffar Iqbal, Archu Singh, Kuldeep Singh Patel, Kanchan Kohli. Development and validation of a high throughput bioanalytical UPLC-MS/MS method for simultaneous determination of tamoxifen and sulphoraphane in rat plasma: Application to an oral

pharmacokineticstudy. Journal of Chromatography B. 2020; 1152:122260

27. Archu Singh, Sadat Shafi, Tanya Upadhyay, Abul Kalam Najmi, Kanchan Kohli, Faheem Hyder Pottoo. Insights into Nanotherapeutic Strategies as an Impending Approach to Liver Cancer Treatment. Current Topics in Medicinal Chemistry. 2020, 20, 1-16.

28. Sradhanjali Mohapatra, Zeenat Iqbal, Sayeed Ahmad, Kanchan Kohli, Uzma Farooq, S Padhi, Mariya Kabir, P Ayash Kumar. Menopausal Remediation and Quality of Life (QoL) Improvement: Insights and Perspectives. 2020

29. Reshal Suri, Yub Raj Neupane, Gaurav K Jain, Kanchan Kohli.Polyoliposomes: novel polyol modified lipidic nanovesicles for dermal and transdermal delivery of drugs. Nanotechnology. 2020

30. Archu Singh, Yub Raj Neupane, Bharti Mangla, Kanchan Kohli. PEGylated liposomes as an emerging therapeutic platform for oral nanomedicine in cancer therapy: in vitro and in vivo assessment. Journal of Molecular Liquids. 2020; 303.

31. Bharti mangla, Kuldeep Singh Patel, Pankaj Kumar, Kanchan Kohli. Validation of forced degradation and stability indicating studies of Tamoxifen in nanoformulation using spectroscopic technique. Materials Today: Proceedings. 2020.

32. Foziyah Zakir, Adil Ahmad, Uzma Farooq, Mohd Aamir Mirza, Alok Tripathi, Divya Singh, Faiyaz Shakeel, Sradhanjali Mohapatra, Farhan J Ahmad, Kanchan Kohli. Design and development of a commercially potential in situ nanoemulgel for the treatment of postmenopausal osteoporosis. Nanomedicine. 2020.

33. Reshal Suri, Yub Raj Neupane, Nikita Mehra, Gaurav K Jain, Kanchan Kohli. Sirolimus loaded Polyol modified liposomes for the treatment of Posterior Segment Eye Diseases. Medical Hypotheses. 2019; 109518.

34. Kriti Soni, Ali Mujtaba, MH Akhter, A Zafar, Kanchan Kohli. Optimization of ethosomalnanogel for topical nano-CUR and Sulphoraphane delivery in effective skincancer therapy.Journal of Microencapsulation, 2019; 1-44;

35. Reshal Suri, Sarwar Beg, Kanchan Kohli. Target strategies for drug delivery bypassing ocular barriers. Journal of Drug Delivery Science and Technology, 2019; 101389.

36. Bharti Mangla, YubRaj Neupane, Archu Singh, Kanchan Kohli. Tamoxifen and Sulphoraphane for the breast cancer management: A synergistic nanomedicine approach. Medical hypotheses2019; 132: 109379

37. Yasir Rahman, Saima Amin, Showkat R Mir, Kanchan Kohli. Pre-Formulation Study for Palatable Microbeads of Lycopene. Journal of Drug Delivery and Therapeutics.2019; 9 (4-A), 320-327

38. Archu Singh, YubRaj Neupane, Bharti Mangla, Kanchan Kohli. Nanostructured Lipid Carriers for oral bioavailability enhancement of Exemestane: Formulation design, in vitro, ex vivo and in vivo studies. Journal of pharmaceutical sciences. 2019.

39. Pankaj Kumar, Bharti Mangla, Archu Singh, Kanchan Kohli. Plant associated microbial techniques in agriculture industry. International Journal of Pharmacy & Life Sciences. 2019; 10 (6).

40. Bharti Mangla, Archu Singh, Pankaj Kumar, Kanchan Kohli. Beneficial effects of herbal drugs in modern medicine for the management of obesity. InternationalJournal of Pharmacy & Life Sciences. 2019; 10 (6).

41. Archu Singh, Bharti Mangla, Pankaj Kumar, Kanchan Kohli. Liposomes as carriers for oral drug delivery. International Journal of Pharmacy & Life Sciences. 2019; 10 (6).

42. Surbhi Ranjan, Bharti Mangla, Archu Singh, Kanchan Kohli. Method Development and Validation of Exemestane and Stress Degradation Studies using UV Spectrophotometry. Latin American journal of pharmacy.2019; 38 (2): 414-423

43. Sarwar Beg, M Rahman, Kanchan Kohli. Quality-by-design approach as a systematic toolfor the development of nanopharmaceutical products.Drug discovery today; 2018.

44. Shamama Javed, W Ahsan, Kanchan Kohli. Pharmacological influences of natural products as bioenhancers of silymarin against carbon tetrachloride-induced hepatotoxicityin rats. Clinical Phytoscience, 2018; 4 (1): 18.

45. Kriti Soni, Kanchan Kohli. Sulforaphane decorated gold nanoparticle for anti-

cancer activity: In vitro and in vivo studies. Pharmaceutical development and technology, 2018; 1-37

46. Nikita Sehgal, Kriti Soni, Navika Gupta, Kanchan Kohli. Microorganism Assisted Synthesis of Gold Nanoparticles: A Review. Asian Journal of Biomedical and Pharmaceutical Sciences. 2018

47. Neha Tyagi, Archu Singh, Kanchan Kohli. New insights towards implications of sea buckthorn oil in human health: a review. International Journal of CurrentInnovation Research. 2018.

48. Md Noushad Javed, Kanchan Kohli, Saima Amin. Risk Assessment Integrated QbD Approach for Development of Optimized Bicontinuous Mucoadhesive Limicubes for OralDelivery of Rosuvastatin. AAPS PharmSciTech. 2017, 1-15

Nafees Ahmad, Farhan Haidar, Saima Amin, Kanchan Kohli. Transdermal Delivery of Lercanidipine: Microscopic Examination, Rheology and Ex Vivo Permeation Mechanistic Study on Rat Skin by Differential Scanning Calorimetry. Current Nanomedicine (Formerly: Recent Patents on Nanomedicine). 2017; 7 (3), 223-236

49. Bharti Mangla, Kanchan Kohli. Pharmaceutical and Therapeutic Potential of Miraculin and Miracle Berry. Tropical Journal of Natural Product Research. 2017;2 (1), 12-17

50. Kriti Soni, M Rizwanullah, Kanchan Kohli. Development and optimization of sulforaphane loaded nanostructured lipid carriers by the Box-Behnken design for improved oral efficacy against cancer: in vitro, ex vivo and in vivo assessment.Artificial cells, nanomedicine, and biotechnology, 2017; 1-17.

51. Archu Singh, Yub Raj Neupane, Bibhu Prasad Panda, Kanchan Kohli. Lipid based Nanoformulation of Lycopene improves oral delivery: formulation optimization, ex vivo assessment and its efficacy against Breast Cancer. Journal of Microencapsulation. 2017.

52. Kashish Aziz. Nafees Ahmed, Kanchan Kohli. Enhanced Anti Arthritic potential of Tactrolimus by Transdermal Nanocarrier System. Journal of Nanoscience and nanotechnology. 2017; 11(7): 4573-4583

53. Vaidehi Garg. Reshal Suri, Gaurav Kumar Jain, Kanchan Kohli. PROGLYCOsomes: A Novel Nano-Vesicle For Ocular Delivery Of Tacrolimus Colloids and Surfaces B Biointerfaces 2017; 157:40-47

54. Kriti soni, Ali Mujtaba, Kanchan Kohli. Lipid drug conjugate nanoparticle as a potential nanocarrier for the oral delivery of pemetrexed diacid: Formulation design, characterization, ex vivo, and in vivo assessment. International Journal of Biological Macromolecules 2017; 103:139-151

55. Ali Mujtaba, Kanchan Kohli. Validated HPLC method for the pharmacokinetic study of oral extended-release cefpodoxime proxetil chitosan–alginate beads in rabbits. International Journal of Biological Macromolecules. 2017; 98: 111–116

56. Manavi Kapur, Kriti Soni, Kanchan Kohli. Green Synthesis of Selenium Nanoparticles from Broccoli, Characterization, Application and Toxicity Advanced Techniques in Biology & Medicine. 2017; 5:198

Ali Mujtaba, Kanchan Kohli. In vitro/ In vivo evaluation of HPMC/alginate based extended-release matrix tablets of cefpodoxime proxetil. International Journal of Biological Macromolecules. 2016; 89: 434-441

57. Javed Ahmad, Niyaz Ahmad, Kanchan Kohli, Showkat R Mir, and Saima Amin. Pharmacokinetic analysis of taxane through a validated ultra-high performance liquid chromatography- synapt mass spectrometry (UHPLC-MS/MS ESI-Q-TOF) method. Current Bioactive compounds. 2016; 12(2): 93-102

58. Abdul Ahad, Mohd Aqil, Kanchan Kohli, Yasmin Sultana, and Mohd Mujeeb. Nano vesicular lipid carriers of angiotensin II receptor blocker. Anti-hypertensive and skin toxicity study in focus. Artificial cells, Nanomedicine and Biotechnology. 2016; 44(3): 1002-1007 3.026

59. Bhulan Kumar Singh, Krishna K. Pillai, Kanchan Kohli, and Ehtaishamul Haque. Cissampelos pareina Linn. Ameliorates thyroxin- induced cardiac hypertrophy in rats. Journal of Ethnopharmacology. 2016; 178: 281-288

60. Manish Srivastava, Kanchan Kohli, Muhir Ali. Formulation development of novel in situ nanogel (NEG) of ketoprofen for the treatment of periodontitis. Drug Delivery. 2016; 23(1):154-166

61. Kriti Soni, Aarushi Gupta, Kanchan Kohli. Sneak peek into chemopreventive potential of Brassica oleracea: Milestones achieved so far. International Journal of Pharmacognosy andPhtyochemical Research. 2016; 8(1)

62. Kriti Soni, Bhavleen Kaur Kukerja, Manavi Kapur and Kanchan Kohli.

Lipid nanoparticles: Future of oral drug delivery and their current trends and regulatory issues. International Journal of current Pharmaceutical Review and Research. 2016; 7(1): 1-18

63. Shamama javed, Kanchan Kohli, and Waquar Ahsan. Solubility and dissolution enhancement of silymarin with fulvic acid carrier. International Journal of Drug Development and Research. 2016; 8:009-014

64. Shamama javed, Kanchan Kohli, Waquar Ahsan. Incorporation of METHOCEL E6 PLV by a Novel Foam Granulation Technique for Dissolution Augmentation of the Poor SolubleSilymarin. Journal of Pharmacy Research. 2016; 10(2): 79-89

65. Abdul Ahad, Mohd Aqil, Kanchan Kohli, Yasmin Sultana, Mohd Mujeeb. Nanovesicular lipid carriers of angiotensin II receptor blocker Anti-hypertensive and skin toxicity study in focus. Artificial cells, Nanomedicine and Biotechnology 2015; 44(3): 1002-1007

66. Babar Iqbal, Azim Akhtar, Nafees Ahmed, Sanjula Baboota, Kanchan Kohli, Amin- ul aziz and Kashish Aziz Enteric Coated Iron Folic Acid Tablets : Compromised Efficacy at Costof Safety BAO Journal of Pharmaceutical Science. 2015; 1(3): 015

67. Md Sabir, Yub Raj Neupane, Manish Srivastava, Saima Amin and Kanchan Kohli. Lipid based nanocarrier of lercanidipine for the management of hypertension.2015; 7:1-9

68. Yub Raj Neupane, Manish Srivastava, Suman Gyenwalee, Nafees Ahmad, Kriti Soni and Kanchan Kohli. Solid Lipid Nanoparticle for the Oral Delivery of Decitabine: Formulationoptimization, Characterization, Stability study and Ex-vivoGut permeation study. Scienceof Advanced Materials. 2015; 7(3):433- 445

69. Javed Ahmad, Showkat R Mir, Kanchan Kohli, Saima Amin. Construction of Pseudoternary Phase Diagram and its Evaluation: Development of Self-dispersible Oral Formulation International Journal of Drug development and Research. 5(2): 84-90

70. Arvind Kukreja, Kanchan Kohli, M Singhal, Chetan Dhal, A Chauhan, P Arun. Development and validation of a sensitive spectrophotometric method for simultaneous estimation of pitavastatin. Indian drugs. 2015; 52(08):17-21

71. Manavi Kapur, Kriti Soni, Bhavleen Kaur Kukereja and Kanchan Kohli. Metal nanoparticles: Synthesis, characterization, toxicity and regulatory aspects. Innovations in Pharmaceuticals and Pharmacotherapy. 2015; 3(4):692-709

72. Bhavleen Kaur Kukreja, Kriti Soni and Kanchan Kohli. Current Market Trends and Regulatory Aspects of Herbal Antioxidants and Natural Dietary Supplements: A boon for health and treatment of diseases. World Journal of Pharmacy and Pharmaceutical Sciences.2015; 4: 2373-2406

73. Kriti Soni and Kanchan Kohli. Broccoli Sulforaphane: An Insight into the Analytical Aspect and Ultraviolet Spectroscopic Method Development and Validation. World Journal of Pharmacy and Pharmaceutical Sciences. 2015; 8(1): 57-63

74. Nafees Ahmad, Saima Amin, Yub Raj Neupane, Kanchan Kohli. Anal fissure nanocarrier of lercanidipine for enhanced transdermal delivery: formulation optimization, ex vivo and in vivo assessment. Expert Opinion on Drug Delivery. 2014

75. Abdul Ahad, Mohd Aqil, Kanchan Kohli, Yasmin Sultana, Mohd Mujeeb. Design, formulation and optimization of valsartan transdermal gel containing iso- eucalyptol as novel permeation enhancer: preclinical assessment of pharmacokinetics in Wistar albino rats. Expert Opinion on Drug Delivery. 2014; 11(8):1149-62

76. Ali Mujtaba, Mushir Ali, Kanchan Kohli. Statistical optimization and characterization of pH-independent extended-release drug delivery of cefpodoxime proxetil using Box- Behnken Design. Chemical Engineering Research and Design. 2014; 92(1):156-16

77. Manish Srivastava, Kanchan Kohli, Mushir Ali. Stability Indicating RP-HPLCMethod for Analysis of Ketoprofen in Bulk Drug and Eugenol Containing Nanoemulsion Gel (NEG) Formulation Using Response Surface Methodology. Current Pharmaceutical Analysis. 2014; 10(2):135-144

78. Hema Chaudhary, Kanchan Kohli, Vikash Kumar. A novel nano-carrier transdermal gel against inflammation. International Journal of Pharmaceutics. 2014; 465(1-2):175-86

79. Javed Ahmad, Showkat R. Mir, Kanchan Kohli, Saima Amin. Effect of oil and co- surfactant on the formation of Solutol HS 15 based colloidal drug carrier by Box– Behnken statistical design. Colloids and Surfaces A Physicochemical and Engineering Aspects. 2014; 453:68–77

80. Vidhi Malika V, Kanchan Kohli, Hema Chaudary, Vikash Kumar. Nano-carrier for accentuated Transdermal drug delivery. Journal of developing drugs 2014; 3(121): 2

81. Yub Raj Neupane, Manish Srivastava, Nafees Ahmad, Neeraj Kumar, Aseem Bhatnagar, Kanchan Kohli. Lipid based nanocarrier system for the potential oral delivery of decitabine: Formulation design, characterization, ex vivo, and in vivo assessment. International Journal of Pharmaceutics. 2014; 477(1-2):601-612 3.862Manish Srivastava, Yub Raj Neupane, Parveen Kumar, Kanchan Kohli. Nanoemulgel (NEG) of Ketoprofen with eugenol as oil phase for the treatment of ligature-induced experimental periodontitis in Wistar rats. Drug Delivery. 2014; 26:1-7 3.09

82. Javed Ahmad, Showkat R Mir, Kanchan Kohli, Saima Amin. Quality by Design Approach for Self-Nanoemulsifying System of Paclitaxel Science of Advanced Materials. 2014; 6:1778–1791

83. Mukesh garg, B.Srivastava, Kanchan Kohli, Simrata Bedi and Pankaj Sharma. Performance Enhancement of Water Soluble Drugs Using Novel Formulation Technique.International Journal of Drug Delivery Technology 2014; 4(3)

84. Eman Abdo Ali, Abu Tahir, Roop K Khar, Kanchan Kohli. A study to Compare Different Techniques to Develop Valsartan Sustained Release Tablets. Journal of Pharmacy Research. 2014; 4(3):1567-1579

85. Ali Mujtaba, Mushir Ali, Kanchan Kohli. Formulation of Extended Release Cefpodoximeproxetil Chitosan-Alginate Beads using Quality by Design Approach. International journalof biological macromolecules. 2014; 69:420-429 3.909

86. Mohammad Javed Ansari, Kanchan Kohli, Javed Ali, Mohammad Khalid Anwar, Shahid Jamil and Mohammad Muqtader Ahmed. Physicochemical, Characterizations and Dissolution Behaviour of Curcumin and alpha-cyclodextrin molecular inclusion complexes. Der Pharmacia Lettre. 2014; 6(6):1-

7

87. Yub Raj Neupane, MD Sabir, Nafees Ahmad, M Ali, Kanchan Kohli. Lipid drug conjugate nanoparticle as a novel lipid nanocarrier for the oral delivery of decitabine: ex vivo gut permeation studies. Nanotechnology 24 (41), 415102 3.404

88. Bhulan Kumar Singh, Krishna Kolappa Pillai, Kanchan Kohli and Syed Ehtaishamul Haque. Effect of Cissampelos pareira root extract on isoproterenol-induced cardiac dysfunction. Journal of natural medicines. 2013; 67(1):51-60.

89. Abdul Ahad, Fahad I Al-Jenoobi Abdullah M Al-Mohizea , Mohd Aqil, and Kanchan Kohli. Transdermal delivery of calcium channel blockers for hypertension.Expert Opinionon Drug Delivery. 2013; 10(8): 1137-1153

90. Hema Chaudhary, Kanchan Kohli, Vikash Kumar. Nano-tansferosomes as a novel carrier for transdermal delivery" International journal of pharmaceutics. 2013; 454(1):367-380. 3.862

91. Ali Mujtaba, Kanchan Kohli, Javed Ali, Sanjula Baboota. Development of HPTLCmethodfor the estimation of ondansetron hydrochloride in bulk drug and sublingualtablets. DrugTesting and Analysis. 2013; 5(2):122-125.

92. Areeg A Shamsher, Naseem A Charoo, Ziyaur Rehman, Krishna K Pillai, and Kanchan Kohli. Tulsi oil as a potential penetration enhancer for celecoxib transdermal gel formulations. Pharmaceutical Development and Technology. 2013;9(1): 21-30

93. Saima Amin, Ahmad Sarfenejad, Javed Ahmad, Kanchan Kohli, and Showkat R. Mir. Nanovesicular Transfersomes for Enhanced Systemic Delivery of Telmisartan. AdvancedScience, Engineering and Medicine. 2013; 5: 299-308

94. Ali Mujtaba, Kanchan Kohli, Javed Ali, and Sanjula Baboota. Formulation and Evaluation of Sublingual Drug Delivery of Ondansetron Hydrochloride Tablets. Advanced Science, Engineering and Medicine. 2013; 5(4): 259-264

95. Abdul Ahad, Mohd Aquil, Kanchan Kohli, Yasmin Sultana, Mohd Mujeeb. Enhanced transdermal delivery of an anti-hypertensive agent via nanoethosomes: statistical optimization, characterization and pharmacokinetics assessment. International journal of Pharmaceutics. 2013; 443(1): 26-38

96. Ali Mujtaba, Mushir Ali, Kanchan Kohli. Influence of formulation variables and process parameters on the release performance of Cefpodoxime proxetil from HPMC and HPMC- Alginate based matrices. Advanced Science, Engineering and Medicine. 2013; 5(9): 950- 956

97. Manu Babbar, Kanchan kohli and Anil Bhandari. Formulation development and evaluation of sol to gel ocular drug delivery system of Brimonidine for conjunctivitis. International Journal of Pharmaceutical Sciences and Research. 2013; 4(2): 687-691

98. Hema Chaudhary, Kanchan Kohli, Vikash Kumar. Nano-Transfersomes as a NovelCarrier for Transdermal Delivery. International journal of Pharmaceutics. 2013;454(1): 367-370

99. Shamama Javed, Kanchan Kohli, Waquar Ahsan, Manish Srivastava, Md.S. Afzal. Liquidchromatography Microemulsion Based HPLC Methods. Reference Module in Chemistry, Molecular Sciences and Chemical Engineering. 2013

100. Rakesh Pahwa, Seema Bisht, Vipin Kumar, Kanchan Kohli, Recent advances in gastric floating drug delivery technology: a review. Current Drug Delivery. 2013; 10(3):286-98.

101. Nitin Parmar, Kanchan Kohli, Saima Amin, Neelam Singla. The Solution, Solid State Stability and kinetic investigation in degradation studies of Lercanidipine. Study of Excipients Compatibility of Lercanidipine. Pharmaceutical Development and Technology.2012; 17(6):730-40

102. Shamama Javed, Kanchan Kohli, Mushir Ali. Forced degradation and pH stability studies of lysergol: An ergolic alkaloid by stability indicating RP-HPLC UV method. Journal of Liquid Chromatography & Related Technologies. 2012; 35(4): 471-4832012

103. Shamama Javed, Kanchan Kohli, Mushir Ali. Solid State Compatibility between Silymarin and Tablet Excipients by Thermal and Non-Thermal Methods, its pH Stability and Solubility Analysis. Journal of Pharmacy Research. 2012; 5(3):1300- 1305.

104. Abdul Ahad, Mohd Aquil, Kanchan Kohli, Yasmin Sultana, Mohd Mujeeb,

Asgar Ali. Formulation and optimization of nanotransferosomes using experimental design technique for accentuated transdermal delivery of valsatan. Nanomedicine: nanotechnology, biologyand medicine. 2012; 8(2): 237-249

105. Hema Chaudhary, Kanchan Kohli, Saima Amin, Saurabh Arora, Vikash Kumar, Sushila Rathee and Permender Rathee. Development and validation of RP-HPLC method for simultaneous estimation of diclofenac diethylamine and curcumin in transdermal gels. Journal of liquid chromatography & related technologies. 2012; 35(1): 174-187.

106. Rakesh Pahwa, Manisha Singh, Vipin Kumar, Kanchan Kohli. Chitosan-based gastroretentive floating drug delivery technology: an updated review. Expertopinion on drug delivery. 2012; 9(5): 525-539

107. Javed Ahmad, Kanchan Kohli, Showkat R. Mir, and Saima Amin. Self-Emulsifying Nano Carriers for Improved Oral Bioavailability of Lipophilic Drugs. Reviews in Adance Sciences and Engineering. 2012; 1: 134-147.

108. Sheelendra Pratap Singh, Wahajuddin, K.S.R. Raju, Mushir M.Ali, and Kanchan Kohli, Girish Kumar Jain. Reduced Bioavailability of Tamoxifen and its Metabolite 4- Hydroxytamoxifen After Oral Administration with Biochanin A (an Isoflavone) in Rats. Phytotherapy Research. 2012; 26(2): 303–307

109. Rakesh Pahwa, Manisha Singh, Vipin Kumar, Kanchan Kohli. Recent advances and patent perspective in gastro-retentive technology. Recent patents on drug delivery and formulation 2012; 6(3): 278-290

110. Bhulan Kumar Singh, Krishna Kolappa Pillai, Kanchan Kohli and Syed Ehtaishamul Haque. Classification and Definitions of Cardiomyopathies Cardiomyopathies - From Basic Research to Clinical Management. 2012

111. Sarwar Beg, Kanchan Kohli, Suryakanta Swain and M. Saquib Hasnain. Development and validation of RP-HPLC method for quantitation of amoxicillin trihydrate in bulk and pharmaceutical formulations using box-behnken experimental design. Journal of liquid chromatography & related technologies. 2012; 35(3):393-406.

112. Raveendra Pai, Kanchan Kohli, Birendra Shrivastava. Compression and evaluation of extended release matrix pellets prepared by the

extrusion/spheronization process into disintegrating tablets. Brazilian Journal of Pharmaceutical Sciences 2012; 6(3): 278-290

113. Azhar Rashikh, Shibli Jameel Ahmad, Krishna Kolappa Pillai, Kanchan Kohli, Abul Kalam Najmi. Aliskiren attenuates myocardial apoptosis and oxidative stress in chronic murine model of cardiomyopathy. Biomedicine andPharmacotherapy. 2012;66(2):138-43.

114. Seemi Siddiqui, S Kumar, Anees Sidiqui, S Paliwal, Kanchan Kohli, R Mishra. Analytical approach to paclitaxel. Hamdard medicus 2012; 55(3)

Shamama Javed, Kanchan Kohli, Mushir Ali. Solid State Compatibility between Silymarin and Tablet excipients by Thermal and Non-thermal Methods, its pH stability and Solubility analysis. Journal of Pharmacy research. 2012; 5(3):133- 1305

115. Seemi Siddiqui, Sarvesh Paliwal, Kanchan Kohli, Anees Siddiqui and Kapendra Sahu. RP-HPLC Method for Estimation and Stress Degradation Study ofPaclitaxel as perICH Guidelines. 2012

116. Abdul Ahad, Mohammed Aqil, Kanchan Kohli, Yasmin Sultana, Mohd. Mujeeb. Role of novel terpenes in transcutaneous permeation of valsartan: Effectiveness and mechanism of action. Drug Development and Industrial Pharmacy. 2011; 37(5):583-96

117. Sarwar Beg, Mohammad Rizwan, Asif M. Sheikh, M. Saquib Hasnain, Khalid Anwer, Kanchan Kohli. Advancement in carbon nanotubes: basics, biomedical applications and toxicity. Journal of Pharmacy and Pharmacology. 2011; 63(2): 141–163

118. Abdul Ahad, Mohammed Aqil, Kanchan Kohli, Yasmin Sultana, Mohd. Mujeeb, Asgar Ali. Interactions between Novel Terpenes and Main Components of Rat and Human Skin: Mechanistic View for Transdermal Delivery of Propranolol Hydrochloride. CurrentDrug Delivery. 2011; 8(2): 213-224(12)

119. Hema Chaudhary, Kanchan Kohli, Saima Amin, Permender Rathee, Vikash Kumar. Optimization and formulation design of gels of Diclofenac and Curcumin for transdermal drug delivery by Box-Behnken statistical design. Journalof Pharmaceutical Science, 2011; 100(2): 580–593

120. Deepak Khera, Nitin Parmar, Kanchan Kohli. Development and validationof stability-indicating HPTLC method for determination of Glycyrrhizic acid in bulk drug and pharmaceutical formulations. Journal of Liquid Chromatography and Related Sciences. 2011; 34(15): 1502-1517.

121. Ravinder Pai, Aruna Pai, Birendra Srivastava, Kanchan Kohli. Development and In Vitro Evaluation of Ketoprofen Extended Release Pellets Using Powder Layering Technique in a Rotary Centrifugal Granulator. Combinatorial Chemistry & High Throughput Screening. 2011; 14(2):138-45

122. Sunny Chopra, Kanchan Kohli, Saurabh Arora and Roop K. Khar In-situ nano- emulsification technique for enhancing oral bioavailability of curcumin and thereby evaluating its anticancer efficacy on human lung adeno-carcinoma epithelial cell line Journal of Pharmacy Research. 2011; 4(11): 4087-4093

123. Shamama Javed, Kanchan Kohli, Mushir Ali. Reassessing Bioavailability ofSilymarin. Alternative Medicines Review. 2011; 16(3): 239-249

124. Neha Nath, G N Singh, Raman M Singh, Kanchan Kohli. Method Development and Estimation of Beta-Carotene by HPTLC in the Fruit Pulp of Mangifera Indica L. International Journal of Chemical and Analytical Science. 2011; 2(6)

125. Bhulan Kumar Singh, Krishna Kolappa Pillai, Kanchan Kohli and Syed Ehtaishamul Haque. Isoproterenol-Induced Cardiomyopathy in Rats: Influence of Acoruscalamus Linn. Cardiovascular Toxicology. 2011; 11(3): 263-271

126. Shamama Javed, Kanchan Kohli and Mushir Ali. Application of Response SurfaceMethodology to Microwave-Assisted Extraction of Lysergol from Ipomoea Genus and Its Characterization by RP HPLC-UV. Journal of Pharmaceutical Innovation. 2011; 6(2): 88-96

127. Nitin Parmar,Neelam Singla, Saima Amin, Kanchan Kohli. Study of co-surfactanteffect on nanoemulsifying area and development of lercanidipine loaded (SNEDDS) self- nanoemulsifying drug delivery system. Colloids and Surfaces B: Biointerfaces. 2011; 86(2): 327-338

128. Raveendra Pai, Kanchan Kohli. Extended release matrix pellets:

preparation and compression into disintegrating tablet. International Journal of Drug Delivery. 2011; 3:329-339

129. Deepak Khera, Kanchan Kohli and Nitin Parmar. Development and validation of stability-indicating HPTLC method for determination of glycyrrhizic acid in bulk drug and pharmaceutical formulations. Journal of Liquid Chromatography & Related Technologies.2011; 34(15): 1502-1517.

130. Raveendra Pai, Kanchan Kohli, Gaurav Jain and Birendra Srivastava. In vitro andin vivo evaluations of ketoprofen extended release pellets prepared using powder layeringtechnique in a rotary centrifugal granulator. Archives of Pharmacal Research. 2011; 34(7):1135-1142.

131. Sheelendra Pratap Singh, Wahajuddin, Mushir Ali, Kanchan Kohli, Girish Kumar Jain. Liquid chromatography–mass spectrometry method for the quantification of tamoxifen and its metabolite 4-hydroxytamoxifen in rat plasma: Application to interaction study with biochanin A (an isoflavone). Journal of Chromatography B. 2011; 879(27): 2845-2851

132. Rakesh Pahwa, Himanshu Dutt, Vipin Kumar and Kanchan Kohli. Pharmacoscintigraphy: An emerging technique for evaluation of various drug delivery systems. Archives of Applied Science Research. 2010; 2(5):92-105

133. Kanchan Kohli, Sanjula Baboota, Mona Dhaliwal. “Physicochemical characterization, in vitro dissolution behavior, and pharmacodynamic studies of rofecoxib- cyclodextrin inclusion compounds. AAPS Pharm Science Tech. 2010; 6(1): 83-90

134. Abdul Ahad, Mohammed Aqil, Kanchan Kohli, Yasmin Sultana, Mohd. Mujeeb. Transdermal Drug Delivery: The Inherent challenges and Technological advancements. Asian Journal of Pharmaceutical Sciences. 2010; 5(6): 276-289

135. Peerzadi Shazia, Kanchan Kohli. Encapsulation of probiotics from microto nano.Nano Digest. Jan 2010; 1(8): 38-40.

136. Shamama Javed, Kanchan Kohli. Nanotechnology in ocular drug delivery.Nano Digest. 2010; 1(9): 42-45.

137. Shamama Javed, Kanchan Kohli, Mushir Ali. Patented bioavailability enhancement techniques of silymarin. Recent Patents on Drug Delivery and

Formulations.2010; 4(2):145-52

138. Kanchan Kohli, Vipin kumar, Shiv Bhagwan, Rakesh Pahwa. Role of natural polymers in development of floating drug delivery systems. Journal pharmacy research. 2010; 3(6):1312-1318

139. Shamama Javed, Kanchan Kohli. Local delivery of minocycline hydrochloride: A therapeutic paradigm in periodontal diseases. Current Drug Delivery, 2010; 7(5):398-406

140. Mohammad Intakhab Alam, Sanjula Baboota, Kanchan Kohli, Javed Ali, Alka Ahuja. Pharmacodynamic evaluation of proniosomal transdermal therapeutic gelcontaining celecoxib. Science Asia. 2010; 36(4): 305-311

141. Areeg A Shamsher, Naseem A Charoo, Kanchan Kohli, Krishna Pillai, Ziyaur Rehman. Effect of transdermally delivered aspirin on blood coagulation parameters.American Journal of Biomedical Sciences. 2010; 2(2): 129-141.

142. Kanchan Kohli, Sunny Chopra, Deepika Dhar, Saurabh Arora and Roop K. Khar. Self-emulsifying drug delivery systems: an approach to enhance oralbioavailability, DrugDiscovery Today. 2010;15(21-22):958-65

143. Mohammad Intakhab Alam, Sarwar Beg, Abdus Samad, Sanjula Baboota, Kanchan Kohli, Javed Ali, Alka Ahuja and M. Akbar. Strategy for effective brain drug delivery. Journal of Pharmaceutical Sciences. 2010; 40(5): 385-403.

144. Saurabh Arora, Sunny Chopra, Kanchan Kohli, Praveen Baliyan,

145. Roop K. Khar Development And Validation Of A New LC-Ms/MS Bio-Analytical Method For The Determination Of Curcumin In Human Plasma Samples. Analytical Chemistry. 2010; 9(1)

146. Saima Amin, Showkat R. Mir, Kanchan Kohli, Babar Ali, Mohd Ali. A study of the chemical composition of black cumin oil and its effect on penetration enhancement from transdermal formulations. Natural Product Research: Formerly Natural ProductLetters. 2010; 24(12):1151 – 1157.

147. Sarwar Beg, Shamama Javed, Kanchan Kohli. Bioavailability enhancement of coenzyme Q10: an extensive review of patents. Recent Patents on Drug Delivery and Formulation. 2010; 4 (3): 245-55

148. Rakesh Pahwa, Neeta, Vipin Kumar, Kanchan Kohli. Clinical Manifestations, Causes and Management Strategies of Peptic Ulcer Disease. International Journal of Pharmaceutical Sciences and Drug Research. 2010; 2(2): 99-106

149. Rakesh Pahwa, Vijay Soni, Prabodh Chander Sharma, Vipin Kumar and Kanchan Kohli. Arformoterol Tartrate: A Review of Pharmacology, Analysis and Clinical Studies. Tropical Journal of Pharmaceutical Research. 2010; 9(6): 595-603.

150. Mohammad Intakhab Alam, Sanjula Baboota, Kanchan Kohli, Javed Ali, Alka Ahuja. Pharmacodynamic therapeutic gel containing celecoxib Science Asia. 2010; 36:305-311

151. Kanchan Kohli, S Rajabnezhad, Saima Amin. Transdermal nano-emulsion drug delivery system of indomethacin. Medicinal chemistry research. 2010; 112- 113

152. Rakesh. Pahwa, Arunima Nath, Prabodh Chander Sharma, Vipin Kumar, Kanchan Kohli. Impact of Helicobacter pylori on the prevalence of gastroduodenal diseases. Drug Invention Today. 2010; 2(5):258-263

153. Rakesh Pahwa, Vijay Soni, Prabodh Chander Sharma, Vipin Kumar and Kanchan Kohli. Arformoterol Tartrate: A Review of Pharmacology, Analysis and Clinical Studies. Tropical Journal of Pharmaceutical Research. 2010; 9(6): 595- 603.

154. Permender Rathee, Hema Chaudhary, Sushila Rathee, Dharmendra Rathee, Vikash Kumar, Kanchan Kohli. Mechanism of action of flavonoids of anti- inflammatory agents: A Review. Inflammation and allergy–Drug targets, 2009, 8, 229- 235.

155. Kanchan Kohli, Permender Rathee, Hema Chaudhary, Sushila Rathee, Vikash Kumar. Radiopharmaceutical: Revolutionary agents for diagnosis. Current Radiopharmaceuticals. 2009

156. Vikash Kumar, Permender Rathee, Kanchan Kohli, Hema Chaudhary, Sushila Rathee. Phytochemical and biological potential of Indrayan: An overview. PharmacognosyReviews. 2009; 3(5): 1-14.

157. Abdul Ahad, Mohammed Aqil, Kanchan Kohli, Hema Chaudhary. Chemical penetration enhancers: a patent review. Expert Opinion Therapeutic Patents, 2009; 19(7): 969 -988.

158. Neelam Singla, G. D. Gupta, Kanchan Kohli, A. K. Singla. A discriminatory and biorelevant dissolution test method for simvastatin drug products. Dissolution Technologies. 2009; 11:13

159. Neelam Singla, G. D. Gupta, Kanchan Kohli, S. Jain. Oral bioavailability of simvastatin novel formulation in albino rats. Journal of Pharmaceutical Science and Technology. 2009; 1(2): 84-87

160. Swati Madan, Gyanendra Nath Singh, Kanchan Kohli, Mohammed Ali, YatendraKumar, Raman Mohan Singh, Om Prakash. Isoflavonoids from Flemingia Strobilifera (L) roots. Acta Polomiae Pharmaceutica. Drug Research. 66(3): 297- 303.

161. Saima Amin, Saeid Rajabnezhad, Kanchan Kohli. Hydrogels as potential drug delivery systems. Scientific Research and Essay. 2009; 3(11): 1175-1183.

162. Saima Amin, Javed Ahmad, Kanchan Kohli. Self-emulsifying nano drug carrier for an Antihyertension Drug" Indian Journal of Pharmaceutical Sciences. 2009; 71(2): 181

163. Abdul Ahad, Mohammed Aqil, Kanchan Kohli, Yasmin Sultana, Mohd. Mujeeb. Skin permeation mechanism of valsartan from transdermally applied gel formulation using 1.8-cineole as permeation enhancer. Journal of pharmacy and pharmacology. 2009; 61: 38

164. Kanchan Kohli, Roop K Khar, Faisal M, Naz Z, Faiyaz Shakeel, Sayeed Ahmed. A new TLC densitometric method for stability assessment of modafinil. Chemia Analityczna 2009; 54 (1):77-88.

165. Hema Chaudhary, Kanchan Kohli, AK Nasa, Vikash Kumar, Permender Rathee. Formulation and evaluation of sodium carboxy methyl guar gels of nimesulide. Indian journal of Pharmaceutical Sciences. 2009; 72(2):181-181

166. Nitin Sharma, Anjana Sharma, Kanchan Kohli, Sourabh Arora. Development andevaluation of release equivalent sustained release formulation

of dextromethorphan HBR using simple technology. International journal of Pharmacy and Pharmaceutical Sciences.2009; 121-127

167. Mohammad Intakhab Alam, Sanjula Baboota, Kanchan Kohli, Javed Ali, Alka Ahuja. Development and Evaluation of Transdermal Patches of Celecoxib. PDA Journal of Pharmaceutical Science and Technology. 2009; 63:429-437

168. Shamama Javed, Kanchan Kohli. Cancer gets the golden treatment. Nano Digest,2009; 1(7): 38-40.

169. Kanchan Kohli, Hema Chaudhary, Permender Rathee, Sushila Rathee, Vikash Kumar. Fullerenes: New Contour to Carbon Chemistry. Pharma Times. 2009; 41(2):9-12.

170. Nitin Dixit, Kanchan Kohli, Sanjula Baboota. Nanoemulsion system forthe transdermal delivery of a poorly soluble cardiovascular drug. PDA Journal of Pharmaceutical Science and Technology. 2008; 62(1): 46-55

171. Mohammad Javed Ansari, Kanchan Kohli, Nitin Dixit. Microemulsion as potentialdrug delivery system: A review. PDA Journal of Pharmaceutical Science and Technology.2008; 62(1): 66-79

172. N. Mallik, Gaurav K. Jain, Kanchan Kohli. Drug development from new molecules and genes from plants. Phytopharmacology and Therapeutic Values 1, Recent Progress inMedicinal Plants. 2008; 19: 107-126.

173. Ziyaur Rehman, Kanchan Kohli, Roop K. Khar, Mohd Ali. In vivo evaluation of colon specific microspheres formulation containing 5-flurouracil in rats. Journal of Pharmacy and Pharmacology. 2008; 60(5): 615-623.

174. Swati Madan, Gyanendra Nath Singh, Yatendra Kumar, Kanchan Kohli, Raman Mohan Singh, Shaukat Rasool Mir and Sayeed Ahmad. A new flavone from Flemingia Strobilifera (Linn) and its Antimicrobial Activity. Tropical Journalof Pharmaceutical Research. 2008; 7(1): 921-927

175. Naseem Ahmad Charoo, Areeg Anwer Ali Shamsher, Kanchan Kohli, Krishna Pillai, Ziyaur Rahman. Improvement in bioavailability of transdermally applied flurbiprofen using tulsi (Ocimum sanctum) and turpentine oil. Colloids andSurfaces B: Biointerfaces, 2008; 65(2): 300-307

176. Saima Amin, Kanchan Kohli, Roop K. Khar, Showkat R. Mir, Krishna K. Pillai. Mechanism of in vitro percutaneous absorption enhancement of carvedilol by penetration enhancers. Pharmaceutical Development and Technology. 2008;13(6): 533–539

177. Shahid Jameel, Kanchan Kohli, Roop K. Khar, Sushma Talegaonkar. Development and validation of stability-indicating HPLC method for simultaneous estimation of aceclofenac and paracetamol in conventional tablets and microspheres formulations. Journal of Chromatography. 2008; 68(7-8): 557-565.

178. Sanjay K. Motwani, Shruti Chopra, Sushma Talegaonkar, Kanchan Kohli, Farhan J. Ahmad and Roop K. Khar. Chitosan–sodium alginate nanoparticles as submicroscopic reservoirs for ocular delivery: Formulation, optimisation and in vitro characterization. European Journal of Pharmaceutics and Biopharmaceutics. 2008; 68(3): 513-525

179. Nitin Dixit, Kanchan Kohli, Sanjula Baboota. Nano-emulsion system for the transdermal delivery of a poorly soluble cardio-vesicular drug PDA. Journal of pharmaceutical science and technology. 2008; 62(1):46-55

180. Yasmin Sultana, Kanchan Kohli, Roop K. Khar, Mohammed Aqil. Effect of pre- treatment of almond oil on UVB induced cutaneous photoaging in Mice. Journal of Cosmetic Dermatology. 2007; 6:14-19.

181. Shahid Jameel, Kanchan Kohli, Roop K. Khar, Sushma Talegaonkar. Sustained release sodium alginate microspheres formulation of acceclofenac and paracetamol as potential combination therapy in arthritis. Journal of Pharmacy and Pharmacology. 2007; 59(1): 43-44

182. Sanjula Baboota, Al-Azaki, Kanchan Kohli, Javed Ali, Nitin Dixit, Faiyaz Shakeel. Development and evaluation of a microemulsion formulation for transdermal delivery of terbinafine. PDA Journal of pharmaceutical Sciences and technology. 2007; 61(4): 276-285

183. Sanjay K. Motwani, Roop K. Khar, Farhan J. Ahmad, Shruti Chopra, Kanchan Kohli, Sushma Talegaonkar. Application of a validated stability indicating densitometric thin layer chromatographic method to stress degradation studies on moxifloxacin. Analytica Chemica Acta. 2007: 582(1): 75-82

184. Swati Madan, Sayeed Ahmad G.N. Singh, Kanchan Kohli, Yatendra Kumar, Raman Singh, Madhukar Garg. Stevia rebaudiana Bertoni- A review. Indian journal of Pharmaceutical Science and Technology. 2007; 61(4): 276-286

185. Ziyaur Rehman, Kanchan Kohli, Roop K. Khar. Characterization of 5-fluorouracilfor Colonic Delivery. AAPS Pharma Science Technology. 2006; 7(2): 1-9

186. Sanjula Baboota, Faiyaz Shakeel, Kanchan Kohli. Formulation and Evaluation ofonce a day transdermal gel of diclofenac diethylamine. Methods and Findings in Experimental and Clinical Pharmacology. 2006; 28(3): 1-6

187. Sanjay K. Motwani, Roop K. Khar, Farhan J. Ahmad, Shruti Chopra, Kanchan Kohli, Sushma Talegaonkar, Zeenat Iqbal. Stability- indicating high performance thin layer chromatography: determination of gatifloxcin as bulk drug and from nanoparticle. Analytica Chimia Acta. 2006; 576: 253-260.

188. 142. Yasmin Sultana, Kanchan Kohli, Roop K. Khar, Mohammed Aqil. Preparation and dissolution characteristics of sustained release dilitiazem Hydrochloride tablets. The East and Central African Journal of Pharmaceutical Sciences. 2006; 9(2): 40-46.

189. Kanchan Kohli, Ziyaur Rahman, H.S. Lamba. Potential Pharmaceutical Interaction. Hamdard Medicus. 2005;11(2): 25-28

190. Sanjula Baboota, Kanchan Kohli, Javed Ali, Alka Ahuja. Cyclodextrin and their application in Biotechnology. The Indian Pharmacist. 2005; 3(25): 3-16

191. Naseem Charoo, Kanchan Kohli, Krishna K. Pillai. Transdermal delivery of flurbiprofen permeation enhancement, design, pharmacokinetic and pharmacodynamic studies in albino rats. Journal of Pharmaceutical Development and Technology. 2005; 10(3): 343-351

192. Kanchan Kohli, Javed Ali, Mohammad Javed Ansari. Curcumin: A natural anti- inflammatory agent. Indian Journal of Pharmacology. 2005; 37(3): 41–147

193. Sanjula Baboota, S Aggarwal, Kanchan Kohli. Coloimetric determination offluoroquinone dosage forms via harge transfer complexation. Indian Pharmacist. 2005; 4(26): 73-75

194. Sayeed Ahmad, Kanchan Kohli, Javed Ali, Roop K. Khar. Stability indicating HPTLC determination of curcumin in bulk drug and pharmaceutical formulations. Journal of Pharmaceutical and Biomedical Analysis. 2005; 39(1-2):132-138.

195. Naseem Charoo, Kanchan Kohli, Krishna K. Pillai. Simple and sensitive high performance liquid chromatography method for the determination of transdermally appliedflurbiprofen in rat plasma and excised skin samples. Journal of Chromatography. 2005; 493-497

196. Alka Puri, Kanchan Kohli, Mohd. Ali, Sanjula Baboota. Characterization of novel buccoadhesive films of clindamycin for pyorrhea. Indian Journal of Pharmaceutical Sciences. 66(4): 560-561.

197. Sanjula Baboota, Mona Dhaliwal, Kanchan Kohli, Javed Ali. Molecular inclusion of rofecoxib with cyclodextrin: A review of its pharmacological properties in laboratory animals. Diepharmazie. 2004; 59(30)

198. Kanchan Kohli, Ziyaur Rahman, H.S. Lamba. Terminalia arjuna: chemsitry and pharmacological profile. Indian Drugs. 2004; 41(11)

199. Anupama Diwan, Vipin Dhall, Kanchan Kohli. Bilayer tablet for oral administered controlled delivery of ciprofloxacin" abstract published in the proceeding of 31st Annual meeting & Exposition of the Controlled Release Societyheld at Hawai, U.S.A. 412, 2004

200. Sanjula Baboota, Mona Dhaliwal, Kanchan Kohli. Improved delivery of rofecoxib by its complexation with cyclodextrin. Indian Journal of Science. 2004; 66(4): 482-483.

201. Naseem A. Charoo, Asgar Ali, Kanchan Kohli, Areeg Anwer Ali Shamsher. Preparation of in-situ forming ophthalmic gels of ciprofloxacin-HCl for the treatment of bacterial keratitis and conjunctivitis. Journal of Pharmaceutical Sciences. 2003; 92(2):407-413

202. Naseem A. Charoo, Kanchan Kohli, Asgar Ali. Comparative evaluation ofin-situ forming ophthalmic gels, ocular inserts and eye-drops of ciprofloxacin hydrochloride for the treatment of bacterial conjunctivitis. Drug Development

and Industrial Pharmacy. 2003; 129(2): 215–221

203. Sanjula Baboota, Rajesh Khanna, Kanchan Kohli. Poisoning and its Management.Hamdard Medicus. 2003; 46(2):121-126

204. Kanchan Kohli, N. Ahmed, Sanjoola Baboota. Herbs in Cosmetics. Hamdard Medicus. 2003; 4:76–79.

205. Shweta Arora, Kanchan Kohli, Asgar Ali. Microbiological evaluation of mucoadhesive buccal tablets of secnidazole against anaerobic strains for the treatment of periodontal diseases" abstract published in proceeding of the 30th Annual meeting & Exposition of the Controlled Release Society held at Glasgow, Scotland, United Kingdom.2003

206. Saima Amin, Asgar Ali, Kanchan Kohli. Permeation enhancers for transdermal drug delivery of metoclopramide HCl- Abstract published in the proceeding, 30th Annual meeting & Exposition of the Controlled Release Society held at Glasgow, Scotland, UnitedKingdom. 2003; 846

207. Kanchan Kohli, Alka Puri, Alka Arora, Sanjula Baboota. Design and characterization of novel buccoadhesive film of doxycycline for the treatment of pyorrhea- Abstract published in the proceeding of 30th Annual meeting & Exposition of the Controlled Release Society held at Glasgow, Scotland, United Kingdom. 2003; 445

208. Anupama Diwan, Kanchan Kohli. A comparative study of efficacy of controlled release iron tablets and normal release tablets- Abstract published in the proceeding of 30th Annual meeting & Exposition of the Controlled Release Society held at Glasgow, Scotland, United Kingdom. 2003; 539

209. Kanchan Kohli and Mohd Ali. "Phytochemical studies of Iranian Anchusa strigosa Linn". In Series Recent Progress in Medicinal Plants, Phytochemistry & Pharmacology, Scitech Pub., U.S.A, 2002; 2: 247-252.

210. Kanchan Kohli, Roop K. Khar, Alka Arora. Development and evaluation of buccoadhesive films of lignocaine Hydrochloride" published in the proceedings of Fourth International Symposium on Advances in Technology & Business Potential of New DrugDelivery system organized by CRS, Indian chapter at ScitechCentre Mumbai from Feb 22–23, 2002

211. Saima Amin, Asgar Ali, Kanchan Kohli. Development and evaluation of transdermal therapeutic system of metoclopramide HCl- proceedings published in the proceedings of Fourth International Symposium on Advances in Technology & Business Potential of New Drug Delivery system organized by CRS, Indianchapter at Scitech Centre, Mumbai from Feb 22 –23, 2002

212. Kanchan Kohli, Roop K. Khar and Alka Arora. Optimization of anti-acne formulation using Tea Tree oil- proceedings published in the proceedings of Fourth International Symposium on Advances in Technology & Business Potential of New Drug Delivery system organized by CRS, Indian chapter at Scitech Centre Mumbai from Feb 22–23, 2002

213. Naseem Charoo, Kanchan Kohli. Non-Steroidal anti-inflammatory drugs as candidates for transdermal therapeutic system. Journal of Science and Pharmacy. 2002; 3:39-40

214. Saima Amin, Asgar Ali, Kanchan Kohli. In vitro and In vivo evaluation of transdermal therapeutic system of Metoclopramide HCl- proceedings published in the 29th International Symposium on Bioactive materials, July 22nd–July 24th2002 at Seoul, Korea

215. S. Arora, Kanchan Kohli, Asgar Ali. Development & evaluation of mucoadhesive Buccal Tablets of secnidazole- published in the proceedings of 29th International Symposium on Bioactive materials, July 22nd –July 25th 2002 at Seoul, Korea

216. Kanchan Kohli, Roop K. Khar, A. Arora. Development & evaluation of mucoadhesive Buccal Tablets of lignocaine HCl- published in the proceedings of 29th International Symposium on Bioactive materials, July 22nd –July 25th 2002 at Seoul, Korea. 434

217. Naseem Charoo, Asgar Ali, Kanchan Kohli. Preparation and evaluation of In-situ forming ophthalmic gels of ciprofloxacin HCl for the treatment of bacterial keratitis and conjunctivitis- proceedings published in the 29th International Symposium on Bioactive materials, July 22nd –July 24th 2002 at Seoul, Korea.

218. Kanchan Kohli, Sanjula Baboota, R. S. Gaud. Continuing Education Programme in Pharmacy Institution. Indian Journal of Pharmacy Education. 2002; 36:152-155.

219. Sanjula Baboota, Kanchan Kohli, Roop K.Khar. Industry–Academic Interaction" abstract published in Indian Journal of Pharmacy education. 2002;

36: 25

220. Alka Arora, Kanchan Kohli, Roop K. Khar. Curriculum Design- abstract published in Indian Journal of Pharmacy education. 2002; 36: 36 –37.

221. Kanchan Kohli. Development and Evaluation of buccoadhesive tablets of amoxicillin for the treatment of pyorrhea" abstract published in European Journal of Pharmaceutical Sciences. 2002; 17: 112

222. Naseem A. Charoo, Kanchan Kohli, Krishna K. Pillai. Transdermal delivery of flurbiprofen: effect of isotonic sodium phosphate buffer of pH 7.4, propylene glycol, isopropyl alcohol and their binary combination of permeation through rat skin- abstract published in European Journal of Pharmaceutical Sciences. 2002; 17: 95.

223. Shweta Arora, Kanchan Kohli, Asgar Ali. Development and evaluation of buccoadhesive films of secnidazole- abstract published in European Journal of Pharmaceutical Sciences. 2002; 17:110.

224. Saima Amin, Asgar Ali, Kanchan Kohli. A new drug delivery system for metoclopramide HCl" abstract published in European Journal of Pharmaceutical Sciences.2002; 17: 88-89.

225. Alka Arora, Kanchan Kohli, Roop K. Khar. The rinsing and socking solution for hydrophilic contact lens, disinfect the lens at ocular pH- abstract published in European Journal of Pharmaceutical Sciences. 2002; 17:89-90.

226. Alka Arora, Roop K. Khar, Kanchan Kohli. Formulation and in-vitro evaluation of sustained release of theophyline tablets, paper published in the proceedings of 28th International Symposium on Controlled Release of Bioactive Materials, held at San Diego,California, U.S.A, 6085, June 23-27, 2001

227. Alka Arora, Roop K. Khar, Kanchan Kohli. Antimicrobial effectiveness of multipurpose solution at varying pH for hydrophilic contact lenses- paper published in the proceedings of 28th International Symposium on Controlled Release ofBioactive Materials, held at San Diego, California, U.S.A 6086, June 23-27, 2001

228. Kanchan Kohli, Yasmin Sultana, Alka Arora, Roop K. Khar. Development and in- vitro evaluation of sustained release of diltiazem hydrochloride tablets- paper published inthe proceedings of 28th International Symposium on Controlled Release of Bioactive Materials, held at San Diego, California, U.S.A, 6117, June 23-27, 2001

229. Kanchan Kohli, Asgar Ali and N. Ahmad. "Fabrication of ocular insert of ciprofloxacin HCl for the treatment of bacterial keratitis and conjunctivitis",

paper published in the proceedings of 28th International Symposium on Controlled Release of Bioactive Materials, held at San Diego, California, U.S.A, 7133, June 23-27, 2001

230. Kanchan Kohli, Roop K. Khar, Mohd. Shahar Yar Khan and Alka Arora. Transmucosal Drug Delivery System for lignocaine Hydrochloride- Abstract published in proceedings of 18th Asian Congress of Pharmaceutical Sciences and 6th Pharmacy Australia Congress. 2000; 52.

231. Kanchan Kohli, Pankaj Aggarwal and Sunil Kumar Jain. Need to Design an Educational Training Programme for Community Health Maintenance- Abstract published in proceedings of 18th Asian Congress of Pharmaceutical Sciences and 6th Pharmacy Australia Congress. 2000; 93

232. Alka Arora, Kanchan Kohli and Roop K. Khar. Delivery of tea tree oil through thecolloidal bed of sterile clay as anti-acne and its comparison with cream and toner- Abstract published in proceedings of 18th Asian Congress of Pharmaceutical Sciences and 6th Pharmacy Australia Congress. 2000; 52

233. S. P. Agarwal, Anita Prakash and Kanchan Kohli. Pharmacological Studies of "Kushta Just" Suspension Formulation, Indian Journal of Pharmaceutical Sciences. 1998;60(4): 225-227.

234. Sachin Kumar, S.N. Sharma, and Kanchan Kohli. Controlled Release of doxycycline hyclate, Eastern Pharmacist. 1992; 185-187

235. Sachin Kumar, S. N. Sharma and Kanchan Kohli. Controlled Release of erythromycin estolate, Eastern Pharmacist. 1992; 125-127.

236. Kanchan Kohli, Jamal S. Qadry, and Mohd. Ali Protein. Amino acids and Ascorbic Acid in some cultivers of Mangnifera Indica. Journal of the Science of Food and Agriculture 1987; 39: 247-252

II. BOOKS/ CHAPTERS PUBLISHED:

1. Kanchan Kohli. Pharmaceutics I Practical Note Book. Piyush Publications; 1995.
2. Kanchan Kohli, Sanjula Mangla Baboota. Pharmaceutics Practical Note Book. Piyush Publications. 2000; 81-86548-34-3
3. Dr. (Mrs.) Kanchan Kohli & Dr. Sanjula Baboota. Text Book of Pharmaceutical Formulation Piyush Book Publications Pvt. Ltd. 2006; 81-86548-69-6
4. **Kanchan Kohli,** Saima Amin. Convention on Herbal Biodiversity: Quantitative Aspect of Research. Herbal Drugs A Twenty First Century Perspective R. K. Sharma and R. Arora. New Delhi, Jaypee. 2006; 650-660.

5. **Kanchan Kohli**, Gaurav K. Jain. Herbal Drugs: regulations across the globe. Herbal Drugs A Twenty First Century Perspective R. K. Sharma and R. Arora. New Delhi, Jaypee. 2006; 624-635.
6. **Kanchan Kohli,** Gaurav K. Jain. Pharmacopoeial Standards of Indian System of Medicine. Herbal Drugs A Twenty First Century Perspective R. K. Sharma and R.Arora. New Delhi, Jaypee. 2006; 650-660.
7. Saima Amin, **Kanchan Kohli**. Biotechnology and Intellectual Property. ScientificResearch and Essays. 2006; 1: 20-25.
8. Prof. Anupama Diwan & Dr.(Mrs.) Kanchan Kohli. General Pharmacy. Pragati Prakashan. 2008; 978-81-8398-524-6

III. PROJECTS COMPLETED

1. Development and Evaluation of Transdermal Therapeutic system of a non steroidal anti-inflammatory drug sponsored by U.G.C of Rs. 5.89 lacs, Duration: 2007-2010.
2. Development of a Novel Delivery System for enhancing the Oral Bioavailability of Curcumin sponsored by Dept. of Science and Technology (D.S.T) of Rs.1.130Crores, Duration: 2008-2010.
3. Formulation and Evaluation of Bioadhesive Gel Preparation for Novel Anti Hypertensive Drugs sponsored by A.I.C.T.E of Rs. 16 lacs, Duration: 2008-2010.
4. Development of nanoparticulate based Drug Delivery System to enhance oral bioavailability and stability of Lycopene: Amount: 18 lacs funded by AICTE, Duration: 2011-2014
5. Design of an optimum solid nano-lipid vesicular system for oral bioavailability ofpoorly soluble lipophilic antihypertensive agent: Amount: 12, 38, 800 funded by UGC, Duration: 2012-2015.

IV. INDIAN PATENTS (APPLIED FOR)

1. Saima Amin, **Kanchan Kohli**, Showkat R. Mir, R. K.Khar & K. K. Pillai "Percutaneous Penetration Enhancing and Skin Irritation Reducing System".**Indian Patent appl.** No. 2658 / DEL / 2007.
2. Anupama Diwan, **Kanchan Kohli,** Javed Ali, Sanjula Baboota. "Gastrotententive Controlled Delivery Tablets For Once Daily Administration of Ciprofloxacin Hydrochloride". **Indian Patent appl No.** 332/ DEL/ 2008.
3. Neelam Singla, **Kanchan Kohli**, G D Gupta. "Self Emulsifying Dosage Form ofSimvastatin". **Indian Patent appl No** 741/ DEL/ 2008**.**

4. **Kanchan Kohli** and Hema Chaudhary. Formulation and optimization of gels of NSAID along with curcuminoids for transdermal drug delivery. Indian patent (AppNo. 918/DEL/2010)
5. M. Aquil, A. Ahad, **Kanchan Kohli,** Y. Sultana, Mohd Mujeeb, A. Ali. Sabinene hydrate as a novel permeation enhancer.Indian Patent,24/8/2010.
6. M. Aquil, A. Ahad, **Kanchan Kohli,** Y. Sultana, Mohd Mujeeb, A. Ali. Alpha-Terpinene as a novel permeation enhancer., Indian Patent. 24/8/2010.
7. Sunny Chopra, **Kanchan Kohli**, Self emulsifying drug delivery system for a curcuminoid based composition, 2010.
8. **Kanchan Kohli**, Sarwer beg, Sachin Gahloi, Saima Amin. Time-dependent releasesystem for amoxicillin trihydrate-composition and method of preparation thereof. IP 1286/DEL/2010. CBR No. 4671 (Indian patent Application)
9. **Kanchan Kohli**, Nitin Parmar, Saima Amin. Self emulsifying drug delivery systemfor a Lercanidipine based composition, 2011.
10. **Kanchan Kohli**,Shamama Javed, Nitin Parmar. Microwave assisted extraction of lysergol from Ipomoea genus.1559/DEL/2011.
11. **Kanchan kohli**, Abhinav Garg. "Self nano emulsifying drug delivery system for aginger active principle based composition" 2496/DEL/2013. (ICMR patent granted)
12. **Kanchan Kohli**, Shamama Javed, A composition for treatment of liver disease, application no. 2651/DEL/2014 (ICMR patent accepted)

1V US PATENT: (GRANTED)

"Self-emulsifying drug delivery system (SNEDDS) for a curcuminoids based composition". Patent no. US 8835509 B2.has been granted in September 16, 2014 and the product has been marketed in 2016.

Sd/-

Dr. Kanchan Kohli

Exhibit 02

ORGANIC COMPOUNDS

Background of the Invention

Field of the Invention

The present invention is directed to dual-acting compounds and combinations of angiotensin receptor blockers and neutral endopeptidase inhibitors, in particular a dual acting molecule wherein the angiotensin receptor blocker and neutral endopeptidase inhibitor are linked via non-covalent bonding, or supramolecular complexes of angiotensin receptor blockers and neutral endopeptidase inhibitors, also described as linked pro-drugs, such as mixed salts or co-crystals, as well as to pharmaceutical combinations containing such a dual-acting compound or combination, methods of preparing such dual-acting compounds and methods of treating a subject with such a dual-acting compound or combination. Specifically, the invention is directed to a dual acting compound or supramolecular complex of two active agents having the same or different modes of action in one molecule.

Related Background Art

Angiotensin II Is a hormone that causes blood vessels to constrict. This, in turn, can result in high blood pressure and strain on the heart. It is known that angiotensin II interacts with specific receptors on the surface of target cells. Two receptor subtypes for angiotensin II, namely AT1 and AT2, have been identified thus far. In recent times, great efforts have been made to identify substances that bind to the AT1 receptor. Angiotensin receptor blockers (ARBs, angiotensin II antagonists) are now known to prevent angiotensin II from binding to its receptors in the walls of blood vessels, thereby resulting in lower blood pressure. Because of the inhibition of the AT1 receptor, such antagonists can be used, therefore, as anti-hypertensives or for the treatment of congestive heart failure, among other indications.

Neutral endopeptidase (EC 3.4.24.11; enkephalinase; atriopeptidase; NEP) is a zinc-containing metalloprotease that cleaves a variety of peptide substrates on the amino side of - hydrophobic residues [see *Pharmacol Rev,* Vol. 45, p. 87 (1993)]. Substrates for this enzyme include, but are not limited to, atrial natriuretic peptide (ANP, also known as ANF), brain natriuretic peptide (BNP), met- and leu-enkephalin, bradykinin, neurokinin A, endothelin-1 and substance P. ANP is a potent vasorelaxant and natriuretic agent [see

J Hypertens, Vol. 19, p. 1923 (2001)]. Infusion of ANP in normal subjects resulted in a reproducible, marked enhancement of natriuresis and diuresis, including increases in fractional excretion of sodium, urinary flow rate and glomerular filtration rate [see *J Clin Pharmacol,* Vol. 27, p. 927 (1987)]. However, ANP has a short half-life in circulation, and NEP in kidney cortex membranes has been shown to be the major enzyme responsible for degrading this peptide [see *Peptides,* Vol. 9, p. 173 (1988)]. Thus, inhibitors of NEP (neutral endopeptidase inhibitors, NEPi) should increase plasma levels of ANP and, hence, are expected to induce natriuretic and diuretic effects.

While substances, such as angiotensin receptor blockers and neutral endopeptidase inhibitors may be useful in the control of hypertension, essential hypertension is a polygenic disease and is not always controlled adequately by monotherapy. Approximately 333 million adults in economically developed countries and about 65 million Americans (1 in 3 adults) had high blood pressure in 2000 [see *Lancet,* Vol. 365, p. 217 (2005); and *Hypertension,* Vol. 44, p. 398 (2004)]. Prolonged and uncontrolled hypertensive vascular disease ultimately leads to a variety of pathological changes in target organs, such as the heart and kidney. Sustained hypertension can lead as well to an increased occurrence of stroke. Therefore, there is a strong need to evaluate the efficacy of anti-hypertensive therapy, an examination of additional cardiovascular endpoints, beyond those of blood pressure lowering, to get further insight into the benefits of combined treatment.

The nature of hypertensive vascular diseases is multifactorial. Under certain circumstances, drugs with different mechanisms of action have been combined. However, just considering any combination of drugs having different modes of action does not necessarily lead to combinations with advantageous effects. Accordingly, there is a need for efficacious combination therapy which does not have deleterious side effects.

Summary of the Invention

In a first aspect, the present invention is directed to a dual-acting compound, such as a supramolecular complex, comprising:

(a) an angiotensin receptor antagonist;

(b) a neutral endopeptidase inhibitor (NEPi); and optionally

(c) a pharmaceutically acceptable cation.

The present invention is also directed to a dual-acting compound, such as a supramolecular complex, obtainable by:

(i) dissolving an angiotensin receptor antagonist and a neutral endopeptidase inhibitor (NEPi) in a suitable solvent;

(ii) dissolving a basic compound of Cat in a suitable solvent, wherein Cat is a cation;

(iii) combining the solutions obtained in steps (i) and (ii);

(iv) precipitation of the solid, and drying same to obtain the dual-acting compound; or alternatively

obtaining the dual-acting compound by exchanging the solvent(s) employed in steps (i) and (ii) by

(iva) evaporating the resulting solution to dryness;

(va) re-dissolving the solid in a suitable solvent;

(via) precipitation of the solid and drying same to obtain the dual-acting compound.

The present invention is also directed to linked pro-drugs comprising:

(a) an angiotensin receptor antagonist or a pharmaceutically acceptable salt thereof; and

(b) a NEPi or a pharmaceutically acceptable salt thereof, wherein the angiotensin receptor antagonist or a pharmaceutically acceptable salt thereof and the NEPi or a pharmaceutically acceptable salt thereof are linked by a linking moiety.

The present invention is also directed to a combination comprising:

(a) a pharmaceutically acceptable salt of an angiotensin receptor antagonist; and

(b) a pharmaceutically acceptable salt of a neutral endopeptidase inhibitor (NEPi);

wherein the pharmaceutically acceptable salt of the angiotensin receptor antagonist and the NEPi is the same and is selected from a salt of Na, K or NH_4.

In preferred embodiments, the angiotensin receptor antagonist and NEPi have acidic groups which facilitate formation of the dual acting compound, such as the supramolecular complex of the present invention.

Preferably, the angiotensin receptor antagonist is selected from the group consisting of valsartan, losartan, irbesartan, telmisartan, eprosartan, candesartan, olmesartan, saprisartan, tasosartan, elisartan and combinations thereof.

In preferred embodiments, the NEPi is selected from the group consisting of: SQ 28,603; N-[N-[1(*S*)-carboxyl-3-phenylpropyl]-(*S*)-phenylalanyl]-(*S*)-isoserine; *N*-[*N*-[(*S*)-carboxy-2-phenyl)ethyl]-(*S*)-phenylalanyl]-β-alanine; -[2(*S*)-mercaptomethyl-3-(2-methylphenyl)-propionyl]methionine; (*cis*-4-[[[1-[2-carboxy-3-(2-methoxyethoxy)propyl]-cyclopentyl]carbonyl]amino]-cyclohexanecarboxylic acid); thiorphan; retro-thiorphan; phosphoramidon; SQ 29072; -(3-carboxy-1-oxopropyl)-(4*S*)-*p*-phenylphenylmethyl)-4-amino-2*R*-methylbutanoic acid ethyl ester; (*S*)-*cis*-4-[1-[2-(5-indanyloxycarbonyl)-3-(2-methoxyethoxy)propyl]-1-cyclopentanecarboxamido]-1-cyclohexanecarboxylic acid; 3-(1-[6-endo-hydroxymethylbicyclo[2,2,1]heptane-2-exo-carbamoyl]cyclopentyl)-2-(2-methoxyethyl)propanoic acid; *N*-(1-(3-(*N*-*t*-butoxycarbonyl-(*S*)-prolylamino)-2(*S*)-*t*-butoxy-carbonylpropyl)cyclopentanecarbonyl)-*O*-benzyl-(*S*)-serine methyl ester; 4-[[2-(mercaptomethyl)-1-*oxo*-3-phenylpropyl]amino]benzoic acid; 3-[1-(*cis*-4-carboxycarbonyl-*cis*-3-butylcyclohexyl-r-1-carbamoyl)cyclopentyl]-2*S*-(2-methoxyethoxymethyl)propanoic acid; ((2*S*)-2-(4-biphenylmethyl)-4-carboxy-5-phenoxyvaleryl)glycine; -(1-(*N*-hydroxycarbamoylmethyl)-1-cyclopentanecarbonyl)-phenylalanine; (*S*)-(2-biphenyl-4-yl)-1-(1*H*-tetrazol-5-yl)ethylamino) methylphosphonic acid; (*S*)-5-(*N*-(2-(phosphonomethylamino)-3-(4-biphenyl)propionyl)-2-aminoethyl)tetrazole; β-alanine; 3-[1,1'-biphenyl]-4-yl-*N*-[diphenoxyphosphinyl)methyl]-*L*-alanyl; N-(2-carboxy-4-thienyl)-3-mercapto-2-benzylpropanamide; 2-(2-mercaptomethyl-3-phenylpropionamido)thiazol-4-ylcarboxylic acid; (*L*)-(1-((2,2-dimethyl-1,3-dioxolan-4-yl)-methoxy)carbonyl)-2-phenylethyl)-*L*-phenylalanyl)-β-alanine; *N*-[*N*-[(*L*)-[1-[(2,2-dimethyl-1,3-dioxolan-4-yl)-methoxy]carbonyl]-2-phenylethyl]-*L*-phenylalanyl]-(*R*)-alanine; -[*N*-[(*L*)-1-carboxy-2-phenylethyl]-*L*-phenylalanyl]-(*R*)-alanine; *N*-[2-acetylthiomethyl-3-(2-methyl-phenyl)propionyl]-methionine ethyl ester; *N*-[2-mercaptomethyl-3-(2-methylphenyl)propionyl]-methionine; [2(*S*)-mercaptomethyl-3-(2-methylphenyl)propanoyl]-(*S*)-isoserine; -(*S*)-[3-mercapto-2-(2-methylphenyl)propionyl]-(*S*)-2-methoxy-(R)-alanine; -[1-[[1(*S*)-benzyloxycarbonyl-3-phenylpropyl]amino]cyclopentylcarbonyl]-(*S*)-isoserine; N-[1-[[1(*S*)-carbonyl-3-phenylpropyl]amino]-cyclopentylcarbonyl]-(*S*)-isoserine; 1,1'-[dithiobis-[2(*S*)-(2-methylbenzyl)-1-*oxo*-3,1-propanediyl]]-*bis*-(*S*)-isoserine; 1,1'-[dithiobis-[2(*S*)-(2-methylbenzyl)-1-*oxo*-3,1-propanediyl]]-*bis*-(*S*)-methionine; *N*-(3-phenyl-2-(mercaptomethyl)-propionyl)-(*S*)-4-(methylmercapto)methionine; *N*-[2-acetylthiomethyl-3-phenyl-propionyl]-3-aminobenzoic acid; -[2-mercaptomethyl-3-phenyl-propionyl]-3-aminobenzoic acid; [1-(2-carboxy-4-phenylbutyl)-cyclopentane-carbonyl]-(*S*)-isoserine;

N[1-(acetylthiomethyl)cyclopentane-carbonyl]-(*S*)-methionine ethyl ester; 3(*S*)-[2-(acetylthiomethyl)-3-phenyl-propionyl]amimo-ε-caprolactam; -(2-acetylthiomethyl-3-(2-methylphenyl)propionyl)-methionine ethyl ester; and combinations thereof. Preferably, the dual-acting compound or combination , in particular the supramolecular complex, is a mixed salt or a co-crystal. It is also preferred that the linked pro-drug is a mixed salt or a co-crystal.

In a second aspect, the present invention is directed to pharmaceutical composition comprising

(a) the aforementioned dual-acting compound or combination, such as the aforementioned complex; and

(b) at least one pharmaceutically acceptable additive.

The present invention is also directed to pharmaceutical compositions comprising a linked pro-drug comprising:

(a) an angiotensin receptor antagonist or a pharmaceutically acceptable salt thereof;

(b) a NEPi or a pharmaceutically acceptable salt thereof,

wherein the angiotensin receptor antagonist or a pharmaceutically acceptable salt thereof and the NEPi or a pharmaceutically acceptable salt thereof are linked by a linking moiety; and

(c) at least one pharmaceutically acceptable additive.

In a third aspect, the present invention is directed to a method of preparing a dual-acting compound, in particular a supramolecular complex, comprising

(a) an angiotensin receptor antagonist;

(b) a neutral endopeptidase inhibitor (NEPi); and optionally

(c) a pharmaceutically acceptable cation selected from the group consisting of Na, K and NH_4;

said method comprising the steps of:

(i) dissolving an angiotensin receptor antagonist and a neutral endopeptidase inhibitor (NEPi) in a suitable solvent;

(ii) dissolving a basic compound of Cat in a suitable solvent, wherein Cat is a cation;

(iii) combining the solutions obtained in steps (i) and (ii);

(iv) precipitation of the solid, and drying same to obtain the dual-acting compound; or alternatively

obtaining the dual-acting compound by exchanging the solvent(s) employed in steps (i) and (ii) by

(iva) evaporating the resulting solution to dryness;

(va) re-dissolving the solid in a suitable solvent;

(via) precipitation of the solid and drying same to obtain the dual-acting compound.

The present invention is also directed to a method of making a linked pro-drug comprising:

(a) an angiotensin receptor antagonist or a pharmaceutically acceptable salt thereof;

(b) a NEPi or a pharmaceutically acceptable salt thereof, wherein the angiotensin receptor antagonist or a pharmaceutically acceptable salt thereof and the NEPi or a pharmaceutically acceptable salt thereof are linked by a linking moiety; and

comprising adding a linking moiety and a solvent to a mixture of an angiotensin receptor antagonist and a NEPi; and

(d) isolating the linked pro-drug.

In a fourth aspect, this invention is directed to a method of treating or preventing a disease or condition, such as hypertension, heart failure (acute and chronic), congestive heart failure, left ventricular dysfunction and hypertrophic cardiomyopathy, diabetic cardiac myopathy, supraventricular and ventricular arrhythmias, atrial fibrillation, atrial flutter, detrimental vascular remodeling, myocardial infarction and its sequelae, atherosclerosis, angina (unstable or stable), renal insufficiency (diabetic and non-diabetic), heart failure, angina pectoris, diabetes, secondary aldosteronism, primary and secondary pulmonary hypertension, renal failure conditions, such as diabetic nephropathy, glomerulonephritis, scleroderma, glomerular sclerosis, proteinuria of primary renal disease, and also renal vascular hypertension, diabetic retinopathy, other vascular disorders, such as migraine, peripheral vascular disease, Raynaud's disease, luminal hyperplasia, cognitive dysfunction (such as Alzheimer's), glaucoma and stroke comprising administering the afore-mentioned dual-acting compound or combination , in particular the supramolecular complex, or the afore-mentioned linked pro-drug, preferably, the complex, to a subject in need of such treatment.

Figure 1 shows a pictorial representation of the unit cell of the supramolecular complex of trisodium [3-((1*S*,3*R*)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(*S*)-3'-methyl-2'-(pentanoyl{2''-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate] hemipentahydrate comprising two asymmetric units. The following color code is used: grey = carbon atom; blue = nitrogen atom; red -= oxygen atom; violet = sodium atom

Detailed Description

The present invention relates to a dual-acting compound or combination, in particular a supramolecular complex, or linked pro-drug or in particular a supramolecular complex of two active agents with different mechanisms of action, namely an angiotensin receptor antagonist and a neutral endopeptidase inhibitor, which can form a unique molecular entity for the treatment of patients with various cardiovascular and/or renal diseases.

One embodiment of the invention is directed to a physical combination comprising:

(a) a pharmaceutically acceptable salt of an angiotensin receptor antagonist; and

(b) a pharmaceutically acceptable salt of a neutral endopeptidase inhibitor (NEPi);

wherein the pharmaceutically acceptable salt of the angiotensin receptor antagonist and the NEPi is the same and is selected from a salt of Na, K or NH_4.

Specifically, it is preferred that the two active agents are combined with each other so as to form a single dual-acting compound, in particular a supramolecular complex. By doing so, a new molecular or supramolecular entity is formed having distinct properties different to the above physical combination.

Thus, the present invention is directed to a dual-acting compound, in particular a supramolecular complex, comprising:

(a) an angiotensin receptor antagonist;

(b) a neutral endopeptidase inhibitor (NEPi); and

(c) a pharmaceutically acceptable cation preferably selected from the group consisting of Na, K and NH_4.

The present invention is also directed to a dual-acting compound, in particular a supramolecular complex, obtainable by:

(i) dissolving an angiotensin receptor antagonist and a neutral endopeptidase inhibitor (NEPi) in a suitable solvent;

(ii) dissolving a basic compound of Cat such as (Cat)OH, $(Cat)_2CO_3$, $(Cat)HCO_3$ in a suitable solvent, wherein Cat is a cation preferably selected from the group consisting of Na, K and NH_4;

(iii) combining the solutions obtained in steps (i) and (ii);

(iv) precipitation of the solid, and drying same to obtain the dual-acting compound; or alternatvely

obtaining the dual-acting compound by exchanging the solvent(s) employed in steps (i) and (ii) by

(iva) evaporating the resulting solution to dryness;

(va) re-dissolving the solid in a suitable solvent;

(via) precipitation of the solid and drying same to obtain the dual-acting compound.

The present invention is further directed to linked pro-drugs comprising:

(a) an angiotensin receptor antagonist or a pharmaceutically acceptable salt thereof; and

(b) a NEPi or a pharmaceutically acceptable salt thereof,

wherein the angiotensin receptor antagonist or a pharmaceutically acceptable salt thereof and the NEPi or a pharmaceutically acceptable salt thereof are linked by a linking moiety.

The two components are each linked to a linking moiety thereby creating a linked pro-drug. Preferably, the linked pro-drug is substantially pure; as used herein, "substantially pure" refers to at least 90%, more preferably at least 95% and most preferably at least 98% purity.

As one preferred embodiment of the present invention, the linked pro-drug has a structure such that by linking the two components with the linking moiety, a supramolecular complex is formed.

For the purpose of the present invention, the term "dual-acting compound" is intended to describe that these compounds have two different modes of action in one compound, one is

the angiotensin receptor blockade resulting from the ARB molecular moiety of the compound and the other is the neutral endopeptidase inhibition resulting from the NEPi molecular moiety of the compound.

For the purpose of the present invention, the term "compound" is intended to describe a chemical substance comprising covalent bonds within the two pharmaceutically active agents, the ARB and the NEPi molecular moieties, and non-covalent interactions between these two pharmaceutically active agents, the ARB and the NEPi molecular moieties. Typically, hydrogen bonding can be observed between the two pharmaceutically active agents, the ARB and the NEPi molecular moieties. Ionic bonds can be present between the cation and one or both of the two pharmaceutically active agents, the ARB and the NEPi molecular moieties. Other types of bonds may also be present within the compound such as van der Waals forces. For illustrative purposes, the dual-acting compound of the present invention could be represented as follows:

$$(ARB)\text{-}(L)_m\text{-}(NEPi)$$

wherein L is a linking rnoiety, such as a cation or is a noncovalent bond and m is an integer from 1 or more. In other words the ARB and NEPi moiety can be connected via non-covalent bonds such as hydrogen bonding. Alternatively or additionally they may be connected via a linking moiety such as a cation.

In one embodiment, the dual-acting compound may be considered to be a linked pro-drug, whereby the linking moiety, such as the cation, linking the two pharmaceutically active agents, the ARB and the NEPi, forms the pro-drug of these agents which are released once the linked pro-drug is ingested and absorbed.

In a preferred embodiment, the dual-acting compound is a complex, in particular a supramolecular complex.

For the purpose of the present invention, the term "supramolecular complex" is intended to describe an interaction between the two pharmaceutically active agents, the cations and any other entity present such as a solvent, in particular water, by means of noncovalent, intermolecular bonding between them. This interaction leads to an association of the species

present in the supramolecular complex distinguishing this complex over a physical mixture of the species.

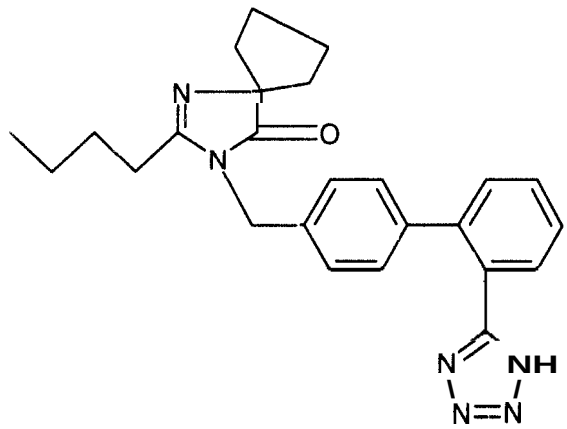
The noncovalent intermolecular bonding can be any interactions known in the art to form such supramolecular complexes, such as hydrogen bonding, van der Waals forces and π-π - stacking. Ionic bonds can also be present. Preferably, there exists ionic bonding and additionally hydrogen bonding to form a network of interactions within the complex. The supramolecular complex exists preferably in the solid state but may also be present in liquid media. As a preferred embodiment of the invention, the complex is crystalline and in this case is preferably a mixed crystal or co-crystal.

Typically, the dual-acting compound, in particular the supramolecular complex shows properties such as melting point, IR spectrum etc. that are different from a physical mixture of the species.

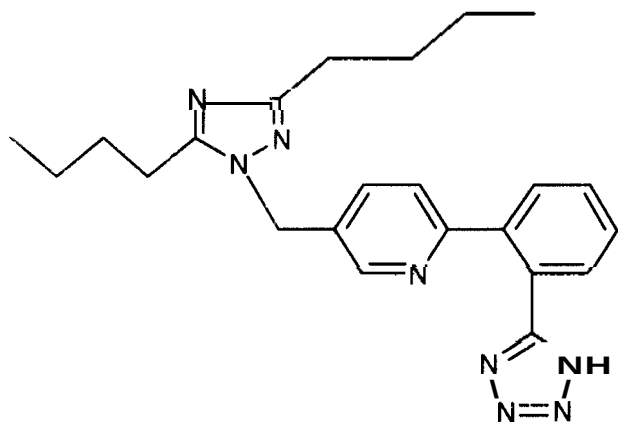
Preferably, the dual-acting compound, in particular the supramolecular complex, has a network of non-covalent bonds, in particular hydrogen bonds, between the two pharmaceutically active agents and any solvent, if present, preferably water. Moreover, it is preferred that the dual-acting compound, in particular the supramolecular complex, has a network of non-covalent bonds, in particular ionic and hydrogen bonds, between the two pharmaceutically active agents, the cation and any solvent, if present, preferably water. The cation is preferably coordinated to several oxygen ligands, thus, providing a linkage between these oxygen ligands. The oxygen ligands come from the carbonyl and carboxylate groups present in the two pharmaceutically active agents and preferably also from any solvent, if present, preferably water.

The dual acting compound comprises a molecular moiety of an angiotensin receptor antagonist. This means that a molecular moiety derived from an angiotensin receptor antagonist is participating in the build-up of the dual-acting compound. The angiotensin receptor antagonist is part of the compound and connected to the NEP inhibitor directly or indirectly via non-covalent bonds. For sake of convenience, throughout the application, the term "angiotensin receptor antagonist" will be used when describing this part of the compound. Angiotensin receptor antagonists (ARBs) suitable for use in the present invention

include, without limitation, valsartan, losartan, irbesartan, telmisartan, eprosartan, candesartan, olmesartan saprisartan, tasosartan, elisartan, the compound with the designation E-1477 of the following formula



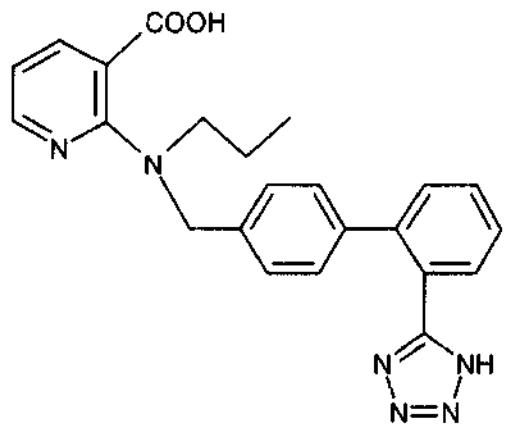
the compound with the designation SC-52458 of the following formula



and

the compound with the designation the compound ZD-8731 of the following formula

- 12 -



Suitable angiotensin II receptor antagonist also includes, but is not limited to, saralasin acetate, candesartan cilexetil, CGP-63170, EMD-66397, KT3-671, LR-B/081, valsartan, A-81282, BIBR-363, BIBS-222, BMS-184698, candesartan, CV-11194, EXP-3174, KW-3433, L-161177, L-162154, LR-B/057, LY-235656, PD-150304, U-96849, U-97018, UP-275-22, WAY-126227, WK-1492.2K, YM-31472, losartan potassium, E-4177, EMD-73495, eprosartan, HN-65021, irbesartan, L-159282, ME-3221, SL-91.0102, Tasosartan, Telmisartan, UP-269-6, YM-358, CGP-49870, GA-0056, L-159689, L-162234, L-162441, L-163007, PD-123177, A-81988, BMS-180560, CGP-38560A, CGP-48369, DA-2079, DE-3489, DuP-167, EXP-063, EXP-6155, EXP-6803, EXP-7711, EXP-9270, FK-739, HR-720, ICI-D6888, ICI-D7155, ICI-D8731, isoteoline, KRI-1177, L-158809, L-158978, L-159874, LR B087, LY-285434, LY-302289, LY-3I5995, RG-13647, RWJ-38970, RWJ-46458, S-8307, S-8308, saprisartan, saralasin, Sarmesin, WK-1360, X-6803, ZD-6888, ZD-7155, ZD-8731, BIBS39, Cl-996, DMP-811, DuP-532, EXP-929, L-163017, LY-301875, XH-148, XR-510, zolasartan and PD-123319.

Also included within the scope of this aspect of the invention are combinations of the above-identified ARBs.

ARBs to be used for preparing the combination or complex in accordance with the present invention can be purchased from commercial sources or can be prepared according to known methods. ARBs may be used for purposes of this invention in their free form, as well as in any suitable salt or ester form.

Preferred salts forms include acid addition salts. The compounds having at least one acid group (e.g., COOH or 5-tetrazolyl) can also form salts with bases. Suitable salts with bases

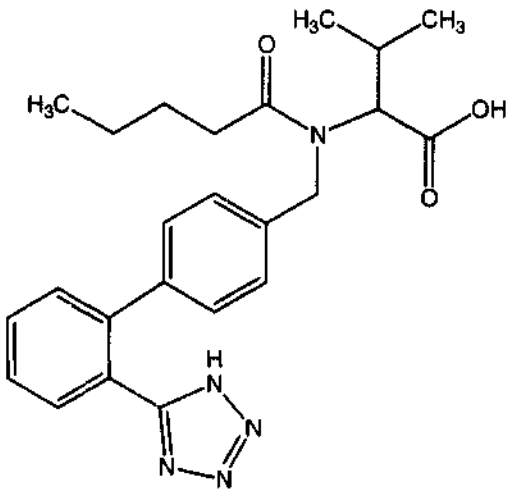
are, e.g., metal salts, such as alkali metal or alkaline earth metal salts, e.g., sodium, potassium, calcium or magnesium salts, or salts with ammonia or an organic amine, such as morpholine, thiomorpholine, piperidine, pyrrolidine, a mono-, di- or tri-lower alkylamine, e.g., ethyl-, tert-butyl-, diethyl-, diisopropyl-, triethyl-, tributyl- or dimethylpropylamine, or a mono-, di- or trihydroxy lower alkylamine, e.g., mono-, di- or tri-ethanolamine. Corresponding internal salts may furthermore be formed. Salts which are unsuitable for pharmaceutical uses but which can be employed, e.g., for the isolation or purification of free compounds I or their pharmaceutically acceptable salts, are also included. Even more preferred salts are, e.g., selected from the mono-sodium salt in amorphous form; di-sodium salt of valsartan in amorphous or crystalline form, especially in hydrate form, thereof.

Mono-potassium salt of valsartan in amorphous form; di-potassium salt of valsartan in amorphous or crystalline form, especially in hydrate form, thereof.

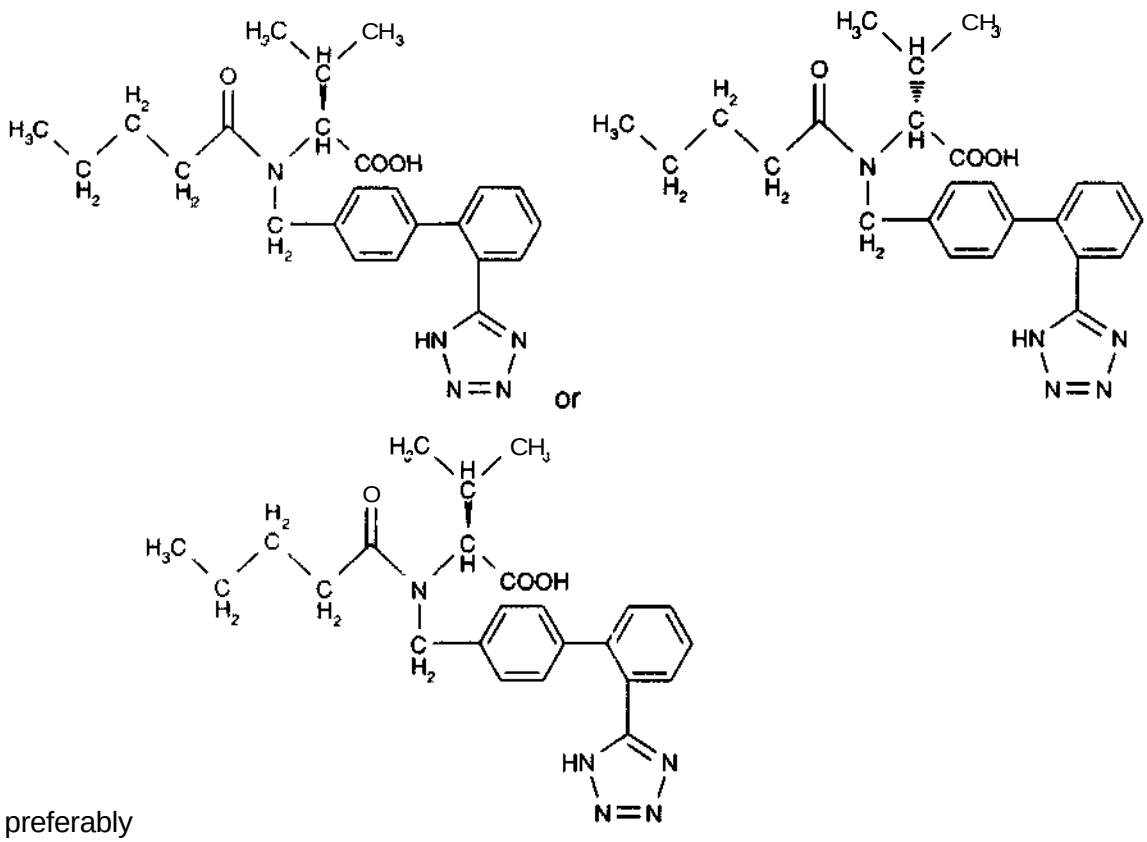
Calcium salt of valsartan in crystalline form, especially in hydrate form, primarily the tetrahydrate thereof; magnesium salt of valsartan in crystalline form, especially in hydrate form, primarily the hexahydrate thereof; calcium/magnesium mixed salt of valsartan in crystalline form, especially in hydrate form; *bis*-diethylammonium salt of valsartan in crystalline form, especially in hydrate form; *s*-dipropylammonium salt of valsartan in crystalline form, especially in hydrate form; *s*-dibutylammonium salt of valsartan in crystalline form, especially in hydrate form, primarily the hemihydrate thereof; mono-*L*-arginine salt of valsartan in amorphous form; *bis*-*L*-arginine salt of valsartan in amorphous form; mono-*L*-lysine salt of valsartan in amorphous form; *bis*-*L*-lysine salt of valsartan in amorphous form.

Preferably when preparing the dual-acting compound, in particular the complex according to the present invention, the free form of the ARB is used.

In a preferred embodiment of this invention, the angiotensin receptor blocker used in the combination or complex of the present invention is Valsartan the molecular structure of which is shown below



Valsartan may be in the racemic form or as one of the two isomers shown below



preferably

Valsartan ((*S*)-*N*-valeryl-*N*-{[2'-(1*H*-tetrazole-5-yl)-biphenyl-4-yl]-methyl}-valine) used according to the present invention can be purchased from commercial sources or can be prepared according to known methods. For example, the preparation of valsartan is described in U.S. Patent No 5,399,578 and EP 0 443 983, the entire disclosure of each of

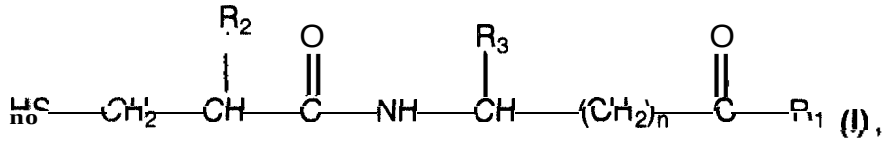
which is incorporated by reference herein. Valsartan may be used for purposes of this invention in its free acid form, as well as in any suitable salt form. Additionally, esters or other derivatives of the carboxylic grouping may be applied for the synthesis of linked pro-drugs, as well as salts and derivatives of the tetrazole grouping. Reference to ARBs includes reference to pharmaceutically acceptable salts thereof.

Preferably, the ARB is a diprotic acid. Thus, the angiotensin receptor blocker has a charge of 0, 1 or 2 depending on the pH of the solution.

In the combination of the present invention, the ARB is in the form of a pharmaceutically acceptable salt selected from Na, K or NH_4, preferably Na. This includes both the mono- and di-salt of these cations, preferably the di-salt. In particular in the case of valsartan this means that both the carboxylic acid moiety and the tetrazole moiety form the salt.

In the dual-acting compound, in particular the supramolecular complex of the present invention, typically the free form of the ARB is employed in the preparation and the cationic species present in the complex is introduced by using a base, e.g. (Cat)OH.

The dual acting compound comprises a molecular moiety of a neutral endopeptidase inhibitor. This means that a molecular moiety derived from a neutral endopeptidase inhibitor is participating in the build-up of the dual-acting compound. The neutral endopeptidase inhibitor is part of the compound and connected to the ARB directly or indirectly via non-covalent bonds. For sake of convenience, throughout the application, the term "neutral endopeptidase inhibitor" will be used when describing this part of the compound. Neutral endopeptidase inhibitors suitable for use in the present invention include those of formula (I)



(I),

wherein

R_2 is alkyl of 1-7 carbons, trifluoromethyl, phenyl, substituted phenyl, -(CH_2)1 to 4-phenyl, or -(CH_2)1 to 4-substituted phenyl;

R_3 is hydrogen, alkyl of 1-7 carbons, phenyl, substituted phenyl, -(CH_2)1 to 4-phenyl or -(CH_2)1 to 4-substituted phenyl;

R_1 is hydroxy, alkoxy of 1-7 carbons or NH_2;

n is an integer from 1-15;

and the term substituted phenyl refers to a substituent selected from lower alkyl of 1-4 carbons, lower alkoxy of 1-4 carbons, lower alkylthio of 1-4 carbons, hydroxy, Cl, Br or F.

Preferred neutral endopeptidase inhibitors of formula (I) include compounds, wherein

R_2 is benzyl;

R_3 is hydrogen;

n is an integer from 1-9; and

R_1 is hydroxy.

Another preferred neutral endopeptidase inhibitor is (3S,2'R)-3-{1-[2'-(ethoxycarbonyl)-4'-phenyl-butyl]-cyclopentan-1-carbonylamino}-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepine-1-acetic acid or a pharmaceutically acceptable salt thereof.

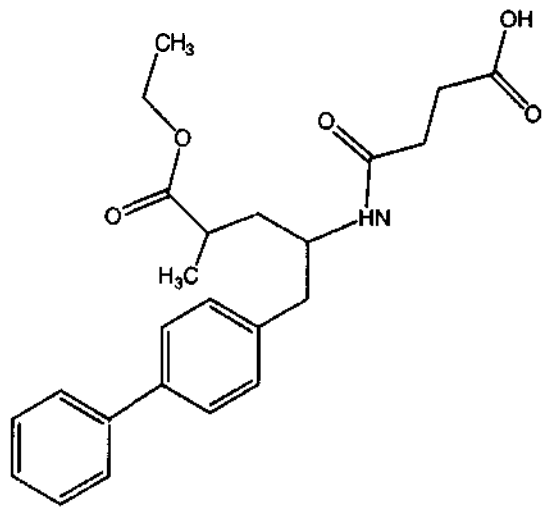
Preferred neutral endopeptidase inhibitors suitable for use in the present invention include, without limitation, SQ 28,603; N-[*N*-[1(*S*)-carboxyl-3-phenylpropyl]-(*S*)-phenylalanyl]-(*S*)-isoserine; N-[N-[((1*S*)-carboxy-2-phenyl)ethyl]-(*S*)-phenylalanyl]-β-alanine; N-[2(*S*)-mercaptomethyl-3-(2-methylphenyl)-propionyl]methionine; (*cis*-4-[[[1-[2-carboxy-3-(2-methoxyethoxy)propyl]-cyclopentyl]carbonyl]amino]-cyclohexanecarboxylic acid); thiorphan; retro-thiorphan; phosphoramidon; SQ 29072; (2*R*,4*S*)-5-biphenyl4-yl-5-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester; *N*-(3-carboxy-1-oxopropyl)-(4*S*)-*p*-phenylphenylmethyl)-4-amino-2*R*-methylbutanoic acid; (*S*)-*cis*-4-[1-[2-(5-indanyloxycarbonyl)-3-(2-methoxyethoxy)propyl]-1-cyclopentanecarboxamido]-1-cyclohexanecarboxylic acid; 3-(1-[6-endo-hydroxymethylbicyclo[2,2,1]heptane-2-exo-carbamoyl]cyclopentyl)-2-(2-methoxyethyl)propanoic acid; *N*-(1-(3-(*N*-*t*-butoxycarbonyl-(*S*)-prolylamino)-2(*S*)-*t*-butoxy-carbonylpropyl)cyclopentanecarbonyl)-*O*-benzyl-(*S*)-serine methyl ester; 4-[[2-(mercaptomethyl)-1-*oxo*-3-phenylpropyl]amino]benzoic acid; 3-[1-(*cis*-4-carboxycarbonyl-*cis*-3-butylcyclohexyl-r-1-carbamoyl)cyclopentyl]-2*S*-(2-methoxyethoxymethyl)propanoic acid; ((2*S*)-2-(4-biphenylmethyl)-4-carboxy-5-phenoxyvaleryl)glycine; (1-(*N*-hydroxycarbamoylmethyl)-1-cyclopentanecarbonyl)-*L*-phenylalanine; (*S*)-(2-biphenyl-4-yl)-1-(1*H*-tetrazol-5-yl)ethylamino) methylphosphonic acid; (*S*)-5-(*N*-(2-(phosphonomethylamino)-3-(4-biphenyl)propionyl)-2-aminoethyl)tetrazole; β-alanine; 3-[1,1'-biphenyl]-4-yl-*N*-[diphenoxyphosphinyl)methyl]-*L*-alanyl; N(2-carboxy-4-

thienyl)-3-mercapto-2-benzylpropanamide; 2-(2-mercaptomethyl-3-phenylpropionamido)thiazol-4-ylcarboxylic acid; (*L*)-(1-((2,2-dimethyl-1,3-dioxolan-4-yl)-methoxy)carbonyl)-2-phenylethyl)-*L*-phenylalanyl)-β-alanine; *N*-[*N*-[(*L*)-[1-[(2,2-dimethyl-1,3-dioxolan-4-yl)-methoxy]carbonyl]-2-phenylethyl]-*L*-phenylalanyl]-(*R*)-alanine; -[*N*-[(*L*)-1-carboxy-2-phenylethyl]-*L*-phenylalanyl]-(*R*)-alanine; N-[2-acetylthiomethyl-3-(2-methyl-phenyl)propionyl]-methionine ethyl ester; *N*-[2-mercaptomethyl-3-(2-methylphenyl)propionyl]-methionine; -[2(*S*)-mercaptomethyl-3-(2-methylphenyl)propanoyl]-(*S*)-isoserine; *N*-(*S*)-[3-mercapto-2-(2-methylphenyl)propionyl]-(*S*)-2-methoxy-(*R*)-alanine; *N*-[1-[[1(*S*)-benzyloxycarbonyl-3-phenylpropyl]amino]cyclopentylcarbonyl]-(*S*)-isoserine; *N*-[1-[[1(*S*)-carbonyl-3-phenylpropyl]amino]-cyclopentylcarbonyl]-(*S*)-isoserine; 1,1'-[dithiobis [2(*S*)-(2-methylbenzyl)-1-*oxo*-3,1-propanediyl]]-*bis*-(*S*)-isoserine; 1,1'-[dithiobis-[2(*S*)-(2-methylbenzyl)-1-*oxo*-3,1-propanediyl]]-*bis*-(*S*)-methionine; *N*-(3-phenyl-2-(mercaptomethyl)-propionyl)-(*S*)-4-(methylmercapto)methionine; *N*-[2-acetylthiomethyl-3-phenyl-propionyl]-3-aminobenzoic acid; *N*-[2-mercaptomethyl-3-phenyl-propionyl]-3-aminobenzoic acid; *N*-[1-(2-carboxy 4-phenylbutyl)-cyclopentane-carbonyl]-(*S*)-isoserine; *N*-[1-(acetylthiomethyl)cyclopentane-carbonyl]-(*S*)-methionine ethyl ester; 3(*S*)-[2-(acetylthiomethyl)-3-phenyl-propionyl]amimo-ε-caprolactam; *N*-(2-acetylthiomethyl-3-(2-methylphenyl)propionyl)-methionine ethyl ester; and combinations thereof.

Neutral endopeptidase inhibitors can be purchased from commercial sources or can be prepared according to known methods, such as those set forth in any of U.S. Patent No. 4,722,810, U.S. Patent No. 5,223,516, U.S. Patent No. 4,610,816, U.S. Patent No. 4,929,641, South African Patent Application 84/0670, UK 69578, U.S. Patent No. 5,217,996, EP 00342850, GB 02218983, WO 92/14706, EP 00343911, JP 06234754, EP 00361365, WO 90/09374, JP 07157459, WO 94/15908, U.S. Patent No. 5,273,990, U.S. Patent No. 5,294,632, U.S. Patent No. 5,250,522, EP 00636621, WO 93/09101, EP 00590442, WO 93/10773, U.S. Patent No. 5,217,996, the disclosure of each of which is incorporated by reference. Neutral endopeptidase inhibitors may be used for purposes of this invention in their free form, as well as in any suitable salt form. Reference to neutral endopeptidase inhibitors includes reference to pharmaceutically acceptable salts thereof.

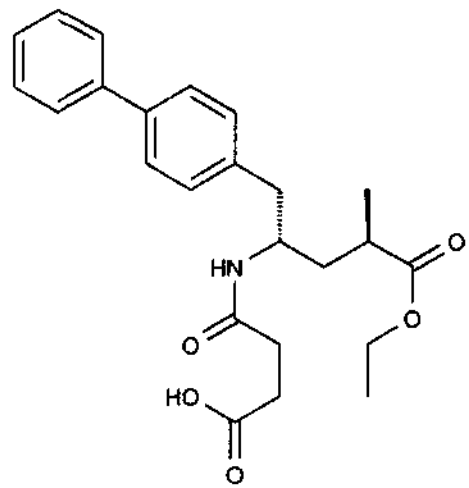
Additionally esters or other derivatives of any carboxylic grouping may be applied for the synthesis of linked pro-drugs, as well as salts and derivatives of any other acidic grouping. In a preferred embodiment of this invention, the NEPi is 5-biphenyl4-yl-5-(3-carboxy-

propionylamino)-2-methyl-pentanoic acid ethyl ester of formula (II) or the respective hydrolysed form 5-biphenyl4-yl-5-(3-carboxy-propionylamino)-2-methyl-pentanoic acid.



(II) .

The compound of formula (II) can exist as the (2*R*,4*S*), (2*R*,4*S*), (2*R*,4*S*) or (2*R*,4*S*) isomer. Preferred is (2*R*,4*S*)-5-biphenyl4-yl-5-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester as shown below:



The compound of formula (II) is a specific inhibitor of NEP and is described in U.S. Patent No. 5,217,996. It can be purchased from commercial sources or can be prepared according to known methods. The compound of formula (II) may be used for purposes of this invention in its free form, as well as in any suitable salt or ester form.

Preferably the NEPi is a monoprotic acid. Thus, the NEPi has a charge of 0 or 1 depending on the pH of the solution.

In the combination of the present invention, the NEPi is in the form of a pharmaceutically acceptable salt selected from Na, K or NH_4, preferably Na.

In the dual-acting compound, in particular the supramolecular complex of the present invention, typically the free form of the NEPi is employed in the preparation and the cationic species present in the complex is introduced by using a base, (Cat)OH.

The dual acting compound preferably comprises non-covalent bonds between the ARB and the NEPi. Alternatively or in addition, it optionally comprises a linking moiety such as a pharmaceutically acceptable cation.

The linking moiety includes, but is not limited to, generally regarded as safe (GRAS) compounds or other pharmacologically acceptable compounds. The linking moiety may be an ion or a neutral molecule. In the case wherein the linking moiety is an ion the linked pro-drug is a salt and when the linking moiety is a neutral molecule the linked pro-drug is a co-crystal. Without being bound by any particular theory, the acidic portion of the ARB and NEPi donate a proton to the basic linking moiety such that all three components then become united to form one molecule. When the linked pro-drug is ingested by the subject intended to be treated the more acidic nature of the ingestion environment causes the linked pro-drug to separate into individual components concomitant with ingestion and absorption and therefore be converted into active agents to provide their beneficial biological action to treat the intended diseases.

In the case of a linked pro-drug salt or the dual-acting compound, the linking moiety or the cation, respectively, is preferably a positively charged mono-, di- or tri-valent cation, an organic base or an amino acid. Preferred cations (Cat) both for the linked pro-drug in general and the dual-acting compound, in particular the complex are basic cations, even more preferably metallic cations. Preferred metallic cations include, but are not limited to Na, K, Ca, Mg, Zn, Fe or NH_4. Amine bases and salt forming agents may also be employed, such as benzathine, hydrabamine, ethylenediamine, n-n-dibenzyl-ethylenediamine, L-arginine, choline hydroxide, N-methyl-glucamine, (Meglumine), L-Lysine, dimethylaminoethanol (Deanol), t-butylamine, diethylamine, 2-(diethylamino)-ethanol, 4-(2-

hydroxyethyl)-morpholine, Thromethanine (TRIS), 4-acetamidophenol, 2-amino-2-methyl-1,3-propanediol, 2-amino-2-methyl-propanol, benzylamine, cyclohexylamine, diethanolamine, ethanolamine, imidazole, piperazine and triethanolamine.

Most preferably, the cation is Na, K or NH_4, such as Na. In one embodiment Ca is preferred.

In the case of a linked pro-drug co-crystal, the linking moiety is may also be a neutral molecule which provides hydrogen-bonding functionality.

In one embodiment, the linked pro-drugs of this invention are represented as set forth below, wherein scheme (1) and (2) represent a salt and scheme (3) represents a co-crystal:

NEPi • Xa• ARB scheme (1)

NEPi • XaYb• ARB scheme (2)

NEPi • Zc• ARB scheme (3),

wherein

X is Ca, Mg, Zn or Fe;

Y is Na, K or NH4;

Z is a neutral molecule; and

a, b and c reflect the stoichiometry of the linked pro-drug, preferably, a, b and c are a valence of 1^+, 2^+ or 3^+.

For the linked pro-drugs of schemes (1) and (2), above, preferably the NEPi is a monoprotic acid and ARB is a diprotic acid. The angiotensin receptor blocker has a charge of 0, 1 or 2 and the NEPi has a charge of 0 or 1 depending on the pH of the solution, while the overall molecule will be neutral. Ratios of ARB to NEPi will be 1:1, 1:2, 1:3, 3:1, 2:1, 1:1, preferably 1:1, 1:2 or 1:3, most preferably 1:1.

Multi-component salts, particularly with zinc and calcium have been reported in the literature, e.g., *Chem Pharm Bull,* Vol. 53, p. 654 (2005). These ions require a coordination geometry that facilitates the crystallization of multi-component systems. The metal ions have coordinating geometries governed by the atomic orbitals for each species

Valsartan comprises two acidic groupings: the carboxylic acid and the tetrazole. In one embodiment of this aspect of the present invention, the molecular structure of linked pro-drugs of valsartan and a NEPi comprise a linkage between the carboxylic acid and the linking moiety or a linkage between the tetrazole grouping and the linking moiety. In yet another embodiment, the linked pro-drug comprises a trivalent linking moiety linked to the valsartan carboxylic acid grouping, the tetrazole grouping and the NEPi grouping.

In an embodiment of this aspect of the invention, valsartan is linked to (2*R*,4*S*)-5-biphenyl4-yl-5-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester by a calcium salt ion.

In a preferred embodiment of the present application, the angiotensin receptor antagonist and the neutral endopeptidase inhibitor are present in a molar ratio of 1:1, 1:2, 1:3, 3:1, 2:1, more preferably 1:1 in the combination as well as in the supramolecular complex. This is also true for the linked pro-drug. Moreover, in the complex, angiotensin receptor antagonist, the . neutral endopeptidase inhibitor and the cation are present in a molar ratio of 1:1:1, 1:1:2, 1:1:3, more preferably 1:1:3. This applies equally to the linked pro-drug.

The combination or the dual-acting compound, in particular the complex of the present invention may contain a solvent. This is particularly preferred in the case of the dual-acting compound, in particular the complex, where the solvent may contribute to the intermolecular structure, e.g. the supramolecular interactions. Preferred solvents include water, methanol, ethanol, 2-propanol, acetone, ethyl acetate, methyl-*t*-butylether, acetonitrile, toluene, and methylene chloride, preferably water. If a solvent is present, one or more molecules per molecule of the active agent can be present. In this case, namely if a stoichiometric amount of the solvent is present, preferably 1, 2, 3, 4 or 5, more preferably 3, molecules of solvent, such as water, can be present per molecule of active agent. Alternatively, the solvent may be present in non-stoichiometric amounts. This means preferably any stoichiometric fraction of the solvent, such as 0.25, 0.5, 0.75, 1.25, 1.5, 1.75, 2.25, 2.5, 2.75, 3.25, 3.5, 3.75, 4.25, 4.5 and 4.75, preferably 2.5, molecules of solvent, such as water, can be present per molecule of active agent. If the dual-acting compound, in particular the complex is in the crystalline form, the solvent may be part of the molecular packing and be trapped in the crystal lattice.

Thus in a preferred embodiment of the present invention, the dual-acting compound, in particular the supramolecular complex is described by the sum formula:

[ARB(NEPi)]$Na_{1-3} \cdot xH_2O$, wherein x is 0, 1, 2 or 3, such as 3, preferably

[ARB(NEPi)]$Na_3 \cdot xH_2O$, wherein x is 0, 1, 2 or 3, such as 3, more preferably

[valsartan ((2*R*,4*S*)-5-biphenyl4-yl-5-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester]Na$ • x H_2O, wherein x is 0, 1, 2 or 3, such as 3.

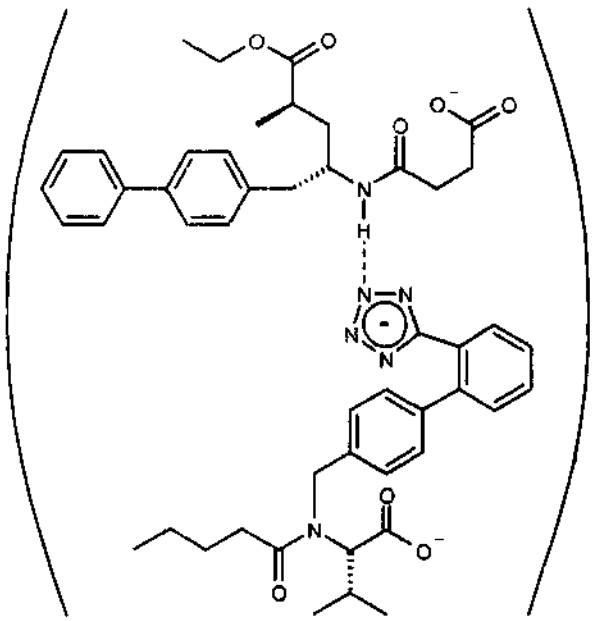
Thus in a preferred embodiment of the present invention, the dual-acting compound, in particular the supramolecular complex is described by the sum formula:

[ARB(NEPi)]$Na_{1-3} \cdot xH_2O$, wherein x is 0 to 3, such as 2.5, preferably

[ARB(NEPi)]$Na_3 \cdot xH_2O$, wherein x is 0 to 3, such as 2.5, more preferably

[(*N*-valeryl-*N*-{[2'-(1*H*-tetrazole-5-yl)-biphenyl-4-yl]-methyl}-valine) (5-biphenyl4-yl-5-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester]$Na_3 \cdot x H_2O$, in particular [((*S*)-*N*-valeryl-*N*-{[2'-(1*H*-tetrazole-5-yl)-biphenyl-4-yl]-methyl}-valine) ((2*R*,4*S*)-5-biphenyl4-yl-5-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester]$Na_3 \cdot x H_2O$, wherein x is 0 to 3, such as 2.5. In this most preferred example, the complex is termed trisodium [3-((1*S*,3*R*)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(*S*)-3'-methyl-2'-(pentanoyl{2''-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate] hemipentahydrate.

A simplified structure of trisodium [3-((1*S*,3*R*)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(*S*)-3'-methyl-2'-(pentanoyl{2''-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate] hemipentahydrate used to formally calculate the relative molecular mass, is shown below.



. 3 Na^+ . 2.5 H_2O

Valsartan comprises two acidic groupings: the carboxylic acid and the tetrazole. In one embodiment of this aspect of the present invention, the molecular structure of the dual-acting compound, in particular, the complex, of valsartan and a NEPi comprises an interaction between the carboxylic acid and the cation, such as Na, or the solvent, such as water, or a linkage between the tetrazole grouping and the cation, such as Na, or the solvent, such as water. In yet another embodiment, the dual-acting compound, in particular, the complex, comprises an interaction between the valsartan carboxylic acid grouping, the tetrazole grouping or the NEPi grouping and the cation, such as Na, or the solvent, such as water.

The combination or dual-acting compound, in particular, the complex, of the present invention is preferably in the solid form. In the solid state it can be in the crystalline, partially crystalline, amorphous, or polymorphous form, preferably in the crystalline form.

The dual-acting compound, in particular, the complex, of the present invention is distinct from a combination of an ARB and a NEPi obtained by simply physically mixing the two active agents. Thus, it can have different properties that make it particularly useful for manufacturing and therapeutic applications. The difference of the dual-acting compound, in particular, the complex, and the combination can be exemplified by the dual-acting compound of (*S*)-*N*-valeryl-*N*-{[2'-(1*H*-tetrazole-5-yl)-biphenyl-4-yl]-methyl}-valine and (2*R*,4*S*)-5-biphenyl4-yl-5-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester

which is characterized by very distinct spectral peaks and shifts that are not observed in the physical mixture.

Specifically, such a dual-acting compound is preferably characterized by an X-ray powder diffraction pattern taken with a Scintag XDS2000 powder diffractometer using Cu-Ka radiation (lamda=1.54056 A) with a Peltier-cooled Silicon detector at room temperature (25degree C). Scan range was from 1.5degree to 40degree in 2 theta with a scan rate of 3degree/minute. The most important reflections in the X-ray diffraction diagram comprise the following interlattice plane intervals:

The preferred characterization of trisodium [3-((1*S*,3*R*)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(*S*)-3'-methyl-2'-(pentanoyl{2''-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate] hemipentahydrate is obtained from the interlattice plane intervals d of the ascertained X-ray diffraction diagrams, whereby, in the following, average values 2Θ in [°] are indicated (error limit of ±0.2)

4.5, 5.5, 5.6, 9.9, 12.8, 15.7, 17.0, 17.1, 17.2, 18.3, 18.5, 19.8, 21.5, 21.7, 23.2, 23.3, 24.9, 25.3, 27.4, 27.9, 28.0, 30.2.

or with an error limit of ±0.1:

4.45, 5.52, 5.57, 9.94, 12.82, 15.66, 17.01, 17.12, 17.2, 18.32, 18.46, 19.76, 21.53, 21.72, 23.17, 23.27, 24.88, 25.3, 27.4, 27.88, 28.04, 30.2.

The most intensive reflections in the X-ray diffraction pattern show the following interlattice plane intervals:

2Θ in [º] : .4.5, 5.6, 12.8, 17.0, 17.2, 19.8, 21.5, 27.4, in particular 4.45, 5.57, 17.01, 17.2, 19.76, 21, 27.4.

A preferred method of checking the above-indicated average values of the interlattice plane intervals and intensities measured by experimentation from X-ray diffraction, for a given substance, consists in calculating these intervals and their intensities from the comprehensive single crystal structure determination. This structure determination yields ceU constants and atom positions, which enable the X-ray diffraction diagram corresponding to the solid to be calculated by means of computer-aided calculation methods. The program used is Powder Pattern within the application software Materials Studio (Accelrys). A

comparison of these data, namely the interlattice plane intervals and intensities of the most important lines of trisodium [3-((1*S*,3*R*)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(*S*)-3'-methyl-2'-(pentanoyl{2''-(tetrazol-5-ylate)biphenyl-4'-ylrnethyl}amino)butyrate] hemipentahydrate, obtained from measurements and from calculating the single crystal data, is illustrated in the table below.

Table

measured		calculated		measured		calculated	
2e in [°]	Intensity	2Θ In [°]	Intensity	2Θ in [°]	Intensity	2Θ in [°3	Intensity
4.45	very strong	4.15	very strong	19.76	strong	19.6	very weak
5.52	Strong	5	strong	21.53	weak	19.8	very weak
5.57	strong	6.5	strong	21.72	very weak	21.4	very weak
9.94	very weak	9.75	weak	23.17	weak	23.1	very weak
12.82	very strong	12.6	weak	23.27	weak	23.15	very weak
15.66	very weak	15.05	strong	24.88	very weak		very weak
17.01	weak	16.9	very strong	25.3	weak	25.3	very weak
17.12	strong	17.1	strong	27.4	weak	27.3	very weak
17.2	weak	17.15	weak	27.88	very weak	27.9	very weak
18.32	weak	18.25	very	28.04	weak		

			weak				
18.46	weak	18.3	weak	30.2	weak		

Relative intensity between 100% to 50% is referred to as very strong, 50% to 10% as strong, 10% to 5% as weak, and below 5% as very weak.

The invention relates to trisodium [3-((1*S*,3*R*)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(*S*)-3'-methyl-2'-(pentanoyl{2''-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate] hemipentahydrate, a crystalline solid which is characterized by the data and parameters obtained from single crystal X-ray analysis and X-ray powder patterns. An in-depth discussion of the theory of the methods of single crystal X-ray diffraction and the definition of the evaluated crystal data and the parameters may be found in Stout & Jensen, X-Ray Structure Determination; A Practical Guide, Mac Millian Co., New York, N.Y. (1968) chapter 3.

Crystal data

sum formula	$C_{48}H_{55}N_6O_8Na_3 \cdot 2.5H_2O$
molecular mass	957.99
crystal colour	colourless
crystal shape	tabular: hexagonal
crystal system	monoclinic
space group	$P2_1$
Cell parameters	a=20.344 A
	b=42.018 Å
	c=20.374 A
	$\alpha = 90^0$
	β=119.29°

	Y = 90°
volume of unit cell	15190.03 Å^3
Z (the number of asymmetric units in the unit cell)	2
calculated density	1.26845 g/cm3

Single crystal X-ray measurement data

diffractometer	Nonius KappaCCD
X-ray generator	Nonius FR571 X-ray generator with a copper rotating anode
temperature	270 K and 150 K

Notes:

Two data sets on two suitable single crystals were collected at two different temperatures to assure no phase change during cooling.

None of the hydrogen atoms on the water or amine nitrogen atoms were observed in the Fourier maps so they were not included in the refinement.

Computer program used to solve the structure

SHELXD (Sheldrick, Göttingen)

In three dimensions, the unit cell is defined by three edge lengths a, b, and c, and three interaxial angles a, β, und γ. In this way, the volume of the unit cell V_c is determined. A differentiated description of these crystal parameters is illustrated in chapter 3 of Stout & Jensen (see above). The details for trisodium [3-((1 *S*,3*R*)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(*S*)-3'-methyl-2'-(pentanoyl{2''-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate] hemipentahydrate from the single crystal measurements, especially the atom coordinates, the isotropic thermal parameters, the coordinates of the hydrogen atoms as well as the corresponding isotropic thermal parameters, show that a monoclinic unit cell exists, its cell content of twelve formula units of $C_{48}H_{55}N_6O_8Na_3 \bullet 2.5\ H_2O$ occurring as a result of two asymmetric units on two-fold positions.

The acentric space group $P2_1$ determined from the single crystal X-ray structure is a common space group for enantiomorphically pure molecules. In this space group there are two general positions which means that for twelve formula units in the unit cell there must be 18 sodium ions and 15 waters in the asymmetric unit.

A pictorial representation of the unit cell of the supramolecular complex of trisodium [3-((1*S*,3*R*)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(*S*)-3'-methyl-2'-(pentanoyl{2''-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate] hemipentahydrate comprising two asymmetric units is shown in Figure 1.

Based on the single crystal structure solution, the asymmetric unit of the trisodium [3-((1*S*,3*R*)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(*S*)-3'-methyl-2'-(pentanoyl{2''-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate] hemipentahydrate supramolecule comprises six each of ARB and NEPi moieties, 18 sodium atoms, and 15 water molecules. Trisodium [3-((1*S*,3*R*)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-utylcarbamoyl)propionate-(*S*)-3'-methyl-2'-(pentanoyl{2''-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate] hemipentahydrate may be considered a sodium supramolecular complex, coordinated by oxygen ligands. These oxygens come from twelve carboxylate groups and eighteen carbonyl groups of the above moieties, and from 13 of the 15 water molecules. The crystal is an infinite 3-dimensional network of these sodium complexes.

Such a compound may also be characterized by an infrared absorption spectrum obtained using Attenuated Total Reflection Fourier Transform Infrared (ATR-FTIR) spectrometer (Nicolet Magna-IR 560) showing the following significant bands, expressed in reciprocal wave numbers (cm^{-1}):

2956 (w), 1711 (st), 1637 (st), 1597 (st), 1488 (w), 1459 (m), 1401 (st), 1357 (w), 1295 (m), 1266 (m), 1176 (w), 1085 (m), 1010 (w), 1942(w), 907 (w), 862 (w), 763 (st), 742 (m), 698 (m), 533 (st). Characteristic to the complex are in particular the following peaks 1711(st), 1637(st), 1597(st) and 1401(st). The error margin for all absorption bands of ATR-IR is $\pm$ 2 cm^{-1}. The intensities of the absorption bands are indicated as follows: (w) = weak; (m) = medium; and (st) = strong intensity.

Such a compound may also be characterized by a Raman spectrum measured by dispersive Raman spectrometer with 785 nm laser excitation source (Kaiser Optical Systems, Inc.) showing the following significant bands expressed in reciprocal wave numbers (cm^{-1}):

3061 (m), 2930 (m, broad), 1612 (st), 1523 (m), 1461 (w), 1427 (w), 1287 (st), 1195 (w), 1108 (w), 11053 (w), 1041 (w), 1011 (w), 997 (m), 866(w), 850 (w), 822 (w), 808 (w), 735 (w), 715 (w), 669 (w), 643 (w), 631 (w), 618 (w), 602 (w), 557 (w), 522 (w), 453 (w), 410 (w), 328 (w).

The error margin for all Raman bands is ± 2 cm^{-1}. The intensities of the absorption bands are indicated as follows: (w) = weak; (m) = medium; and (st) = strong intensity.

Such a compound may also be characterized by distinct melting properties measured by differential scanning calorimetry (DSC). Using Q1000 (TA Instruments) instrument, the melting onset temperature and the peak maximum temperature for such a complex are observed at 139°C and 145°C, respectively. The heating rate is 10 K/min.

The second embodiment of the present invention is directed to pharmaceutical compositions comprising a combination, a linked pro-drug or a dual-acting compound, in particular the complex as described herein and at least one pharmaceutically acceptable additive. The details regarding the combination and the complex, including the ARB and the NEPi, are as described above with regard to the first embodiment of the invention.

The pharmaceutical compositions according to the invention can be prepared in a manner known per se and are those suitable for enteral, such as oral or rectal, and parenteral administration to mammals (warm-blooded animals), including man, comprising a therapeutically effective amount of the combination or dual-acting compound, in particular the complex, alone or in combination with at least one pharmaceutically acceptable carrier, especially suitable for enteral or parenteral application. Typical oral formulations include tablets, capsules, syrups, elixirs and suspensions. Typical injectable formulations include solutions and suspensions.

Pharmaceutically acceptable additives suitable for use in the present invention include, without limitation and provided they are chemically inert so that they do not adversely affect the combination or the dual-acting compound, in particular the complex of the present invention, diluents or fillers, disintegrants, glidants, lubricants, binders, colorants and

combinations thereof. The amount of each additive in a solid dosage formulation may vary within ranges conventional in the art. Typical pharmaceutically acceptable carriers for use in the formulations described above are exemplified by: sugars, such as lactose, sucrose, mannitol and sorbitol; starches, such as cornstarch, tapioca starch and potato starch; cellulose and derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and methyl cellulose; calcium phosphates, such as dicalcium phosphate and tricalcium phosphate; sodium sulfate; calcium sulfate; polyvinylpyrrolidone; polyvinyl alcohol; stearic acid; alkaline earth metal stearates, such as magnesium stearate and calcium stearate; stearic acid; vegetable oils, such as peanut oil, cottonseed oil, sesame oil, olive oil and corn oil; non-ionic, cationic and anionic surfactants; ethylene glycol polymers; β-cyclodextrin; fatty alcohols; and hydrolyzed cereal solids, as well as other non-toxic compatible fillers, binders, disintegrants, buffers, preservatives, antioxidants, lubricants, flavoring agents and the like commonly used in pharmaceutical formulations.

Pharmaceutical preparations for enteral or parenteral administration are, e.g., in unit dose forms, such as coated tablets, tablets, capsules or suppositories and also ampoules. These are prepared in a manner which is known *per se,* e.g., using conventional mixing, granulation, coating, solubilizing or lyophilizing processes. Thus, pharmaceutical compositions for oral use can be obtained by combining the linked pro-drug, combination or dual-acting compound, in particular the complex with solid excipients, if desired, granulating a mixture which has been obtained, and, if required or necessary, processing the mixture or granulate into tablets or coated tablet cores after having added suitable auxiliary substances.

The dosage of the active compounds in the combination or dual-acting compound, in particular the complex can depend on a variety of factors, such as mode of administration, homeothermic species, age and/or individual condition. The projected efficacy in animal disease models ranges from about 0.1 mg/kg/day to about 1000 mg/kg/day given orally, and the projected dose for human treatment ranges from about 0.1 mg/day to about 2000 mg/day. Preferred ranges are from about 40 mg/day to about 960 mg/day of the linked pro-drug, preferably about 80 mg/day to about 640 mg/day. The ARB component is administered in a dosage of from about 40 mg/day to about 320 mg/day and the NEPi component is administered in a dosage of from about 40 mg/day to about 320 mg/day. More specifically, the dosages of ARB/NEPi, respectively, include 40 mg/40 mg, 80 mg/80 mg, 160 mg/160 mg, 320 mg/320 mg, 40 mg/80 mg, 80 mg/160 mg, 160 mg/320 mg, 320 mg/640 mg, 80 mg/40 mg, 160 mg/80 mg and 320 mg/160 mg, respectively. These dosages are "therapeutically effective amounts". Preferred dosages for the linked pro-drug, combination or dual-acting compound, in particular the complex of the pharmaceutical composition according to the present invention are therapeutically effective dosages.

The pharmaceutical compositions may contain in addition another therapeutic agent, e.g., each at an effective therapeutic dose as reported in the art. Such therapeutic agents include:

a) antidiabetic agents such as insulin, insulin derivatives and mimetics; insulin secretagogues such as the sulfonylureas, e.g., Glipizide, glyburide and Amaryl; insulinotropic sulfonylurea receptor ligands such as meglitinides, e.g., nateglinide and repaglinide; peroxisome proliferator-activated receptor (PPAR) ligands; protein tyrosine phosphatase-1B (PTP-1B) inhibitors such as PTP-112; GSK3 (glycogen synthase kinase-3) inhibitors such as SB-517955, SB-4195052, SB-216763, NN-57-05441 and NN-57-05445; RXR ligands such as GW-0791 and AGN-194204; sodium-dependent glucose cotransporter inhibitors such as T-1095; glycogen phosphorylase A inhibitors such as BAY R3401; biguanides such as metformin; alpha-glucosidase inhibitors such as acarbose; GLP-1 (glucagon like peptide-1), GLP-1 analogs such as Exendin-4 and GLP-1 mimetics; and DPPIV (dipeptidyl peptidase IV) inhibitors such as LAF237;

b) hypolipidemic agents such as 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase inhibitors, e.g., lovastatin, pitavastatin, simvastatin, pravastatin, cerivastatin, mevastatin, velostatin, fluvastatin, dalvastatin, atorvastatin, rosuvastatin and rivastatin; squalene

synthase inhibitors; FXR (farnesoid X receptor) and LXR (liver X receptor) ligands; cholestyramine; fibrates; nicotinic acid and aspirin;

c) anti-obesity agents such as orlistat; and

d) anti-hypertensive agents, e.g., loop diuretics such as ethacrynic acid, furosemide and torsemide; angiotensin converting enzyme (ACE) inhibitors such as benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perinodopril, quinapril, ramipril and trandolapril; inhibitors of the Na-K-ATPase membrane pump such as digoxin; ACE/NEP inhibitors such as omapatrilat, sampatrilat and fasidotril; p-adrenergic receptor blockers such as acebutolol, atenolol, betaxolol, bisoprolol, metoprolol, nadolol, propranolol, sotalol and timolol; inotropic agents such as digoxin, dobutamine and milrinone; calcium channel blockers such as amlodipine, bepridil, diltiazem, felodipine, nicardipine, nimodipine, nifedipine, nisoldipine and verapamil; aldosterone receptor antagonists; and aldosterone synthase inhibitors. Most preferred combination partners are diuretics, such as hydrochlorothiazide, and/or calcium channel blockers, such as amlodipine or a salt thereof.

Other specific anti-diabetic compounds are described by Patel Mona in *Expert Opin Investig Drugs,* 2003, 12(4), 623-633, in the figures 1 to 7, which are herein incorporated by reference. A compound of the present invention may be administered either simultaneously, before or after the other active ingredient, either separately by the same or different route of administration or together in the same pharmaceutical formulation.

The structure of the therapeutic agents identified by code numbers, generic or trade names may be taken from the actual edition of the standard compendium "The Merck Index" or from databases, e.g., Patents International (e.g. IMS World Publications). The corresponding content thereof is hereby incorporated by reference.

Accordingly, the present invention provides pharmaceutical compositions in addition a therapeutically effective amount of another therapeutic agent, preferably selected from antidiabetics, hypoiipidemic agents, anti-obesity agents or anti-hypertensive agents, most preferably from antidiabetics, anti-hypertensive agents or hypoiipidemic agents as described above.

The person skilled in the pertinent art is fully enabled to select a relevant test model to prove the efficacy of a combination of the present invention in the hereinbefore and hereinafter indicated therapeutic indications.

Representative studies are carried out with trisodium [3-((1 *S*,3*R*)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(*S*)-3'-methyl-2'-(pentanoyl{2''-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate] hemipentahydrate, e.g. applying the following methodology:

The antihypertensive and neutral endopeptidase 24.11 (NEP)-inhibitory activities of trisodium [3-((1*S*,3*R*)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(*S*)-3'-methyl-2'-(pentanoyl{2''-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate] hemipentahydrate is assessed in conscious rats. The blood pressure-lowering effect is evaluated in double-transgenic rats (dTGRs) that overexpress both human renin and its substrate, human angiotensinogen (Bohlender, et al, High human renin hypertension in transgenic rats. Hypertension; 29(1 Pt 2):428-34, 1997). Consequently, these animals exhibit an angiotensin II-dependent hypertension. The NEP-inhibitory effect of trisodium [3-((1*S*,3*R*)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(*S*)-3'-methyl-2'-(pentanoyl{2''-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate] hemipentahydrate is determined in conscious Sprague-Dawley rats infused with exogenous atrial natriuretic peptide (ANP). Potentiation of plasma ANP levels is used as an index of NEP inhibition in vivo. In both models, trisodium [3-((1*S*,3*R*)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(*S*)-3'-methyl-2'-(pentanoyl{2''-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate] hemipentahydrate is administered orally as a powder in gelatin mini capsules. The results are summarized below.

- Trisodium [3-((1 *S*,3*R*)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(*S*)-3'-methyl-2'-(pentanoyl{2''-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate] hemipentahydrate exhibits a dose-dependent and long-lasting antihypertensive effect after oral administration in conscious dTGRs, a rat model of fulminant hypertension.
- Oral administration of trisodium [3-((1 *S*,3*R*)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(*S*)-3'-methyl-2'-(pentanoyl{2''-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate] hemipentahydrate rapidly and dose-dependently inhibits NEP with a long duration of action, as reflected by its potentiation of plasma ANP

immunoreactivity (ANPir) in conscious Sprague-Dawley rats infused with exogenous ANP.

Antihypertensive effect in vivo

The dTGRs are instrumented with radiotelemetry transmitters for continuous measurement of arterial blood pressure and heart rate. Animals are randomly assigned to vehicle (empty capsule) or treatment (at 2, 6, 20 or 60 mg/kg, p.o.) groups. Baseline 24-hr mean arterial pressure (MAP) is approximately 170-180 mmHg in all groups. Trisodium [3-((1*S*,3*R*)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(*S*)-3'-methyl-2'-(pentanoyl{2''-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate] hemipentahydrate dose-dependently reduces MAP. The values obtained from the treatment groups are dose-dependent, and the results from the three highest doses are significantly different from the vehicle controls

Inhibition of NEP in vivo

The extent and duration of trisodium [3-((1*S*,3*R*)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(*S*)-3'-methyl-2'-(pentanoyl{2''-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate] hemipentahydrate for NEP inhibition in vivo is assessed with methodologies as described previously (Trapani, et al, CGS 35601 and its orally active prodrug CGS 37808 as triple inhibitors of endothelin-converting enzyme-1, neutral endopeptidase 24.11, and angiotensin-converting enzyme. J Cardiovasc Pharmacol; 44(Suppl 1):S211-5, 2004). Rat ANP(1-28) is infused intravenously at a rate of 450 ng/kg/min in conscious, chronically cannulated, male Sprague-Dawley rats. After one hour of infusion, rats are randomly assigned to one of six groups: untreated control, vehicle (empty capsule) control, or one of four doses of drug (2, 6, 20, or 60 mg/kg, p.o.). ANP infusion is continued for an additional eight hours. Blood samples are collected for measuring plasma ANPir by a commercial enzyme immunoassay kit at -60 min (i.e., before initiating ANP infusion), -30 min (after 30 min of ANP infusion), 0 min ("baseline"; after 60 min of ANP infusion but before dosing with drug or its vehicle), and at 0.25, 0.5, 1, 2, 3, 4, 5, 6, 7, and 8 hr post-dosing.

Before ANP infusion, ANPir is low (0.9-1.4 ng/ml) and similar in all six groups. ANP infusion rapidly (by 30 min) elevates ANPir to ~10 ng/ml. This ANPir level is sustained for the duration of the experiment in the untreated and vehicle control groups. In contrast, trisodium

[3-((1*S*,3*R*)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(*S*)-3'-methyl-2'-(pentanoyl{2''-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate] hemipentahydrate rapidly (within 15 min) and dose-dependently augments ANPir. In summary, orally administered LCZ696 rapidly and dose-dependently inhibited NEP with a long duration of action as reflected by the potentiation of plasma ANPir.

The available results indicate an unexpected therapeutic effect of a compound according to the invention.

In a third aspect, the present invention is directed to a method of making a linked pro-drug of an ARB or a pharmaceutically acceptable salt thereof and a NEPi or a pharmaceutically acceptable salt thereof comprising the steps of:

(a) adding an inorganic salt forming agent to a solvent to form a linked pro-drug salt forming solution;

(b) adding the salt forming solution to a mixture of an ARB and a NEPi such that the ARB and NEPi form a linked pro-drug; and

(c) isolating the linked pro-drug.

Preferably, the components are added in an equivalent amount.

The inorganic salt forming agent includes, but is not limited to, calcium hydroxide, zinc hydroxide, calcium methoxide, calcium acetate, calcium hydrogen carbonate, calcium formate, magnesium hydroxide, magnesium acetate, magnesium formate and magnesium hydrogen carbonate, sodium hydroxide, sodium methoxide, sodium acetate, sodium formate. The inorganic salt forming agent releases the linking moiety into the solvent such that when an ARB and a NEPi are present a linked pro-drug is formed.

Solvents included in the scope of the present invention include, but are not limited to, solvents in which the ARB, NEPi and inorganic salt forming agent preferably exhibit a lower solubility that allows the linked pro-drug to crystallize. Such solvents may comprise, but are not limited to, water, methanol, ethanol, 2-propanol, ethylacetate, methyl-*t*-butylether, acetonitrile, toluene, and methylene chloride and mixtures of such solvents.

The inorganic salt forming agent and the solvent when combined should have a pH which promotes linked pro-drug formation. The pH may be between about 2 and about 6, preferably between about 3 and about 5, most preferably between 3.9 and 4.7.

The linked pro-drug is isolated by crystallization and chromatography. Specific types of chromatography include, e.g., ligand specific resin chromatography, reverse phase resin chromatography and ion-exchange resin chromatography.

A specific example comprises contacting a divalent salt of one component with a mono-valent salt of the other component of the linked pro-drug. Specifically the mixed salt of valsartan and a mono-basic NEPi are synthesized by contacting the calcium salt of valsartan with the sodium salt of the NEPi component. Isolation of the desired mixed salt is carried out by selective crystallization or chromatography using ligand specific resins, reverse phase resins or ion-exchange resins. Similarly this process can be conducted with a monovalent salt of both components, such as the sodium salt of both components.

In another embodiment of this aspect of the invention, a co-crystal of the linked pro-drug is obtained. In a method of making a linked pro-drug co-crystal the inorganic salt forming agent is replaced with a neutral molecule which provides hydrogen binding properties. The solvent may be part of the molecular packing and be trapped in the crystal lattice.

In a preferred embodiment of the third aspect, the present invention is directed to a method of preparing a dual-acting compound comprising

(a) an angiotensin receptor antagonist;

(b) a neutral endopeptidase inhibitor (NEPi); and optionally

(c) a pharmaceutically acceptable cation;

said method comprising the steps of:

(i) dissolving an angiotensin receptor antagonist and a neutral endopeptidase inhibitor (NEPi) in a suitable solvent;

(ii) dissolving a basic compound of Cat in a suitable solvent, wherein Cat is a cation;

(iii) combining the solutions obtained in steps (i) and (ii);

(iv) precipitation of the solid, and drying same to obtain the dual-acting compound; or alternatively

obtaining the dual-acting compound by exchanging the solvent(s) employed in steps (i) and (ii) by

(iva) evaporating the resulting solution to dryness;

(va) re-dissolving the solid in a suitable solvent;

(via) precipitation of the solid and drying same to obtain the dual-acting compound.

The details regarding the complex, including the ARB, the NEPi and the cation, are as described above with regard to the first embodiment of the invention.

Preferably, in step (i) the ARB and the NEPi are added in an equivalent molar amount. Both the ARB and the NEPi are preferably used in the free form. The solvent used in step (i) may be any solvent that allows dissolution of both the ARB and the NEPi. Preferred solvents include those mentioned above, namely water, methanol, ethanol, 2-propanol, acetone, ethyl acetate, isoprapyl acetate, methyl-*t*-butylether, acetonitrile, toluene, DMF, NMF and methylene chloride and mixtures of such solvents, such as ethanol-water, methanol-water, 2-propanol-water, acetonitrile-water, acetone-water, 2-propanol-toluene, ethyl acetate-heptane, isopropyl acetate-acetone, methyl-t-butyl ether-heptane, methyl-t-butyl ether-ethanol, ethanol-heptane, acetone-ethyl acetate, actetone-cyclohexane, toluene-heptane, more preferably acetone.

Preferably, in step (ii) the basic compound of Cat is a compound capable of forming a salt with the acidic functionalities of the ARB and the NEPi. Examples include those mentioned above, such as calcium hydroxide, zinc hydroxide, calcium methoxide, calcium ethoxide, calcium acetate, calcium hydrogen carbonate, calcium formate, magnesium hydroxide, magnesium acetate, magnesium formate, magnesium hydrogen carbonate, sodium hydroxide, sodium carbonate, sodium hydrogen carbonate, sodium methoxide, sodium ethoxide, sodium acetate, sodium formate, potassium hydroxide, potassium carbonate, potassium hydrogen carbonate, potassium methoxide, potassium ethoxide, potassium acetate, potassium formate, ammonium hydroxide, ammonium methoxide, ammonium ethoxide, and ammonium carbonate. Perchlorates may also be used. Amine bases or salt forming agents such a those mentioned above may also be used, in particular benzathine, L-arginine, cholin, ethylene diamine, L-lysine or piperazine. Typically an inorganic base is

employed with Cat as specified herein. More preferably, the basic compound is (Cat)OH, $(Cat)_2CO_3$, $(Cat)HCO_3$, still more preferably Cat(OH), such as NaOH. The basic compound is employed in an amount of at least 3 equivalents relative to either the ARB or the NEPi, preferably it is employed in stoichiometric amount to obtain the dual-acting compound, in particular the complex with three cations. The solvent used in step (ii) may be any solvent or mixtures of solvents that allow dissolution of Cat(OH). Preferred solvents include water, methanol, ethanol, 2-propanol, acetone, ethylacetate, isopropyl acetate, methyl-*t*-butylether, acetonitrile, toluene, and methylene chloride and mixtures of such solvents, more preferably water.

In step (iii) the solutions obtained in steps (i) and (ii) are combined. This can take place by adding the solution obtained in step (i) to the solution obtained in step (ii) or vice versa, preferably, the solution obtained in step (ii) to the solution obtained in step (i).

According to the first alternative, once combined and preferably mixed, the dual-acting compound, in particular the complex precipitates in step (iv). This mixing and precipitation is typically effected by stirring the solutions for an appropriate amount of time such as 20 min to 6 h, preferably 30 min to 3 h, more preferably 2 h, at room temperature. It is advantageous to add seeds of the dual acting compound. This method facilitates precipitation.

In step (iv) according to this first alternative, a co-solvent is typically added. The co-solvent employed is a solvent in which the ARB and the NEPi in the complexed form exhibit a lower solubility that allows the compound to precipitate. Distillation, either continuous or stepwise, with replacement by this co-solvent results in a mixture predominantly of the co-solvent. Preferred solvents include ethanol, 2-propanol, acetone, ethylacetate, isopropyl acetate, methyl-*t*-butylether, acetonitrile, toluene, and methylene chloride and mixtures of such solvents, more preferably isopropyl acetate. Preferably, a minimum amount of solvent is employed to facilitate precipitation. The solid is collected, e.g. by filtration, and is dried to obtain the dual-acting compound, in particular the complex in accordance with the present invention. The drying step can be performed at room temperature or elevated temperature such as 30 to 60 °C, preferably 30 to 40 °C. Reduced pressure can be employed to facilitate removal of the solvent, preferably, drying is effected at ambient pressure or reduced pressure of e.g. 10 to 30 bar, such as 20 bar.

According to a second alternative, once combined and preferably mixed, the dual-acting compound, in particular the complex the mixture preferably forms a clear solution. This mixing is typically effected by stirring the solutions for an appropriate amount of time such as 20 min to 6 h, preferably 30 min to 3 h, more preferably 1 h, at room temperature. If necessary, the temperature may be raised so as to ensure a clear solution.

The obtained mixture is then further treated by solvent exchange to obtain the dual-acting compound, in particular the complex.

In step (iva) according to this second alternative, the solution is preferably evaporated to dryness at elevated temperatures such as > room temperature to 50 °C, more preferably 30 to 40 °C.

Preferably, in step (va) the solvent or solvent mixture employed is a solvent in which the ARB and the NEPi in the complexed form exhibit a lower solubility that allows the dual-acting compound, in particular the complex to precipitate. Preferred solvents include the ones mentioned above for step (i), such as water, ethanol, 2-propanol, acetone ethylacetate, isopropyl acetate, methyl-*t*-butylether, acetonitrile, toluene, and methylene chloride and mixtures of such solvents, more preferably isopropyl acetate. Preferably, a minimum amount of solvent or solvent mixture is employed to facilitate precipitation.

In step (via) precipitation can take place at room temperature. It can be effected by leaving the mixture standing or by agitating the mixture, preferably by agitating it. This is preferably effected by stinring and/or sonication. After precipitation, the solid is collected, e.g. by filtration, and is dried to obtain the compound in accordance with the present invention. The drying step can be performed at room temperature or elevated temperature such as 30 to 60 °C, preferably room temperature. Reduced pressure can be employed to facilitate removal of the solvent, preferably, drying is effected at ambient pressure.

In a fourth aspect, this invention is directed to a method of treating or preventing a disease or condition, such as hypertension, heart failure (acute and chronic) congestive heart failure, left ventricular dysfunction and hypertrophic cardiomyopathy, diabetic cardiac myopathy, supraventricular and ventricular arrhythmias, atrial fibrillation, atrial flutter, detrimental vascular remodeling, myocardial infarction and its sequelae, atherosclerosis, angina (unstable or stable), renal insufficiency (diabetic and non-diabetic), heart failure, angina

pectoris, diabetes, secondary aldosteronism, primary and secondary pulmonary hypertension, renal failure conditions, such as diabetic nephropathy, glomerulonephritis, scleroderma, glomerular sclerosis, proteinuria of primary renal disease, and also renal vascular hypertension, diabetic retinopathy, other vascular disorders, such as migraine, peripheral vascular disease, Raynaud's disease, luminal hyperplasia, cognitive dysfunction (such as Alzheimer's), glaucoma and stroke comprising administering the afore-mentioned combination, linked pro-drug or he dual-acting compound, in particular the complex to a subject in need of such treatment.

The combination, linked pro-drug or he dual-acting compound, in particular the complex of the first embodiment may be administered alone or in the form of a pharmaceutical composition according to the second embodiment. Information regarding dosing, i.e., the therapeutically effective amount, etc., is the same regardless of how the combination, linked pro-drug or he dual-acting compound, in particular the complex is administered.

The combination, linked pro-drug or he dual-acting compound, in particular the complex is beneficial over a combination of ARBs or neutral endopeptidase inhibitors alone or other ARB/NEPi combinations with regard to use as first line therapy, ease of formulation and ease of manufacture.

Specific embodiments of the invention will now be demonstrated by reference to the following examples. It should be understood that these examples are disclosed solely by way of illustrating the invention and should not be taken in any way to limit the scope of the present invention.

Example 1

Preparation of [valsartan ((2*R*,4*S*)-5-biphenyl4-yl-5-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester]Na_3 • 2.5 H_2O

The dual-acting compound of valsartan and (2*R*,4*S*)-5-biphenyl4-yl-5-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester is prepared by dissolving 0.42g of (2*R*,4*S*)-5-biphenyl4-yl-5-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester free acid (~95% purity) and 0.41 g of valsartan free acid in 40ml acetone. Separately, 0.111g of NaOH are dissolved in 7ml H_2O. The two solutions are combined and stirred at room temperature for 1 hour and a clear solution was obtained. The solution is evaporated at 35°C

to yield a glassy solid. The glassy solid residue is then charged with 40ml acetone and the resulting mixture is stirred and sonicated until precipitation occurred (~ 5 minutes). The precipitate was filtered and the solid is dried at room temperature in open air for 2 days until a constant mass of the crystalline solid is obtained.

Characterization by various methods could confirm the presence of both valsartan and (2*R*,4*S*)-5-biphenyl4-yl-5-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester and complex formation in contrast to a simple physical mixture. Significant spectral peaks for the complex are observed e.g. in the XRPD, IR, and Raman spectroscopy which are not present for the physical mixture. See below for details on the characterization.

Example 2

Alternative Preparation of [valsartan ((2*R*,4*S*)-5-biphenyl4-yl-5-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester]Na_3 • 2.5 H_2O

The dual acting compound of valsartan and (2*R*,4*S*)-5-biphenyl4-yl-5-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester is prepared by dissolving 22.96 mmol of (2*R*,4*S*)-5-biphenyl4-yl-5-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester free acid (~95% purity) and valsartan (10.00 g; 22.96 mmol) in acetone (300 mL). The suspension is stirred at room temperature for 15 min to obtain a clear solution. A solution of NaOH (2.76 g; 68.90 mmol) in water (8 mL) water is then added to this solution over a period of 10 min. Solids start to precipitate in 10 min. Alternatively, precipitation can be induced by seeding. The suspension is stirred at 20-25 °C for 2 h. This suspension is concentrated at 15-30 °C under reduced pressure (180-250 mbar) to a batch volume of ~150 mL. Isopropyl acetate (150 mL) is then added to the batch and the suspension is concentrated again at 15-30 °C under reduced pressure (180-250 mbar) to a batch volume of ~150 mL. This operation (addition of 150 mL of isopropyl acetate to the batch and concentration) is repeated once again. The suspension is stirred at 20-25 °C for 1 h. The solids are collected by filtration under nitrogen over a Büchner funnel, washed with isopropyl acetate (20 mL), and dried at 35 °C under reduced pressure (20 mbar) to afford the compound.

Characterization revealed the same product as in Example 1.

Example 3

Alternative Preparation of [valsartan ((2*R*,4*S*)-5-biphenyl4-yl-5-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester]Na_3 • 2.5 H_2O using seeding

A reactor is charged with 2.00 kg (2,323 mmol) of AHU377 calcium salt and 20 L of isopropyl acetate. The suspension is stirred at 23 ± 3 °C, and 4.56 L of 2 *N* HCl was added. The mixture is stirred at 23 ± 3 °C for 15 min to obtain a clear two-phase solution. The organic layer is separated and washed with 3 x 4.00 L of water. The organic layer is concentrated at 30-100 mbar and 22 ± 5 °C to ~3.5 L (3.47 kg) of AHU377 free acid isopropyl acetate solution as a colorless solution.

To the above reactor containing ~3.5 L (3.47 kg) of AHU377 free acid isopropyl acetate solution is added 1.984 kg (4,556 mmol) of Valsartan and 40 L of acetone. The reaction mixture is stirred at 23 ± 3 °C to obtain a clear solution which is filtered into a reactor. To the reaction mixture is added a solution of 547.6 g (13,690 mmol) of NaOH in 1.0 L of water at 23 ± 3 °C (which was pre-cooled to 20 ± 5 °C and in-line filtered) over a period of 15-30 min while maintaining the internal temperature at 20-28 °C (slightly exothermic). The flask is rinsed with 190 mL of water and added into the reaction mixture. The reaction mixture is stirred at 23 ± 3 °C for 15 min and a slurry of 4.0 g of [valsartan ((2*R*,4*S*)-5-biphenyl4-yl-5-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester]Na_3 • 2.5 H_2O seeds in 50 mL of isopropyl acetate is added. The mixture is stirred at 23 ± 3 °C for 2 h to obtain a suspension. The suspension is heated to an internal temperature at 40 ± 3 °C over a period of 20 min and 20 L of isopropyl acetate is added over a period of 20 min while maintaining the internal temperature at 40 ± 3 °C . The suspension is stirred at this temperature for an additional 30 min. The mixture is concentrated at an internal temperature at 35 ± 5 °C (Tj 45 ± 5 °C) under reduced pressure (200-350 mbar) to ~35 L of a white slurry (solvent collected: ~25 L). Then 30 L of isopropyl acetate is added the mixture is concentrated at an internal temperature at 35 ± 5 °C (T_j 45 ± 5 °C) under reduced pressure (100-250 mbar) to ~30 L of a white slurry (solvent collected: ~40 L). Again 40 L of isopropyl acetate is added and the mixture is concentrated at an internal temperature at 35 ± 5 °C (Tj 45 ± 5 °C) under reduced pressure (100*200 mbar) to ~30 L of a white slurry (solvent collected: ~30 L). The reaction

mixture is cooled to 23 ± 3 °C over ~20 min and stirred at this temperature for an additional 3 h. The solid is collected by filtration under nitrogen over a polypropylene pad on Büchner tunnel. The solid is washed with 2 X 5 L of isopropyl acetate and dried at 35 °C under reduced pressure (20 mbar) until isopropyl acetate content <0.5% to afford the above product as a white solid.

Characterization revealed the same product as in Example 1.

X-ray powder diffraction

Calculation of the interlattice plane intervals from the X-ray powder pattern taken with a Scintag XDS2000 powder diffractometer for the most important lines for the sample give the following results:

d in [A] : 21.2(s), 17.0(w), 7.1 (s), 5.2(w), 4.7(w), 4.6(w), 4.2(w), 3.5(w), 3.3(w)

The error margin for all interlattice plane intervals is ± 0.1 A. The intensities of the peaks are indicated as follows: (w) = weak; (m) = medium; and (st) = strong.

Average values 2Θ in [°] are indicated (error limit of ±0.2)

4.5, 5.5, 5.6, 9.9, 12.8, 15.7, 17.0, 17.1, 17.2, 18.3, 18.5, 19.8, 21.5, 21.7, 23.2, 23.3, 24.9, 25.3, 27.4, 27.9, 28.0, 30.2.

Elemental analysis

Elemental analysis gives the following measured values of the elements present in the sample. The findings of the elemental analysis, within the error limits, correspond to the overall formula of $H_{55}N_8O_8Na_2)\cdot 2.5H_2O$

Found	C: 60.05%	H: 6.24%	N: 8.80%
Calculated*	C: 60.18%	H: 6.31%	N: 8.77%

Infrared spectroscopy

The infrared absorption spectrum for the sample obtained using Attenuated Total Reflection Fourier Transform Infrared (ATR-FTIR) spectrometer (Nicolet Magna-IR 560) shows the following significant bands, expressed in reciprocal wave numbers (cm^{-1}):

2956 (w), 1711 (st), 1637 (st), 1597 (st), 1488 (w), 1459 (m), 1401 (st), 1357 (w), 1295 (m), 1266 (m), 1176 (w), 1085 (m), 1010 (w), 1942(w), 907 (w), 862 (w), 763 (st), 742 (m), 698 (m), 533 (st).

The error margin for all absorption bands of ATR-IR is ± 2 cm^{-1}.

The intensities of the absorption bands are indicated as follows: (w) = weak; (m) = medium; and (st) = strong intensity.

Raman spectroscopy

Raman spectrum of the sample measured by dispersive Raman spectrometer with 785 nm laser excitation source (Kaiser Optical Systems, Inc.) shows the following significant bands expressed in reciprocal wave numbers (cm^{-1}):

3061 (m), 2930 (m, broad), 1612 (st), 1523 (m), 1461 (w), 1427 (w), 1287 (st), 1195 (w), 1108 (w), 11053 (w), 1041 (w), 1011 (w), 997 (m), 866(w), 850 (w), 822 (w), 808 (w), 735 (w), 715 (w), 669 (w), 643 (w), 631 (w), 618 (w), 602 (w), 557 (w), 522 (w), 453 (w), 410 (w), 328 (w).

The error margin for all Raman bands is ± 2 cm^{-1}.

The intensities of the absorption bands are indicated as follows: (w) = weak; (m) = medium; and (st) = strong intensity.

High Resolution CP-MAS ^{13}C NMR Spectroscopy

The samples are investigated by high resolution CP-MAS (Cross Polarization Magic Angle Spinning) ^{13}C NMR spectroscopy using a Bruker-BioSpin AVANCE 500 NMR spectrometer equipped with a 300 Watt high power ^{1}H, two 500 Watt high power X-amplifiers, necessary high power pre-amplifiers, a "MAS" controller and a 4 mm BioSolids high resolution Bruker probe.

Each sample is packed in a 4mm ZrO_2 rotor. Critical experimental parameters are 3 msec ^{13}C contact times, 12 KHz spinning speed at the magic angle,. a "ramped" contact time, using a "SPINAL64" ^{1}H decoupling scheme, a recycle delay of 10 secs and 1024 scans at 293 deg K. The chemical shifts are referenced with respect to an external Glycine carbonyl at 176.04 ppm.

High resolution CP-MAS ^{13}C NMR shows the following significant peaks (ppm):

179.0, 177.9 177.0, 176.7, 162.0, 141.0, 137.2, 129.6, 129.1, 126.7, 125.3, 64.0, 61.5, 60.4, 50.2, 46.4, 40.6, 38.6, 33.5, 32.4, 29.8, 28.7, 22.3, 20.2, 19.1, 17.8, 16.8, 13.1, 12.1, 11.1.

A physical mixture of individual Na salts of Valsartan and (2*R*,4*S*)-5-biphenyl4-yl-5-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester revealed a simple inert mixture of the two salts. However, the sample of the complex prepared in Example 1 exhibited distinctly different spectral features in comparison to a 1:1 mixture of the sodium salts.

DSC and TGA

As measured by differential scanning calorimetry (DSC) using Q1000 (TA Instruments) instrument, the melting onset temperature and the peak maximum temperature for the sample is observed at 139°C and 145°C, respectively.

As shown by DSC and thermogravimetric analysis (TGA), upon heating, the water of hydration is released in two steps: the first step occurs below 100°C and the second step above 120°C.

Both DSC and TGA instruments are operated at a heating rate of 10 K/min.

Example 4

Preparation of Linked Pro-Drug of Scheme (1)

Linked pro-drug of valsartan calcium salt and (2*R*,4*S*)-5-biphenyl4-yl-5-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester is prepared at room temperature by dissolving 114 mg of the calcium salt of valsartan and 86 mg of (2*R*,4*S*)-5-biphenyl4-yl-5-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester free acid in 2 mL methanol, followed by methanol evaporation. The glassy solid residue is then charged with 3 mL of acetonitrile and equilibrated by 10 min. sonication, followed by 20 hours of magnetic stirring.

Approximately 120 mg of white solids are collected by filtration. Liquid chromatography (LC) and elemental analysis indicate 1:1 ratio between (2*R*,4*S*)-5-biphenyl4-yl-5-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester and valsartan. The sample is amorphous by X-ray powder diffraction.

Preparation of Linked Pro-Drug of Scheme (2)

Linked pro-drug of valsartan calcium salt and (2*R*,4*S*)-5-biphenyl4-yl-5-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester and Tris is prepared at room temperature by dissolving 57 mg of the calcium salt of valsartan, 43 mg of (2*R*,4*S*)-5-biphenyl4-yl-5-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester free acid, and 12.6 mg of *tris*(hydroxymethyl)aminomethane (Tris) in 2 mL methanol, followed by methanol evaporation. The glassy solid residue is then charged with 3 mL of acetonitrile and equilibrated by 10 min. sonication, followed by 20 hours of magnetic stirring. Approximately 83 mg of white solids are collected by filtration. LC and elemental analysis indicate 1:1 ratio between (2*R*,4*S*)-5-biphenyl4-yl-5-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester and valsartan. The sample is amorphous by X-ray powder diffraction.

While the invention has been described above with reference to specific embodiments thereof, it is apparent that many changes, modifications, and variations can be made without departing from the inventive concept disclosed herein. Accordingly, it is intended to embrace all such changes, modifications and variations that fall within the spirit and broad scope of the appended claims. All patent applications, patents, and other publications cited herein are incorporated by reference in their entirety.

Exhibit 03

AMENDED CLAIMS (CLEAN COPY)

We claim:

1. A compound comprising the Angiotensin Receptor Antagonist valsartan and the NEP Inhibitor (2R,4S)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2- methyl-pentanoic acid ethyl ester having the formula [((S)-N-valeryl-N-{[2'-(1 H-tetrazole-5-yl)-biphenyl-4-yl]-methyl}-valine) ((2R,4S)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester)]Na_3 • x H_2O, wherein x is 0 to 3.

2. The compound as claimed in claim 1, wherein x is 2.5.

3. The compound as claimed in claim 2, which is trisodium [3-((1S,3R)-1- biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(S)-3'- methyl-2'-(pentanoyl{2''-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate] hemipentahydrate.

4. The compound as claimed in claim 1-3, wherein the compound is in crystalline form.

5. The compound as claimed in any one of claims 1 to 4 as and when used in a preparation of pharmaceutical composition or medicament.

6. A method of preparing the compound as claimed in any of claims 1 to 4, said method comprising the steps of:

(i) dissolving (S)-N-valeryl-N-{[2'-(1H-tetrazole-5-yl)-biphenyl-4-yl]-methyl}-valine or a salt thereof and (2R,4S)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2- methylpentanoic acid ethyl ester or a salt thereof in a suitable solvent;

(ii) dissolving a basic Na compound in a suitable solvent;

(iii) combining the solutions obtained in steps (i) and (ii);

(iv) precipitation of the solid, and drying same to obtain the dual-acting compound; or alternatively

obtaining the compound by exchanging the solvent(s) employed in steps (i) and (ii) by

(iva) evaporating the resulting solution to dryness; (va) re-dissolving the solid in a suitable solvent;

(via) precipitation of the solid and drying same to obtain the compound.

7. The method as claimed in claim 6 wherein the suitable solvent in steps (i) and/or (iva) is acetone.

8. The method as claimed in claims 6 or 7, wherein the basic Na compound is NaOH, Na_2CO_3, $NaHCO_3$, NaOMe, NaOAc or NaOCHO.

Dated this 6th day of June, 2020

Hemant Singh
Inttl Advocare
Agent for the Applicant

Exhibit 04

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
24 July 2003 (24.07.2003)

PCT

(10) International Publication Number
WO 03/059345 A1

(51) International Patent Classification[7]: A61K 31/41, 31/192, 31/216, A61P 9/12, 9/10, 13/12, 25/28, 3/10

(21) International Application Number: PCT/EP03/00415

(22) International Filing Date: 16 January 2003 (16.01.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/349,660 17 January 2002 (17.01.2002) US

(71) Applicant *(for all designated States except AT, US)*: **NOVARTIS AG** [CH/CH]; Lichtstrasse 35, CH-4056 Basel (CH).

(71) Applicant *(for AT only)*: **NOVARTIS PHARMA GMBH** [AT/AT]; Brunner Strasse 59, A-1230 Vienna (AT).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **WEBB, Randy, Lee** [US/US]; 17 Honeyman Drive, Flemington, NJ 08822 (US). **KSANDER, Gary, Michael** [US/US]; 342 Woolf Road, Milford, NJ 08848 (US).

(74) Agent: **GROS, Florent**; Novartis AG, Corporate Intellectual Property, Patent & Trademark Department, CH-4002 Basel (CH).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LT, LU, LV, MA, MD, MK, MN, MX, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SE, SG, SK, TJ, TM, TN, TR, TT, UA, US, UZ, VC, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 03/059345 A1

(54) Title: PHARMACEUTICAL COMPOSITIONS COMPRISING VALSARTAN AND NEP INHIBITORS

(57) Abstract: The invention relates a pharmaceutical composition comprising a combination of (i) the AT 1- antagonist valsartan or a pharmaceutically acceptable salt thereof and (ii) a NEP inhibitor or a pharmaceutically acceptable salt thereof and optionally a pharmaceutically acceptable carrier and to a method for the treatment or prevention of a condition or disease selected from the group consisting of hypertension, heart failure such as (acute and chronic) congestive heart failure, left ventricular dysfunction and hypertrophic cardiomyopathy, diabetic cardiac myopathy, supraventricular and ventricular arrhythmias, atrial fibrillation, atrial flutter, detrimental vascular remodeling, myocardial infarction and its sequelae, atherosclerosis, angina (whether unstable or stable), renal insufficiency (diabetic and non-diabetic), heart failure, angina pectoris, diabetes, secondary aldosteronism, primary and secondary pulmonary hypertension, renal failure conditions, such as diabetic nephropathy, glomerulonephritis, scleroderma, glomerular sclerosis, proteinuria of primary renal disease, and also renal vascular hypertension, diabetic retinopathy, the management of other vascular disorders, such as migraine, peripheral vascular disease, Raynaud's disease, luminal hyperplasia, cognitive dysfunction (such as Alzheimer's), glaucoma and stroke, comprising administering a therapeutically effective amount of the pharmaceutical composition to a mammal in need thereof.

PHARMACEUTICAL COMPOSITIONS COMPRISING VALSARTAN AND NEP INHIBITORS

Angiotensin II interacts with specific receptors on the surface of the target cell. It has been possible to identify receptor subtypes that are termed e.g. AT 1- and AT 2-receptors. In recent times great efforts have been made to identify substances that bind to the AT 1-receptor. Such active ingredients are often termed angiotensin II antagonists. Because of the inhibition of the AT 1-receptor such antagonists can be used e.g. as antihypertensives or for the treatment of congestive heart failure, among other indications. Angiotensin II antagonists are therefore understood to be those active ingredients which bind to the AT 1-receptor subtype.

Inhibitors of the renin angiotensin system are well known drugs that lower blood pressure and exert beneficial actions in hypertension and in congestive heart failure as described, for example, in N. Eng. J. Med. 316, 23 (1987) p. 1429-1435. A large number of peptide and non-peptide inhibitors of the renin angiotensin system are known, the most widely studied being the ACE inhibitors, which includes the drugs captopril, enalapril, lisinopril, benazepril and spirapril. Although a major mode of action of ACE inhibitors involves prevention of formation of the vasoconstrictor peptide Ang II, it has been reported in Hypertension, 16, 4 (1990) p. 363-370 that ACE cleaves a variety of peptide substrates, including the vasoactive peptides bradykinin and substance P. Prevention of the degradation of bradykinin by ACE inhibitors has been demonstrated, and the activity of the ACE inhibitors in some conditions has been reported in Circ. Res., 66, 1 (1990) p. 242-248 to be mediated by elevation of bradykinin levels rather than inhibition of Ang II formation. Consequently, it cannot be presumed that the effect of an ACE inhibitor is due solely to prevention of angiotensin formation and subsequent inhibition of the renin angiotensin system.

Neutral endopeptidase (EC 3.4.24.11; enkephalinase; atriopeptidase; NEP) is a zinc-containing metalloprotease that cleaves a variety of peptide substrates on the amino terminal side of aromatic amino acids. See Biochem. J., 241, (1987) p. 237-247. Substrates for this enzyme include, but are not limited to, atrial natriuretic factors (ANF, also known as ANP), brain natriuretic peptide (BNP), met and leu enkephalin, bradykinin, neurokinin A, and substance P.

ANPs are a family of vasodilator, diuretic and antihypertensive peptides which have been the subject of many recent reports in the literature, for example Annu. Rev. Pharm. Tox., 29, (1989) p. 23-54. One form, ANF 99-126, is a circulating peptide hormone which is released from the heart during conditions of cardiac distension. The function of ANF is to

maintain salt and water homeostasis as well as to regulate blood pressure. ANF is rapidly inactivated in the circulation by at least two processes: a receptor-mediated clearance reported in Am. J. Physiol., 256 (1989) p. R469-R475 and an enzymatic inactivation via NEP reported in Biochem. J., 243 (1987) p. 183-187. It has been previously demonstrated that inhibitors of NEP potentiate the hypotensive, diuretic, natriuretic and plasma ANF responses to pharmacological injection of ANF in experimental animals. The potentiation of ANF by two specific NEP inhibitors is reported by Sybertz et al. in J. Pharmacol. Exp. Ther. 250, 2 (1989) p. 624-631 and in Hypertension, 15, 2 (1990) p. 152-161, while the potentiation of ANF by NEP in general was disclosed in U.S. Patent No. 4,749,688. In U.S. Patent No. 4,740, 499 Olins disclosed the use of thiorphan and kelatorphan to potentiate atrial peptides. Moreover, NEP inhibitors lower blood pressure and exert ANF-like effects such as diuresis and increased cyclic guanosine 3',5'-monophosphate (cGMP) excretion in some forms of experimental hypertension. The antihypertensive action of NEP inhibitors is mediated through ANF because antibodies to ANF will neutralize the reduction in blood pressure.

Prolonged and uncontrolled hypertensive vascular disease ultimately leads to a variety of pathological changes in target organs such as the heart and kidney. Sustained hypertension can lead as well to an increased occurrence of stroke. Therefore, there is a strong need to evaluate the efficacy of antihypertensive therapy, an examination of additional cardiovascular endpoints, beyond those of blood pressure lowering, to get further insight into the benefits of combined treatment.

The nature of hypertensive vascular diseases is multifactorial. Under certain circumstances, drugs with different mechanisms of action have been combined. However, just considering any combination of drugs having different mode of action does not necessarily lead to combinations with advantageous effects. Accordingly, there is a need for more efficacious combination therapy which has less deleterious side effects.

In one aspect the present invention relates to pharmaceutical combinations comprising valsartan or pharmaceutically acceptable salts thereof and a neutral endopeptidase (NEP) inhibitor or a pharmaceutically effective salts thereof, optionally in the presence of a pharmaceutically acceptable carrier and pharmaceutical compositions comprising them.

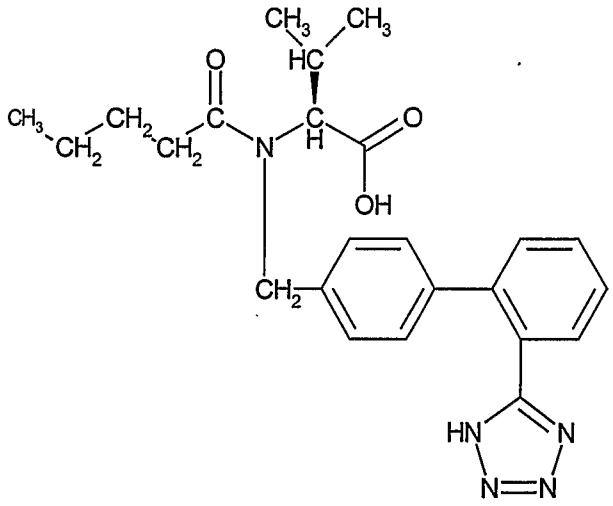
In another embodiment the present invention relates to methods of treating cardiac and renal related conditions by administration of the pharmaceutical composition comprising valsartan plus a NEP inhibitor or relates to the use of a pharmaceutical composition

comprising valsartan or pharmaceutically acceptable salts thereof and a neutral endopeptidase (NEP) inhibitor or a pharmaceutically effective salts thereof.

In another embodiment of the invention the present invention relates to a pharmaceutical composition comprising valsartan or pharmaceutically acceptable salts thereof and a neutral endopeptidase (NEP) inhibitor or a pharmaceutically effective salts thereof and a diuretic, especially hydrochlorothiazide.

Valsartan is the AT 1 receptor antagonist (S) –N-(1-carboxy-2-methyl-prop-1-yl)-N-pentanoyl-N-[2;(1H-tetrazol-5-yl)biphenyl-4-yl-methyl]amine of formula (I)

and is disclosed in EP 0443983 A and United States Patent 5,399,578, the disclosures of

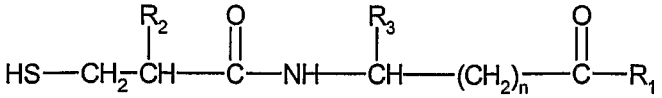


(I)

which are incorporated herein in their entirety as if set forth herein.

A NEP inhibitor useful in said combination is a compound of the formula (II)

(II)



and pharmaceutically acceptable salts thereof wherein:

R_2 is alkyl of 1 to 7 carbons, trifluoromethyl, phenyl, substituted phenyl, -$(CH_2)_{1\ to\ 4}$-phenyl, or -$(CH_2)_{1\ to\ 4}$-substituted phenyl;

R_3 is hydrogen, alkyl of 1 to 7 carbons, phenyl, substituted phenyl, -$(CH_2)_{1\ to\ 4}$-phenyl, or -$(CH_2)_{1\ to\ 4}$-substituted phenyl;

R_1 is hydroxy, alkoxy of 1 to 7 carbons, or NH_2;

n is an integer from 1 to 15; and

the term substituted phenyl refers to a substituent selected from lower alkyl of 1 to 4 carbons, lower alkoxy of 1 to 4 carbons, lower alkylthio of 1 to 4 carbons, hydroxy, Cl, Br, or F.

Preferred selective neutral endopeptidase inhibitors of formula II include compounds wherein:

R_2 is benzyl;

R_3 is hydrogen;

n is an integer from 1 to 9; and

R_1 is hydroxy.

Even more preferred selective neutral endopeptidase inhibitors of formula II are reported in the literature as SQ 28,603 which is the compound of formula II wherein:

R_2 is benzyl;

R_3 is hydrogen;

n is one; and

R_1 is hydroxy.

The preparation of the selective neutral endopeptidase inhibitors of formula II wherein R_2 is other than trifluoromethyl are disclosed by Delaney et al. in U.S. Patent No. 4,722,810. The preparation of the selective neutral endopeptidase inhibitors of formula II wherein R_2 is trifluoromethyl are disclosed by Delaney et al in U.S. Patent No. 5,223,516.

NEP inhibitors within the scope of the present invention include compounds disclosed in U.S. Patent No. 4,610,816, herein incorporated by reference, including in particular N-[N-[1(S)-carboxyl-3-phenylproplyl]-(S)-phenylalanyl]-(S)-isoserine and N-[N-[((1S)-carboxy-2-phenyl)ethyl]-(S)-phenylalanyl]-β-alanine; compounds disclosed in U.S. Patent No. 4,929,641, in particular N-[2(S)-mercaptomethyl-3-(2-methylphenyl)-propionyl]methionine; SQ 28603 (N-[2-(mercaptomethyl)-1-oxo-3-phenylpropyl]-β-alanine), disclosed in South African Patent Application 84/0670; UK 69578 (cis-4-[[[1-[2-carboxy-3-(2-methoxyethoxy)propyl]-cyclopentyl]carbonyl]amino]-cyclohexanecarboxylic acid) and its active enantiomer(s); thiorphan and its enantiomers; retro-thiorphan; phosphoramidon; and SQ 29072 (7-[[2-(mercaptomethyl)-1-oxo-3-phenylpropyl]amino]-heptanoic acid). Also suitable for use are any pro-drug forms of the above-listed NEP inhibitors, e.g., compounds in which one or more carboxylic acid groups are esterified.

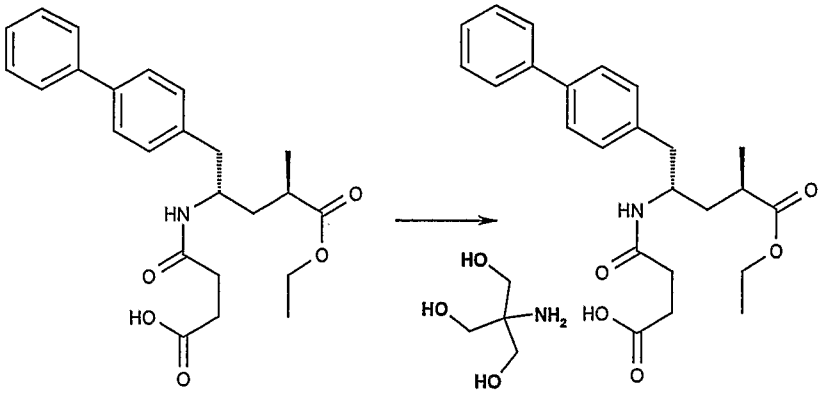
NEP inhibitors within the scope of the present invention also include the compounds disclosed in U.S. Patent No. 5,217,996, particularly, N-(3-carboxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester and N-(3-carboxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid or in each case a pharmaceutically acceptable salt thereof; the compounds disclosed in EP 00342850, particularly (S)-cis-4-[1-[2-(5-indanyloxycarbonyl)-3-(2-methoxyethoxy)propyl]-1-cyclopentanecarboxamido]-1-cyclohexanecarboxylic acid; the compounds disclosed in GB 02218983, particularly 3-(1-[6-endo-hydroxymethylbicyclo[2,2,1]heptane-2-exo-carbamoyl]cyclopentyl)-2-(2-methoxyethyl)propanoic acid; the compounds disclosed in WO 92/14706, particularly N-(1-(3-(N-t-butoxycarbonyl-(S)-prolylamino)-2(S)-t-butoxy-carbonylpropyl)cyclopentanecarbonyl)-O-benzyl-(S)-serine methyl ester; the compounds disclosed in EP 00343911; the compounds disclosed in JP 06234754; the compounds disclosed in EP 00361365, particularly 4-[[2-(Mercaptomethyl)-1-oxo-3-phenylpropyl]amino]benzoic acid; the compounds disclosed in WO 90/09374, particularly 3-[1-(Cis-4-carboxycarbonyl-cis-3-butylcyclohexyl-r-1-carboamoyl)cyclopentyl]-2S-(2-methoxyethoxymethyl)propanoic acid; the compounds disclosed in JP 07157459, particularly N-((2S)-2-(4-biphenylmethyl)-4-carboxy-5-phenoxyvaleryl)glycine; the compounds disclosed in WO 94/15908 particularly N-(1-(N-hydroxycarbamoylmethyl)-1-cyclopentanecarbonyl)-L-phenylalanine; the compounds disclosed in U.S. Patent No. 5,273,990 particularly (S)-(2-biphenyl-4-yl)-1-(1H-tetrazol-5-yl)ethylamino) methylphosphonic acid; the compounds disclosed in U.S. Patent No. 5,294,632 particularly (S)-5-(N-(2-(phosphonomethylamino)-3-(4-biphenyl)propionyl)-2-aminoethyl)tetrazole; the compounds disclosed in U.S. Patent No. 5,250,522, particularly β-Alanine, 3-[1,1'-biphenyl]-4-yl-N-[diphenoxyphosphinyl)methyl]-L-alanyl; the compounds disclosed in EP 00636621, particularly N-(2-carboxy-4-thienyl)-3-mercapto-2-benzylpropanamide; the compounds disclosed in WO 93/09101, particularly 2-(2-mercaptomethyl-3-phenylpropionamido)thiazol-4-ylcarboxylic acid; the compounds disclosed in EP 00590442 particularly ((L)-(1-((2,2-dimethyl-1,3-dioxolan-4-yl)-methoxy)carbonyl)-2-phenylethyl)-L-phenylalanyl)-β-alanine, N-[N-[(L)-[1-[(2,2-dimethyl-1,3-dioxolan-4-yl)-methoxy]carbonyl]-2-phenylethyl]-L-phenylalanyl]-(R)-alanine, N-[N-[(L)-1-carboxy-2-phenylethyl]-L-phenylalanyl]-(R)-alanine, N-[2-acetylthiomethyl-3-(2-methyl-phenyl)propionyl]-methionine ethyl ester, N-[2-mercaptomethyl-3-(2-methylphenyl)propioyl]-methionine, N-[2(S)-mercaptomethyl-3-(2-methylphenyl)propanoyl]-(S)-isoserine, N-(S)-[3-mercapto-2-(2-methylphenyl)propionyl]-(S)-2-methoxy-(R)-alanine, N-[1-[[1(S)-benzyloxycarbonyl-3-

phenylpropyl]amino]cyclopentylcarbonyl]-(S)-isoserine, N-[1-[[1(S)-carbonyl-3-phenylpropy]amino]-cyclopentylcarbonyl]-(S)-isoserine, 1,1'-[dithiobis-[2(S)-(2-methylbenzyl)-1-oxo-3,1-propanediyl]]-bis-(S)-isoserine, 1,1'-[dithiobis-[2(S)-(2-methylbenzyl)-1-oxo-3,1-propanediyl]]-bis-(S)-methionine, N-(3-phenyl-2-(mercaptomethyl)-propionyl)-(S)-4-(methylmercapto)methionine, N-[2-acetylthiomethyl-3-phenyl-propionyl]-3-aminobenzoic acid,
N-[2-mercaptomethyl-3-phenyl-propionyl]-3-aminobenzoic acid, N-[1-(2-carboxy-4-phenylbutyl)-cyclopentanecarbonyl]-(S)-isoserine, N-[1-(acetylthiomethyl)cyclopentane-carbonyl]-(S)-methionine ethyl ester, 3(S)-[2-(acetylthiomethyl)-3-phenyl-propionyl]amimo-ε-caprolactam; and the compounds disclosed in WO 93/10773 particularly N-(2-acetylthiomethyl-3-(2-methylphenyl)propionyl)-methionine ethyl ester.

A diuretic is, for example, a thiazide derivative selected from the group consisting of chlorothiazide, hydrochlorothiazide, methylclothiazide, and chlorothalidon. The most preferred is hydrochlorothiazide.

The compounds to be combined can be present as pharmaceutically acceptable salts. If these compounds have, for example, at least one basic center, they can form acid addition salts. Corresponding acid addition salts can also be formed having, if desired, an additionally present basic center. The compounds having at least one acid group (for example COOH) can also form salts with bases. Corresponding internal salts may furthermore be formed, if a compound comprises e.g. both a carboxy and an amino group.

With respect to N-(3-carboxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester, preferred salts include the sodium salt disclosed in U.S. Patent No. 5,217,996, the triethanolamine salt and the tris(hydroxymethyl)aminomethane salt. Preparation of the triethanolamine salt and the tris(hydroxymethyl)aminomethane salt may be carried out as follows:
Triethanolamine - To N-(3-carboxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester (349 mg, 0.848 mmol) is added 5 ml of ethyl ether and 0.113 ml (0.848 mmol) of triethanolamine in 1 ml of ethyl acetate. The solid was collected and dried melting at 69-71 °C



Tris(hydroxymethyl) aminomethane - To N-(3-carboxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester (3.2 g (7.78 mmol) is added 32 ml of ethyl acetate and 940 mg (7.78 mmol) tris(hydroxymethyl)aminomethane. The suspension is diluted with 45 ml of ethyl acetate and refluxed overnight (~20 hr). The reaction is cooled to 0°C, filtered, solid washed with ethyl acetate and dried melting at 114-115 °C.

The salts of N-(3-carboxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester formed with triethanolamine and tris(hydroxymethyl) aminomethane are novel and can be used as NEP inhibitors. Another embodiment of the present invention are said new salts, their use as NEP inhibitors, especially for preventing and treating of conditions and disease associated with the inhibition on NEP, pharmaceutical composition comprising these salts and their combination with valsartan, especially for the treatment of conditions and diseases as disclosed for the combinations of the present invention hereinbefore or hereinafter.

It has surprisingly been found that, a combination of valsartan and a NEP inhibitor achieves greater therapeutic effect than the administration of valsartan, ACE inhibitors or NEP inhibitors alone and promotes less angioedema than is seen with the administration of a vasopeptidase inhibitor alone. Greater efficacy can also be documented as a prolonged duration of action. The duration of action can be monitored as either the time to return to baseline prior to the next dose or as the area under the curve (AUC) and is expressed as the product of the change in blood pressure in millimeters of mercury (change in mmHg) and the duration of the effect (minutes, hours or days).

Further benefits are that lower doses of the individual drugs to be combined according to the present invention can be used to reduce the dosage, for example, that the dosages need not only often be smaller but are also applied less frequently, or can be used

to diminish the incidence of side effects. The combined administration of valsartan or a pharmaceutically acceptable salt thereof and a NEP inhibitor or a pharmaceutically acceptable salt thereof results in a significant response in a greater percentage of treated patients, that is, a greater responder rate results, regardless of the underlying etiology of the condition. This is in accordance with the desires and requirements of the patients to be treated.

It can be shown that combination therapy with valsartan and a NEP inhibitor results in a more effective antihypertensive therapy (whether for malignant, essential, reno-vascular, diabetic, isolated systolic, or other secondary type of hypertension) through improved efficacy as well as a greater responder rate. The combination is also useful in the treatment or prevention of heart failure such as (acute and chronic) congestive heart failure, left ventricular dysfunction and hypertrophic cardiomyopathy, diabetic cardiac myopathy, supraventricular and ventricular arrhythmias, atrial fibrillation, atrial flutter or detrimental vascular remodeling. It can further be shown that a valsartan and NEP inhibitor therapy proves to be beneficial in the treatment and prevention of myocardial infarction and its sequelae. A valsartan plus NEP inhibitor combination is also useful in treating atherosclerosis, angina (whether stable or unstable), and renal insufficiency (diabetic and non-diabetic). Furthermore, combination therapy using valsartan and a NEP inhibitor can improve endothelial dysfunction, thereby providing benefit in diseases in which normal endothelial function is disrupted such as heart failure, angina pectoris and diabetes. Furthermore, the combination of the present invention may be used for the treatment or prevention of secondary aldosteronism, primary and secondary pulmonary hypertension, renal failure conditions, such as diabetic nephropathy, glomerulonephritis, scleroderma, glomerular sclerosis, proteinuria of primary renal disease, and also renal vascular hypertension, diabetic retinopathy, the management of other vascular disorders, such as migraine, peripheral vascular disease, Raynaud's disease, luminal hyperplasia, cognitive dysfunction (such as Alzheimer's), glaucoma and stroke.

The structure of the active agents identified by generic or tradenames or code nos. may be taken from the actual edition of the standard compendium "The Merck Index" or from databases, e.g. Life Cycle Patents International (e.g. IMS World Publications). The corresponding content thereof is hereby incorporated by reference. Any person skilled in the art is fully enabled to identify the active agents and, based on these references, likewise enabled to manufacture and test the pharmaceutical indications and properties in standard test models, both in vitro and in vivo.

The subject matter of NEP inhibitors referred to in e.g. US patents, EP, , GB, JP or WO patent applications is herewith incorporated by reference, especially corresponding NEP inhibitors and pharmaceutically acceptable salts and pharmaceutical compositions thereof, that are claimed or disclosed in the working examples.

The person skilled in the pertinent art is fully enabled to select a relevant test model to prove the efficacy of a combination of the present invention in the hereinbefore and hereinafter indicated therapeutic indications.

Representative studies are carried out with a combination of valsartan and N-(3-carboxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester, e.g. applying the following methodology:
Drug efficacy is assessed in various animal models including the deoxycorticosterone acetate - salt rat (DOCA-salt) and the spontaneously hypertensive rat (SHR), either maintained on a normal salt diet or with salt loading (4-8% salt in rat chow or 1% NaCl as drinking water).

The DOCA-salt test model utilizes either an acute or chronic study protocol. An acute study procedure involves assessment of the effects of various test substances over a six-hour experimental period using rats with indwelling femoral arterial and venous catheters. The Acute Study Procedure evaluates test substances for their ability to reduce blood pressure during the established phase of DOCA-salt hypertension. In contrast, the Chronic Study Procedure assesses the ability of test substances to prevent or delay the rise in blood pressure during the development phase of DOCA-salt hypertension. Therefore, blood pressure will be monitored in the chronic study procedure by means of a radiotransmitter. The radiotransmitter is surgically implanted into the abdominal aorta of rats, prior to the initiation of DOCA-salt treatment and thus, prior to the induction of hypertension. Blood pressure is chronically monitored for periods of up 6 weeks (approximately one week prior to DOCA-salt administration and for 5 weeks thereafter).

Rats are anesthetized with 2-3% isoflurane in oxygen inhalant followed by Amytal sodium (amobarbital) 100 mg/kg, ip. The level of anesthesia is assessed by a steady rhythmic breathing pattern.

Acute study procedure:

Rats undergo a unilateral nephrectomy at the time of DOCA implantation. Hair is clipped on the left flank and the back of the neck and scrubbed with sterile alcohol swabs and

povidone/iodine. During surgery rats are placed on a heating pad to maintain body temperature at 37 degrees C.

A 20mm incision is made through the skin and underlying muscle to expose the left kidney. The kidney is freed of surrounding tissue, exteriorized and two ligatures (3-0 silk) are tied securely around the renal artery and vein proximal to their juncture with the aorta. The renal artery and vein are then severed and the kidney removed. The muscle and skin wounds are closed with 4-0 silk suture and stainless steel wound clips, respectively. At the same time, a 15mm incision is made on the back of the neck and a 3-week-release pellet (Innovative Research of America, Sarasota, Florida) containing deoxycorticosterone acetate (100 mg/kg) is implanted subcutaneously. The wound is then closed with stainless-steel clips and both wounds are treated with povidone/iodine; the rats are given a post-surgical intramuscular injection of procaine penicillin G (100,000 U) and buprenorphine (0.05 – 0.1 mg/kg) s.c. The rats are immediately placed on 1% NaCl + 0.2% KCl drinking water; this treatment continues for at least 3 weeks at which time the animals have become hypertensive and available for experimentation.

Forty-eight hours prior to experimentation, animals are anesthetized with isoflurane and catheters are implanted in the femoral artery and vein for measuring arterial pressure, collection of blood, and administration of test compounds. Rats are allowed to recover for 48 hours while tethered in a Plexiglas home cage, which also serves as the experimental chamber.

Chronic study procedure:

This procedure is the same as above except that rats are implanted with a radiotransmitter, 7-10 days prior to the unilateral nephrectomy and initiation of DOCA and salt. In addition, rats do not undergo surgery for placement of femoral arterial and venous catheters. Radiotransmitters are implanted as described in M.K. Bazil, C. Krulan and R.L. Webb. Telemetric monitoring of cardiovascular parameters in conscious spontaneously hypertensive rats. J.Cardiovasc. Pharmacol. 22: 897-905, 1993.

Protocols are then set-up on the computer for measurement of blood pressure, heart rate, etc, at predetermined time points. Baseline data is collected at various time points and over various time intervals. For example, baseline or pre-dose values usually consist of data collection and averaging over 3 consecutive, 24-hour time periods prior to drug administration.

Blood pressure, heart rate and activity are determined at various pre-selected time points before, during, and after drug administration. All measurements are performed in unrestrained and undisturbed animals. The maximum study time, determined by battery life, could be as long as nine months. For studies of this duration, rats are dosed orally (1-3 ml/kg vehicle), no more than twice daily or drug is administered via the drinking water or mixed with food. For studies of a shorter duration, that is, up to 8 weeks, drugs are given via subcutaneously implanted osmotic minipumps. Osmotic minipumps are selected based on drug delivery rate and time. Valsartan dosages range from 1 to 10 mg/kg/day and N-(3-carboxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester range from 10 to 50 mg/kg/day.

Additionally, SHR are utilized to study the effects of valsartan in combination with N-(3-carboxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester. The hypertensive background of the SHR is modified either by chronic salt loading in an effort to suppress the renin angiotensin system (RAS) or chronic salt depletion to activate the RAS in the SHR. These manipulations will be carried out to more extensively evaluate the efficacy of the various test substances. Experiments performed in spontaneously hypertensive rats (SHR) are supplied by Taconic Farms, Germantown, New York (Tac:N(SHR)fBR). A radiotelemetric device (Data Sciences International, Inc., St. Paul, Minnesota) is implanted into the lower abdominal aorta of all test animals between the ages of 14 to 16 weeks of age. All SHR are allowed to recover from the surgical implantation procedure for at least 2 weeks prior to the initiation of the experiments. Cardiovascular parameters are continuously monitored via the radiotransmitter and transmitted to a receiver where the digitized signal is then collected and stored using a computerized data acquisition system. Blood pressure (mean arterial, systolic and diastolic pressure) and heart rate are monitored in conscious, freely moving and undisturbed SHR in their home cages. The arterial blood pressure and heart rate are measured every 10 minutes for 10 seconds and recorded. Data reported for each rat represent the mean values averaged over a 24 hour period and are made up of the 144-10 minute samples collected each day. The baseline values for blood pressure and heart rate consist of the average of three consecutive 24 hour readings taken prior to initiating the drug treatments. All rats are individually housed in a temperature and humidity controlled room and are maintained on a 12 hour light dark cycle.

In addition to the cardiovascular parameters, weekly determinations of body weight also are recorded in all rats. Treatments are administered in the drinking water, via daily oral gavage or in osmotic minipumps as stated above. If given in drinking water, water consumption is

measured five times per week. Valsartan and N-(3-carboxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester doses for individual rats are then calculated based on water consumption for each rat, the concentration of drug substance in the drinking water, and individual body weights. All drug solutions in the drinking water are made up fresh every three to four days. Typical dosages for valsartan in drinking water range from 3 to 30 mg/kg/day whereas the dosage of N-(3-carboxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester is highly dependent upon the specific agent used. In most situations, a daily dose will not exceed 50 mg/kg/day when administered as the monotherapy. In combination, lower dosages of each agent are used and correspondingly, valsartan is given in the range of 1 to 30 mg/kg/day and N-(3-carboxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester in dosages below 50 mg/kg/day. However, in cases wherein the responder rate is increased with combination treatment, the dosages are identical to those used as monotherapy.

When drugs are administered by oral gavage, the dose of valsartan ranges from 1 to 50 mg/kg/day and N-(3-carboxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester does not exceed 100 mg/kg/day.

Upon completion of the chronic studies, SHR or DOCA-salt rats are anesthetized and the heart rapidly removed. After separation and removal of the atrial appendages, left ventricle and left plus right ventricle (total) are weighed and recorded. Left ventricular and total ventricular mass are then normalized to body weight and reported. All values reported for blood pressure and cardiac mass represent the group mean $\pm$ sem.

Vascular function and structure are evaluated after treatment to assess the beneficial effects of the combination. SHR are studied according to the methods described by Intengan HD, Thibault G, Li JS, Schiffrin EL, Circulation 1999, 100 (22): 2267-2275. Similarly, the methodology for assessing vascular function in DOCA-salt rats is described in Intengan HD, Park JB, Schiffrin, EL, Hypertension, 1999, 34(4 Part 2): 907-913.

The available results indicate an unexpected therapeutic effect of a combination according to the invention.

In one aspect is the object of this invention to provide a pharmaceutical combination composition, e.g. for the treatment or prevention of a condition or disease selected from the group consisting of hypertension, heart failure such as (acute and chronic) congestive heart failure, left ventricular dysfunction and hypertrophic cardiomyopathy, diabetic cardiac

myopathy, supraventricular and ventricular arrhythmias, atrial fibrillation, atrial flutter, detrimental vascular remodeling, myocardial infarction and its sequelae, atherosclerosis, angina (whether unstable or stable), renal insufficiency (diabetic and non- diabetic), heart failure, angina pectoris, diabetes, secondary aldosteronism, primary and secondary pulmonary hypertension, renal failure conditions, such as diabetic nephropathy, glomerulonephritis, scleroderma, glomerular sclerosis, proteinuria of primary renal disease, and also renal vascular hypertension, diabetic retinopathy, the management of other vascular disorders, such as migraine, peripheral vascular disease, Raynaud's disease, luminal hyperplasia, cognitive dysfunction (such as Alzheimer's), glaucoma and stroke which composition comprises (i) the AT 1-antagonists valsartan or a pharmaceutically acceptable salt thereof and (ii) a NEP inhibitor or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier. A further active ingredient may be a diuretic, especially hydrochlorothiazide.

In this composition, components (i) and (ii) can be obtained and administered together, one after the other or separately in one combined unit dose form or in two separate unit dose forms. The unit dose form may also be a fixed combination.

A further aspect of the present invention is a method for the treatment or prevention of a condition or disease selected from the group consisting of hypertension, heart failure such as (acute and chronic) congestive heart failure, left ventricular dysfunction and hypertrophic cardiomyopathy, diabetic cardiac myopathy, supraventricular and ventricular arrhythmias, atrial fibrillation, atrial flutter, detrimental vascular remodeling, myocardial infarction and its sequelae, atherosclerosis, angina (whether unstable or stable), renal insufficiency (diabetic and non- diabetic), heart failure, angina pectoris, diabetes, secondary aldosteronism, primary and secondary pulmonary hypertension, renal failure conditions, such as diabetic nephropathy, glomerulonephritis, scleroderma, glomerular sclerosis, proteinuria of primary renal disease, and also renal vascular hypertension, diabetic retinopathy, the management of other vascular disorders, such as migraine, peripheral vascular disease, Raynaud's disease, luminal hyperplasia, cognitive dysfunction (such as Alzheimer's), glaucoma and stroke, comprising administering a therapeutically effective amount of combination of (i) the AT 1-antagonists valsartan or a pharmaceutically acceptable salt thereof and (ii) a NEP inhibitor or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier to a mammal in need of such treatment.

A therapeutically effective amount of each of the component of the combination of the present invention may be administered simultaneously or sequentially and in any order.

The corresponding active ingredient or a pharmaceutically acceptable salt thereof may also be used in form of a hydrate or include other solvents used for crystallization.

The pharmaceutical compositions according to the invention can be prepared in a manner known per se and are those suitable for enteral, such as oral or rectal, and parenteral administration to mammals (warm-blooded animals), including man, comprising a therapeutically effective amount of the pharmacologically active compound, alone or in combination with one or more pharmaceutically acceptable carriers, especially suitable for enteral or parenteral application. Typical oral formulations include tablets, capsules, syrups, elixirs and suspensions. Typical injectable formulations include solutions and suspensions.

The typical pharmaceutically acceptable carriers for use in the formulations described above are exemplified by: sugars such as lactose, sucrose, mannitol and sorbitol; starches such as cornstarch, tapioca starch and potato starch; cellulose and derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and methyl cellulose; calcium phosphates such as dicalcium phosphate and tricalcium phosphate; sodium sulfate; calcium sulfate; polyvinylpyrrolidone; polyvinyl alcohol; stearic acid; alkaline earth metal stearates such as magnesium stearate and calcium stearate; stearic acid; vegetable oils such as peanut oil, cottonseed oil, sesame oil, olive oil and corn oil; non-ionic, cationic and anionic surfactants; ethylene glycol polymers; betacyclodextrin; fatty alcohols; and hydrolyzed cereal solids, as well as other non-toxic compatible fillers, binders, disintegrants, buffers, preservatives, antioxidants, lubricants, flavoring agents, and the like commonly used in pharmaceutical formulations.

The invention also relates to combining separate pharmaceutical compositions in kit form. That is a kit combining two separate units: a valsartan pharmaceutical composition and a NEP inhibitor pharmaceutical composition. The kit form is particularly advantageous when the separate components must be administered in different dosage forms (e.g. parenteral valsartan formulation and oral NEP formulation) or are administered at different dosage intervals.

These pharmaceutical preparations are for enteral, such as oral, and also rectal or parenteral, administration to homeotherms, with the preparations comprising the pharmacological active compound either alone or together with customary pharmaceutical auxiliary substances. For example, the pharmaceutical preparations consist of from about 0.1 % to 90 %, preferably of from about 1 % to about 80 %, of the active compounds.

Pharmaceutical preparations for enteral or parenteral administration are, for example, in unit dose forms, such as coated tablets, tablets, capsules or suppositories and also ampoules. These are prepared in a manner which is known per se, for example using conventional mixing, granulation, coating, solubulizing or lyophilizing processes. Thus, pharmaceutical preparations for oral use can be obtained by combining the active compounds with solid excipients, if desired granulating a mixture which has been obtained, and, if required or necessary, processing the mixture or granulate into tablets or coated tablet cores after having added suitable auxiliary substances.

The dosage of the active compound can depend on a variety of factors, such as mode of administration, homeothermic species, age and/or individual condition.

Preferred dosages for the active ingredients of the pharmaceutical combination according to the present invention are therapeutically effective dosages, especially those which are commercially available.

Normally, in the case of oral administration, an approximate daily dose of from about 1 mg to about 360 mg is to be estimated e.g. for a patient of approximately 75 kg in weight.

Valsartan is supplied in the form of suitable dosage unit form, for example, a capsule or tablet, and comprising a therapeutically effective amount, e.g. from about 20 to about 320 mg, of valsartan which may be applied to patients. The application of the active ingredient may occur up to three times a day, starting e.g. with a daily dose of 20 mg or 40 mg of valsartan, increasing via 80 mg daily and further to 160 mg daily up to 320 mg daily. Preferably, valsartan is applied once a day or twice a day in heart failure patients with a dose of 80 mg or 160 mg, respectively, each. Corresponding doses may be taken, for example, in the morning, at mid-day or in the evening. Preferred is q.d. or b.i.d. administration in heart failure.

In case of NEP inhibitors, preferred dosage unit forms are, for example, tablets or capsules comprising e.g. from about 20 mg to about 800 mg, preferably from about 50 mg to about 700 mg, even more preferably from about 100 mg to about 600 mg and even more preferably from about 100 mg to about 300 mg, administered once a day.

In case of diuretics, preferred dosage unit forms are, for example, tablets or capsules comprising e.g. from about 5 mg to about 50 mg, preferably from about 6.25 mg to about 25 mg. A daily dose of 6.25 mg, 12.5 mg or 25 mg of hydrochlorothiazide is preferably administered once a day.

The above doses encompass a therapeutically effective amount of the active ingredients of the present invention.

The following examples illustrate the above-described invention; however, it is not intended to restrict the scope of this invention in any manner.

Formulation Example 1:

Film-Coated Tablets:

Components	Composition Per Unit (mg)	Standards
Granulation		
Valsartan [= active ingredient]	80.00	
Microcrystalline cellulose/ Avicel PH 102	54.00	NF, Ph. Eur
Crospovidone	20.00	NF, Ph. Eur
Colloidal anhydrous silica / colloidal silicon dioxide / Aerosil 200	0.75	Ph. Eur/ NF
Magnesium stearate	2.5	NF, Ph. Eur
Blending		
Colloidal anhydrous silica / colloidal silicon dioxide / Aerosil 200	0.75	Ph. Eur/ NF
Magnesium stearate	2.00	NF, Ph. Eur
Coating		
Purified water *)	-	
DIOLACK pale red 00F34899	7.00	
Total tablet mass	167.00	

*) Removed during processing.

The film-coated tablet is manufactured e.g. as follows:

A mixture of valsartan, microcrystalline cellulose, crospovidone, part of the colloidal anhydrous silica/colloidal silicon dioxide/Aerosile 200, silicon dioxide and magnesium stearate is premixed in a diffusion mixer and then sieve through a screening mill. The resulting mixture is again pre-mixed in a diffusion mixer, compacted in a roller compactor and then sieve through a screening mill. To the resulting mixture, the rest of the colloidal anhydrous silica/colloidal silicon dioxide/Aerosile 200 are added and the final blend is made

in a diffusion mixer. The whole mixture is compressed in a rotary tabletting machine and the tablets are coated with a film by using Diolack pale red in a perforated pan.

Formulation Example 2:

Film-coated tablets:

Components	Composition Per Unit (mg)	Standards
Granulation		
Valsartan [= active ingredient]	160.00	
Microcrystalline cellulose/ Avicel PH 102	108.00	NF, Ph. Eur
Crospovidone	40.00	NF, Ph. Eur
Colloidal anhydrous silica / colloidal silicon dioxide / Aerosil 200	1.50	Ph. Eur/ NF
Magnesium stearate	5.00	NF, Ph. Eur
Blending		
Colloidal anhydrous silica / colloidal silicon dioxide / Aerosil 200	1.50	Ph. Eur/ NF
Magnesium stearate	4.00	NF, Ph. Eur
Coating		
Opadry Light Brown 00F33172	10.00	
Total tablet mass	330.00	

The film-coated tablet is manufactured e.g. as described in Formulation Example 1.

Formulation Example 3:

Film-Coated Tablets:

Components	Composition Per Unit (mg)	Standards
Core: Internal phase		
Valsartan [= active ingredient]	40.00	
Silica, colloidal anhydrous (Colloidal silicon dioxide) [= Glidant]	1.00	Ph. Eur, USP/NF
Magnesium stearate [= Lubricant]	2.00	USP/NF
Crospovidone [Disintegrant]	20.00	Ph. Eur
Microcrystalline cellulose [= Binding agent]	124.00	USP/NF
External phase		
Silica, colloidal anhydrous, (Colloidal silicon dioxide) [= Glidant]	1.00	Ph. Eur, USP/NF
Magnesium stearate [Lubricant]	2.00	USP/NF
Film coating		
Opadry® brown OOF 16711*)	9.40	
Purified Water**)	-	
Total tablet mass	199.44	

*) The composition of the Opadry® brown OOF16711 coloring agent is tabulated below.

**) Removed during processing

Opadry® Composition:

Ingredient	Approximate % Composition
Iron oxide, black (C.I. No. 77499, E 172)	0.50
Iron oxide, brown (C.I. No. 77499, E 172	0.50
Iron oxide, red (C.I. No. 77491, E 172)	0.50
Iron oxide, yellow (C.I. No. 77492, E 172)	0.50
Macrogolum (Ph. Eur)	4.00
Titanium dioxide (C.I. No. 77891, E 171)	14.00
Hypromellose (Ph. Eur)	80.00

The film-coated tablet is manufactured e.g. as described in Formulation Example 1.

Formulation Example 4:

Capsules:

Components	Composition Per Unit (mg)
Valsartan [= active ingredient]	80.00
Microcrystalline cellulose	25.10
Crospovidone	13.00
Povidone	12.50
Magnesium stearate	1.30
Sodium lauryl sulphate	0.60
Shell	
Iron oxide, red (C.I. No. 77491, EC No. E 172)	0.123
Iron oxide, yellow (C.I. No. 77492, EC No. E 172)	0.123
Iron oxide, black (C.I. No. 77499, EC No. E 172)	0.245
Titanium dioxide	1.540
Gelatin	74.969
Total tablet mass	209.50

The tablet is manufactured e.g. as follows:

Granulation/Drying

Valsartan and microcrystallin cellulose are spray-granulated in a fluidized bed granulator with a granulating solution consisting of povidone and sodium lauryl sulphate dissolved in purified water. The granulate obtained is dried in a fluidized bed dryer.

Milling/Blending

The dried granulate is milled together with crospovidone and magnesium stearate. The mass is then blended in a conical srew type mixer for approximately 10 minutes.

Encapsulation

The empty hard gelatin capsules are filled with the blended bulk granules under controlled temperature and humidity conditions. The filed capsules are dedusted, visually inspected, weightchecked and quarantined until by Quality assurance department.

Formulation Example 5:

Capsules:

Components	Composition Per Unit (mg)
Valsartan [= active ingredient]	160.00
Microcrystalline cellulose	50.20
Crospovidone	26.00
Povidone	25.00
Magnesium stearate	2.60
Sodium lauryl sulphate	1.20
Shell	
Iron oxide, red (C.I. No. 77491, EC No. E 172)	0.123
Iron oxide, yellow (C.I. No. 77492, EC No. E 172)	0.123
Iron oxide, black (C.I. No. 77499, EC No. E 172)	0.245
Titanium dioxide	1.540

Gelatin	74.969
Total tablet mass	342.00

The formulation is manufactured e.g. as described in Formulation Example 4.

Formulation Example 6:

Hard Gelatine Capsule:

Components	Composition Per Unit (mg)
Valsartan [= active ingredient]	80.00
Sodium laurylsulphate	0.60
Magnesium stearate	1.30
Povidone	12.50
Crospovidone	13.00
Microcrystalline cellulose	21.10
Total tablet mass	130.00

Formulation Example 7:

A hard gelatin capsule, comprising as active ingredient e.g. (S)-N-(1-carboxy-2-methylprop-1-yl)-N-pentanoyl-N-[2'(1H-tetrazol-5-yl)biphenyl-4-yl-methyl]amine, can be formulated, for example, as follows:

Composition:

(1) valsartan	80.0 mg
(2) microcrystalline cellulose	110.0 mg
(3) polyvidone K30	45.2 mg
(4) sodium lauryl sulfate	1.2 mg
(5) crospovidone	26.0 mg
(6) magnesium stearate	2.6 mg

Components (1) and (2) are granulated with a solution of components (3) and (4) in water. The components (5) and (6) are added to the dry granulate and the mixture is filled into size 1 hard gelatin capsules.

All publications and patents mentioned herein are incorporate by reference in their entirety as if set forth in full herein.

What is claimed is:

1. A pharmaceutical composition comprising (i) the AT 1-antagonist valsartan or a pharmaceutically acceptable salt thereof and (ii) a NEP inhibitor or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

2. The pharmaceutical composition of claim 1, wherein the NEP inhibitor is selected from the group consisting of SQ 28,603, N-[N-[1(S)-carboxyl-3-phenylproplyl]-(S)-phenylalanyl]-(S)-isoserine, N-[N-[((1S)-carboxy-2-phenyl)ethyl]-(S)-phenylalanyl]-β-alanine, N-[2(S)-mercaptomethyl-3-(2-methylphenyl)-propionyl]methionine, (cis-4-[[[1-[2-carboxy-3-(2-methoxyethoxy)propyl]-cyclopentyl]carbonyl]amino]-cyclohexanecarboxylic acid), thiorphan, retro-thiorphan, phosphoramidon, SQ 29072, N-(3-carboxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester, (S)-cis-4-[1-[2-(5-indanyloxycarbonyl)-3-(2-methoxyethoxy)propyl]-1-cyclopentanecarboxamido]-1-cyclohexanecarboxylic acid, 3-(1-[6-endo-hydroxymethylbicyclo[2,2,1]heptane-2-exo-carbamoyl]cyclopentyl)-2-(2-methoxyethyl)propanoic acid, N-(1-(3-(N-t-butoxycarbonyl-(S)-prolylamino)-2(S)-t-butoxy-carbonylpropyl)cyclopentanecarbonyl)-O-benzyl-(S)-serine methyl ester, 4-[[2-(Mercaptomethyl)-1-oxo-3-phenylpropyl]amino]benzoic acid, 3-[1-(Cis-4-carboxycarbonyl-cis-3-butylcyclohexyl-r-1-carboamoyl)cyclopentyl]-2S-(2-methoxyethoxymethyl)propanoic acid, N-((2S)-2-(4-biphenylmethyl)-4-carboxy-5-phenoxyvaleryl)glycine, N-(1-(N-hydroxycarbamoylmethyl)-1-cyclopentanecarbonyl)-L-phenylalanine, (S)-(2-biphenyl-4-yl)-1-(1H-tetrazol-5-yl)ethylamino) methylphosphonic acid, (S)-5-(N-(2-(phosphonomethylamino)-3-(4-biphenyl)propionyl)-2-aminoethyl)tetrazole, β-Alanine, 3-[1,1'-biphenyl]-4-yl-N-[diphenoxyphosphinyl)methyl]-L-alanyl, N-(2-carboxy-4-thienyl)-3-mercapto-2-benzylpropanamide, 2-(2-mercaptomethyl-3-phenylpropionamido)thiazol-4-ylcarboxylic acid, (L)-(1-((2,2-dimethyl-1,3-dioxolan-4-yl)-methoxy)carbonyl)-2-phenylethyl)-L-phenylalanyl)-β-alanine, N-[N-[(L)-[1-[(2,2-dimethyl-1,3-dioxolan-4-yl)-methoxy]carbonyl]-2-phenylethyl]-L-phenylalanyl]-(R)-alanine, N-[N-[(L)-1-carboxy-2-phenylethyl]-L-phenylalanyl]-(R)-alanine, N-[2-acetylthiomethyl-3-(2-methyl-phenyl)propionyl]-methionine ethyl ester, N-[2-mercaptomethyl-3-(2-methylphenyl)propioyl]-methionine, N-[2(S)-mercaptomethyl-3-(2-methylphenyl)propanoyl]-(S)-isoserine, N-(S)-[3-mercapto-2-(2-methylphenyl)propionyl]-(S)-2-methoxy-(R)-alanine, N-[1-[[1(S)-benzyloxycarbonyl-3-phenylpropyl]amino]cyclopentylcarbonyl]-(S)-isoserine, N-[1-[[1(S)-carbonyl-3-

phenylpropy]amino]-cyclopentylcarbonyl]-(S)-isoserine, 1,1'-[dithiobis-[2(S)-(2-methylbenzyl)-1-oxo-3,1-propanediyl]]-bis-(S)-isoserine, 1,1'-[dithiobis-[2(S)-(2-methylbenzyl)-1-oxo-3,1-propanediyl]]-bis-(S)-methionine, N-(3-phenyl-2-(mercaptomethyl)-propionyl)-(S)-4-(methylmercapto)methionine, N-[2-acetylthiomethyl-3-phenyl-propionyl]-3-aminobenzoic acid, N-[2-mercaptomethyl-3-phenyl-propionyl]-3-aminobenzoic acid, N-[1-(2-carboxy-4-phenylbutyl)-cyclopentanecarbonyl]-(S)-isoserine, N-[1-(acetylthiomethyl)cyclopentane-carbonyl]-(S)-methionine ethyl ester, 3(S)-[2-(acetylthiomethyl)-3-phenyl-propionyl]amimo-ε-caprolactam and N-(2-acetylthiomethyl-3-(2-methylphenyl)propionyl)-methionine ethyl ester, or in each case, a pharmaceutically acceptable salt thereof.

3. The pharmaceutical composition of claim 2, wherein the NEP inhibitor is N-(3-carboxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester is a triethanolamine or tris(hydroxymethyl)aminomethane salt thereof or N-(3-carboxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid or a pharmaceutically acceptable salt thereof.

4. The pharmaceutical composition of claim 1 further comprising a diuretic.

5. A kit comprising in separate containers in a single package pharmaceutical compositions comprising in one container a pharmaceutical composition comprising a NEP inhibitor and in a second container a pharmaceutical composition comprising valsartan.

6. A method for the treatment or prevention of a condition or disease selected from the group consisting of hypertension, heart failure such as (acute and chronic) congestive heart failure, left ventricular dysfunction and hypertrophic cardiomyopathy, diabetic cardiac myopathy, supraventricular and ventricular arrhythmias, atrial fibrillation, atrial flutter, detrimental vascular remodeling, myocardial infarction and its sequelae, atherosclerosis, angina (whether unstable or stable), renal insufficiency (diabetic and non- diabetic), heart failure, angina pectoris, diabetes, secondary aldosteronism, primary and secondary pulmonary hypertension, renal failure conditions, such as diabetic nephropathy, glomerulonephritis, scleroderma, glomerular sclerosis, proteinuria of primary renal disease, and also renal vascular hypertension, diabetic retinopathy, the management of other vascular disorders, such as migraine, peripheral vascular disease, Raynaud's disease, luminal hyperplasia, cognitive dysfunction (such as Alzheimer's), glaucoma and stroke,

comprising administering a therapeutically effective amount of combination of (i) the AT 1-antagonists valsartan or a pharmaceutically acceptable salt thereof and (ii) a NEP inhibitor or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier to a mammal in need of such treatment.

7. A method as claimed in claim 6, wherein the NEP inhibitor is selected from the group consisting of SQ 28,603, N-[N-[1(S)-carboxyl-3-phenylproplyl]-(S)-phenylalanyl]-(S)-isoserine, N-[N-[((1S)-carboxy-2-phenyl)ethyl]-(S)-phenylalanyl]-β-alanine, N-[2(S)-mercaptomethyl-3-(2-methylphenyl)-propionyl]methionine, (cis-4-[[[1-[2-carboxy-3-(2-methoxyethoxy)propyl]-cyclopentyl]carbonyl]amino]-cyclohexanecarboxylic acid), thiorphan, retro-thiorphan, phosphoramidon, SQ 29072, N-(3-carboxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester, (S)-cis-4-[1-[2-(5-indanyloxycarbonyl)-3-(2-methoxyethoxy)propyl]-1-cyclopentanecarboxamido]-1-cyclohexanecarboxylic acid, 3-(1-[6-endo-hydroxymethylbicyclo[2,2,1]heptane-2-exo-carbamoyl]cyclopentyl)-2-(2-methoxyethyl)propanoic acid, N-(1-(3-(N-t-butoxycarbonyl-(S)-prolylamino)-2(S)-t-butoxy-carbonylpropyl)cyclopentanecarbonyl)-O-benzyl-(S)-serine methyl ester, 4-[[2-(Mercaptomethyl)-1-oxo-3-phenylpropyl]amino]benzoic acid, 3-[1-(Cis-4-carboxycarbonyl-cis-3-butylcyclohexyl-r-1-carboamoyl)cyclopentyl]-2S-(2-methoxyethoxymethyl)propanoic acid, N-((2S)-2-(4-biphenylmethyl)-4-carboxy-5-phenoxyvaleryl)glycine, N-(1-(N-hydroxycarbamoylmethyl)-1-cyclopentanecarbonyl)-L-phenylalanine, (S)-(2-biphenyl-4-yl)-1-(1H-tetrazol-5-yl)ethylamino) methylphosphonic acid, (S)-5-(N-(2-(phosphonomethylamino)-3-(4-biphenyl)propionyl)-2-aminoethyl)tetrazole, β-Alanine, 3-[1,1'-biphenyl]-4-yl-N-[diphenoxyphosphinyl)methyl]-L-alanyl, N-(2-carboxy-4-thienyl)-3-mercapto-2-benzylpropanamide, 2-(2-mercaptomethyl-3-phenylpropionamido)thiazol-4-ylcarboxylic acid, (L)-(1-((2,2-dimethyl-1,3-dioxolan-4-yl)-methoxy)carbonyl)-2-phenylethyl)-L-phenylalanyl)-β-alanine, N-[N-[(L)-[1-[(2,2-dimethyl-1,3-dioxolan-4-yl)-methoxy]carbonyl]-2-phenylethyl]-L-phenylalanyl]-(R)-alanine, N-[N-[(L)-1-carboxy-2-phenylethyl]-L-phenylalanyl]-(R)-alanine, N-[2-acetylthiomethyl-3-(2-methyl-phenyl)propionyl]-methionine ethyl ester, N-[2-mercaptomethyl-3-(2-methylphenyl)propioyl]-methionine, N-[2(S)-mercaptomethyl-3-(2-methylphenyl)propanoyl]-(S)-isoserine, N-(S)-[3-mercapto-2-(2-methylphenyl)propionyl]-(S)-2-methoxy-(R)-alanine, N-[1-[[1(S)-benzyloxycarbonyl-3-phenylpropyl]amino]cyclopentylcarbonyl]-(S)-isoserine, N-[1-[[1(S)-carbonyl-3-phenylpropy]amino]-cyclopentylcarbonyl]-(S)-isoserine, 1,1'-[dithiobis-[2(S)-(2-methylbenzyl)-

1-oxo-3,1-propanediyl]]-bis-(S)-isoserine, 1,1'-[dithiobis-[2(S)-(2-methylbenzyl)-1-oxo-3,1-propanediyl]]-bis-(S)-methionine, N-(3-phenyl-2-(mercaptomethyl)-propionyl)-(S)-4-(methylmercapto)methionine, N-[2-acetylthiomethyl-3-phenyl-propionyl]-3-aminobenzoic acid, N-[2-mercaptomethyl-3-phenyl-propionyl]-3-aminobenzoic acid, N-[1-(2-carboxy-4-phenylbutyl)-cyclopentanecarbonyl]-(S)-isoserine, N-[1-(acetylthiomethyl)cyclopentane-carbonyl]-(S)-methionine ethyl ester, 3(S)-[2-(acetylthiomethyl)-3-phenyl-propionyl]amimo-ε-caprolactam and N-(2-acetylthiomethyl-3-(2-methylphenyl)propionyl)-methionine ethyl ester, and in each case, a pharmaceutically acceptable salt thereof.

8. The method of claim 6, wherein the NEP inhibitor is N-(3-carboxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester is a triethanolamine or tris(hydroxymethyl)aminomethane salt thereof or N-(3-carboxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid or a pharmaceutically acceptable salt thereof.

9. A triethanolamine salt of N-(3-carboxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester

10. A tris(hydroxymethyl)aminomethane salt of N-(3-carboxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester.

11. A pharmaceutical composition comprising the salt of claim 9.

12. A pharmaceutical composition comprising the salt of claim 10.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/00415

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/41 A61K31/192 A61K31/216 A61P9/12 A61P9/10
A61P13/12 A61P25/28 A61P3/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01 74348 A (BRISTOL MYERS SQUIBB CO ;WOLF ROBERT A (US); CHANG PAUL I (US); RE) 11 October 2001 (2001-10-11) page 1, line 9,10 page 14, line 8; claims 1,3 page 8, line 6 page 12, line 1,2 ---	1,4-6
Y	US 5 217 996 A (KSANDER GARY) 8 June 1993 (1993-06-08) cited in the application claims 5,6 ---	1-12
X	EP 0 498 361 A (SCHERING CORP) 12 August 1992 (1992-08-12)	1-8
Y	claims 1,2,4,5,9 column 14, line 41-54 --- -/--	1-12

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 May 2003	20/05/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Veronese, A

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/00415

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 726 072 A (SQUIBB BRISTOL MYERS CO) 14 August 1996 (1996-08-14) claim 1; examples 1,2	1-8
P,X	WO 02 092622 A (NOVARTIS ERFIND VERWALT GMBH ;NOVARTIS AG (CH); FINK CYNTHIA ANNE) 21 November 2002 (2002-11-21) page 23, line 14 page 1, paragraphs 1-3 claims 1,12	1,5,6
P,X	WO 02 06253 A (NOVARTIS ERFIND VERWALT GMBH ;MARTI ERWIN (CH); NOVARTIS AG (CH);) 24 January 2002 (2002-01-24) claims 1,12 See page 36, ACE/NEP inhibitor	1,5,6

International Application No. PCT/EP 03 /00415

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1,2, 5, 7, relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the NEP inhibitors having the formula II as disclosed in the description at page 3, and the ones disclosed in claim 3, 8-12.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/00415

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 6-8 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 03/00415

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 0174348	A	11-10-2001	AU	8728901 A	15-10-2001
			EP	1267855 A2	02-01-2003
			WO	0174348 A2	11-10-2001
			US	2002004500 A1	10-01-2002
US 5217996	A	08-06-1993	AU	666902 B2	29-02-1996
			AU	3184293 A	29-07-1993
			CA	2087652 A1	23-07-1993
			EP	0555175 A1	11-08-1993
			FI	930195 A	23-07-1993
			HU	63376 A2	30-08-1993
			JP	5310664 A	22-11-1993
			MX	9300310 A1	01-07-1993
			NO	930193 A	23-07-1993
			NZ	245716 A	26-07-1995
			US	5354892 A	11-10-1994
			ZA	9300421 A	22-07-1993
EP 0498361	A	12-08-1992	AU	1256692 A	07-09-1992
			EP	0498361 A2	12-08-1992
			IE	920375 A1	12-08-1992
			WO	9213564 A1	20-08-1992
EP 0726072	A	14-08-1996	AU	4339896 A	15-08-1996
			CA	2168066 A1	09-08-1996
			EP	0726072 A2	14-08-1996
			JP	8245385 A	24-09-1996
WO 02092622	A	21-11-2002	WO	02092622 A2	21-11-2002
			US	2002183260 A1	05-12-2002
WO 0206253	A	24-01-2002	AU	8967201 A	30-01-2002
			WO	0206253 A1	24-01-2002
			NO	20030232 A	17-01-2003

Exhibit 05

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
24 January 2002 (24.01.2002)

PCT

(10) International Publication Number
WO 02/06253 A1

(51) International Patent Classification[7]: C07D 257/04, A61K 31/41, A61P 9/12

(21) International Application Number: PCT/EP01/08253

(22) International Filing Date: 17 July 2001 (17.07.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
00115556.3 19 July 2000 (19.07.2000) EP

(71) Applicant *(for all designated States except AT, US)*: **NOVARTIS AG** [CH/CH]; Lichtstrasse 35, CH-4056 Basel (CH).

(71) Applicant *(for AT only)*: **NOVARTIS-ERFINDUNGEN VERWALTUNGSGESELLSCHAFT M.B.H.** [AT/AT]; Brunner Strasse 59, A-1230 Vienna (AT).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **MARTI, Erwin** [CH/CH]; Im Langen Loh 181, CH-4054 Basel (CH). **OSWALD, Hans, Rudolf** [CH/CH]; Bumelochstrasse 25, CH-4656 Starrkirch-Wil (CH). **BÜHLMAYER, Peter** [CH/CH]; Hangstrasse 18, CH-4144 Arlesheim (CH). **MARTERER, Wolfgang** [DE/DE]; Scheffelstrasse 29, 79102 Freiburg (DE).

(74) Agent: **BECKER, Konrad**; Novartis AG, Corporate Intellectual Property, Patent & Trademark Dept., CH-4002 Basel (CH).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

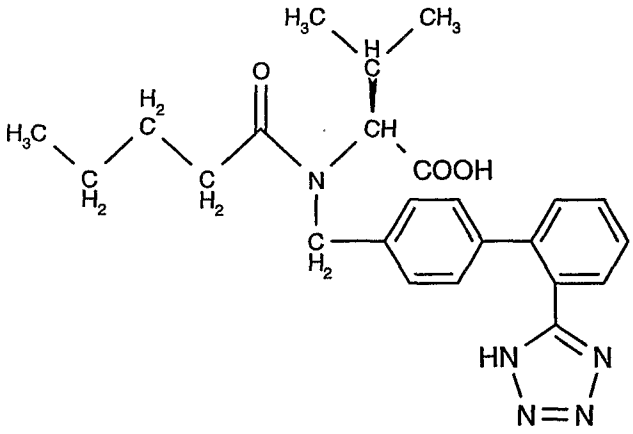
WO 02/06253 A1

(54) Title: VALSARTAN SALTS

(57) Abstract: The invention relates to new salts of valsartan or crystalline, also partly crystalline and amorphous salts of valsartan, the respective production and usage, and pharmaceutical preparations containing such a salt.

VALSARTAN SALTS

The invention relates to new salts of the AT_1 receptor antagonist (S)-N-(1-carboxy-2-methyl-prop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)-biphenyl-4-yl-methyl]-amine (valsartan) of formula



(I).

The active ingredient valsartan is the free acid which is described specifically in EP 0443983, especially in example 16; it has two acidic hydrogen atoms: (i) the hydrogen atom (H atom) of the carboxyl group, and (ii) that of the tetrazole ring. Accordingly, one acidic H atom (primarily the carboxyl H atom) or both acidic H atoms may be replaced by a monovalent or higher valent, e.g. divalent, cation. Mixed salts may also be formed.

EP 443983 does not disclose any specific salts of valsartan. Also, it does not mention any special properties of salts. Meanwhile, the active ingredient valsartan has been introduced as an anti-hypertensive agent in a series of countries under the trade name DIOVAN.

The free acid valsartan has a melting point in a closed crucible of 80 to 95°C and in an open crucible of 105 to 110°C and a melting enthalpy of 12 kJ/mol. The optical rotation is $[\alpha]^{20}_D = (-70 \pm 2)^0$ for a concentration of c = 1% in methanol.

The density of the valsartan crystals and of the salt hydrates was determined by a helium pycnometer (Accupyc 1330 of Micromeritics, Norcross, GA, USA). The density for the crystals of the free acid valsartan is 1.20 ± 0.02.

The X-ray diffraction diagram consists essentially of a very broad, diffuse Xray reflection; the free acid is therefore characterised as almost amorphous under X-ray. The melting point linked with the measured melting enthalpy of 12 kJ/mol unequivocally confirm the existence of a considerable residual arrangement in the particles or structural domains for the free acid valsartan.

There is a need for more stable, e.g. crystalline forms of valsartan, which are even easier to manage in the drying or grinding processes following the final stage of the chemical preparation process and also in the steps for preparing the pharmaceutical formulations. Many futile attempts have been made to find improved forms through salt formation, the forms ideally being as crystalline as possible, as well as physically and chemically stable. Only the salts according to the invention, their solvates and polymorphous forms thereof exhibit the desired improved properties.

The formation of salts of valsartan with the desired advantageous properties has proved to be difficult. In the majority of cases, for example, amorphous salts with little stability are obtained (such as hard foams, waxes or oils). Extensive research has shown that the salts of valsartan according to the invention have proved to be particularly advantageous compared with the free acid valsartan.

The objects of the present invention are salts of valsartan which are selected from the group consisting of the monosodium salt, the monopotassium salt, the dipotassium salt, the magnesium salt, the calcium salt, the bis-diethylammonium salt, the bis-dipropylammonium salt, the bis-dibutylammonium salt, the mono-L-arginine salt, the bis-L-arginine salt, the mono-L-lysine salt and the bis-L-lysine salt, as well as salt mixtures, or respectively, an amorphous form, a solvate, especially hydrate, as well as a polymorphous form thereof, the respective production and usage, and pharmaceutical preparations containing such salts.

The objects of the present invention are salts of valsartan which are selected from the group consisting of the monosodium salt, the monopotassium salt, the dipotassium salt, the magnesium salt, the calcium salt, the bis-diethylammonium salt, the bis-dipropylammonium salt, the bis-dibutylammoniumsalt, the mono-L-arginine salt, the bis-L-arginine salt, the

mono-L-lysine salt and the bis-L-lysine salt, or respectively, an amorphous form, a solvate, especially hydrate, as well as a polymorphous form thereof.

Salt mixtures are (i) single salt forms from different cations selected from the above group or (ii) mixtures of those single salt forms which exist for example in the form of conglomerates.

Preferred salts are for example selected from the
mono-sodium salt in amorphous form;
di-sodium salt of valsartan in amorphous or crystalline form, especially in hydrate form, thereof.
Mono-potassium salt of valsartan in amorphous form;
di-potassium salt of valsartan in amorphous or crystalline form, especially in hydrate form, thereof.
calcium salt of valsartan in crystalline form, especially in hydrate form, primarily the tetrahydrate thereof;
magnesium salt of valsartan in crystalline form, especially in hydrate form, primarily the hexahydrate thereof;
calcium/magnesium mixed salt of valsartan in crystalline form, especially in hydrate form;
bis-diethylammonium salt of valsartan in crystalline form, especially in hydrate form;
bis-dipropylammonium salt of valsartan in crystalline form, especially in hydrate form;
bis-dibutylammonium salt of valsartan in crystalline form, especially in hydrate form, primarily the hemihydrate thereof;
mono-L-arginine salt of valsartan in amorphous form;
bis-L-arginine salt of valsartan in amorphous form;
mono-L-lysine salt of valsartan in amorphous form;
bis-L-lysine salt of valsartan in amorphous form.

The salts according to the invention preferably exist in isolated and essentially pure form, for example in a degree of purity of >95%, preferably >98%, primarily >99%. The enantiomer purity of the salts according to the invention is >98%, preferably >99%.

Compared with the free acid, the salts according to the invention, or the amorphous forms, solvates such as salt hydrates, and also the corresponding polymorphous forms thereof,

have unexpectedly advantageous properties. Under given conditions, the crystalline salts and crystalline salt hydrates have a clear melting point which is linked with a marked, endothermic melting enthalpy. The crystalline salts according to the invention are stable and are of better quality than valsartan also during storage and distribution. The amorphous or partially amorphous salts have limited stability, i.e. as the solid, they have a restricted stability range. To be stabilised, they require certain measures which can be achieved for example by galenic formulations.

In addition, both the crystalline and the amorphous salts according to the invention have a high degree of dissociation in water and thus substantially improved water solubility. These properties are of advantage, since on the one hand the dissolving process is quicker and on the other hand a smaller amount of water is required for such solutions. Furthermore, the higher water solubility can, under certain conditions, also lead to increased biological availability of the salts or salt hydrates in the case of solid dosage forms. Improved properties are beneficial especially to the patients. Furthermore, some of the salts according to the invention have proved to be exceptionally physically stable, particularly the alkaline earth salts. For different relative humidities at room temperature and also at a slightly higher temperatures, the salt hydrates according to the invention show practically no water absorption or water loss over a wide range of humidities and for periods of a few hours, e.g. four hours. Also, for example, the melting point of the salts according to the invention will not be changed by storing under different relative humidities.

Improved physicochemical properties of certain salts or certain salt hydrates are of great importance both when they are produced as a pharmaceutically active substance and when producing, storing and applying the galenic preparation. In this way, starting with improved constancy of the physical parameters, an even higher quality of the formulations can be guaranteed. The high stability of the salts or salt hydrates also give the possibility of attaining economic advantages by enabling simpler process steps to be carried out during working up. The high crystallinity of certain salt hydrates allows the use of a choice of analytical methods, especially the various X-ray methods, the usage of which permits a clear and simple analysis of their release to be made. This factor is also of great importance to the quality of the active substance and its galenic forms during production, storage and administration to the patients. In addition, complex provisions for stabilising the active ingredient in the galenic formulations can be avoided.

The invention accordingly relates to crystalline, also partly crystalline and amorphous salts of valsartan.

As well as the solvates, such as hydrates, the invention also relates to polymorphous forms of the salts according to the invention.

Solvates and also hydrates of the salts according to the invention may be present, for example, as hemi-, mono-, di-, tri-, tetra-, penta-, hexa-solvates or hydrates, respectively. Solvents used for crystallisation, such as alcohols, especially methanol, ethanol, aldehydes, ketones, especially acetone, esters, e.g. ethyl acetate, may be embedded in the crystal grating. The extent to which a selected solvent or water leads to a solvate or hydrate in crystallisation and in the subsequent process steps or leads directly to the free acid is generally unpredictable and depends on the combinations of process conditions and the various interactions between valsartan and the selected solvent, especially water. The respective stability of the resulting crystalline or amorphous solids in the form of salts, solvates and hydrates, as well as the corresponding salt solvates or salt hydrates, must be determined by experimentation. It is thus not possible to focus solely on the chemical composition and the stoichiometric ratio of the molecules in the resulting solid, since under these circumstances both differing crystalline solids and differing amorphous substances may be produced.

The description salt hydrates for corresponding hydrates may be preferred, as water molecules in the crystal structure are bound by strong intermolecular forces and thereby represent an essential element of structure formation of these crystals which, in part, are extraordinarily stable. However, water molecules are also existing in certain crystal lattices which are bound by rather weak intermolecular forces. Such molecules are more or less integrated in the crystal structure forming, but to a lower energetic effect. The water content in amorphous solids can, in general, be clearly determined, as in crystalline hydrates, but is heavily dependent on the drying and ambient conditions. In contrast, in the case of stable hydrates, there are clear stoichiometric ratios between the pharmaceutical active substance and the water. In many cases these ratios do not fulfil completely the stoichiometric value, normally it is approached by lower values compared to theory because of certain crystal defects. The ratio of organic molecules to water molecules for the weaker bound water may

vary to a considerable extend, for example, extending over di-, tri- or tetra-hydrates. On the other hand, in amorphous solids, the molecular structure classification of water is not stoichiometric; the classification may however also be stoichiometric only by chance.

In some cases, it is not possible to classify the exact stoichiometry of the water molecules, since layer structures form, e.g. in the alkali metal salts, especially in the potassium salt, so that the embedded water molecules cannot be determined in defined form.

For the crystalline solids having identical chemical composition, the different resulting crystal gratings are summarised by the term polymorphism.

Any reference hereinbefore and hereinafter, to the salts according to the invention is to be understood as referring also to the corresponding solvates, such as hydrates, and polymorphous modifications, and also amorphous forms, as appropriate and expedient.

Especially preferred are the tetrahydrate of the calcium salt of valsartan and the hexahydrate of the magnesium salt of valsartan.

The X-ray diffraction diagram of powders of these two salt hydrates has a number of discrete X-ray reflections, and practically no signs of non-crystalline or amorphous portions. The degree of crystallisation of these defined salt hydrates is therefore surprisingly high. Equally, relatively large crystals may be cultured from certain salt hydrates, and in the crystallographic sense these are single crystals. Such single crystals allow the structure of the solid to be determined. It is effected by computer-aided evaluation of the reflection intensities measured by an X-ray diffractometer.

This process for determining the structure of a crystal enables, under normal conditions such as high physical, chemical and enantiomeric purity of the gauged crystals, a clear determination of the structure to be carried out on a molecular or atomic level, namely symmetry and size of the elementary cells, atom positions and temperature factors, and from the ascertained cell volume, the X-ray-photographic density is shown on the basis of a molecular weight. At the same time, the X-ray-photographic structure determination supplies details of its quality.

The outstanding properties of these two salt hydrates are based on the crystals, which form these salts by incorporating four or six water molecules per valsartan molecule. Thus, practically perfect three-dimensional crystal gratings are produced. These two salts have water solubility that is several times better than the free acid of valsartan, and this is especially surprisingly at high melting points and melting enthalpies, which are eight or five times greater than the free acid. The extraordinary crystal gratings of these two salt hydrates are the basis for the chemical and physical stability of these two compounds.

The particularly notable salt hydrate is the tetrahydrate of the calcium salt of valsartan. In a closed specimen container, for a heating rate of $T_r = 10\ K \bullet min^{-1}$ it has a melting point of 205 ± 1.5 °C and a melting enthalpy of 98 ± 4 $kJ \bullet Mol^{-1}$. The tetrahydrate of the calcium salt of valsartan is not stable at elevated temperatures both in respect of the hydrate water and in respect of the structure of the molecule. The indicated melting point is a hydrate melting point which can only be measured in a closed specimen container. Gold containers with a wall thickness of 0.2 mm were used; after weighing in samples of between 2 and 4 mg salt hydrate, they were sealed by cold welding. These gold containers have an internal free volume of ca. 22 microlitres. The amounts of the sample and the volume of the pressurised containers must be suitably adapted, so that strong dehydration of the salt hydrates cannot take place during measurement of the melting point. The partial pressure of the water at 205° Celsius is ca. 18 bar, so that with an open container in DSC (Differential Scanning Calorimeter) during measurement of the melting point, conversion to the anhydrate takes place. If the data from several heating rates (T_r= 10, 20, 40 $K \bullet min^{-1}$) are extrapolated to a continuously rapid heating rate, a melting point of 213 ± 2 °C and a melting enthalpy of 124 ± 5 $kJ \bullet Mol^{-1}$ result. Both the high hydrate melting point and the amount of the melting enthalpy are an expression of the exceptional stability of the crystal grating of the tetrahydrate of the calcium salt of valsartan. These two thermodynamic characteristics illustrate the advantageous physical properties, compared to the free acid, with the two corresponding data, namely a melting point in the closed system of 90°C and a melting enthalpy of 12 $kJ \bullet Mol^{-1}$. These thermodynamic data, together with the X-ray data, prove the high stability of this crystal grating. They are the foundation for the special physical and chemical resistance of the tetrahydrate of the calcium salt of valsartan.

A measurement of the infrared absorption spectrum of the tetrahydrate of the calcium salt of valsartan in a potassium bromide compressed tablet shows the following significant

bands expressed in reciprocal wave numbers (cm^{-1}): 3750 – 3000 (st); 3400 – 2500 (st); 1800 – 1520 (st); 1500 – 1380 (st); 1380 – 1310 (m); 1290 – 1220 (w); 1220 – 1190 (w); 1190 – 1160 (w); 1160 – 1120 (w); 1120 – 1050 (w); 1030 – 990 (m); 989 – 960 (w), 950 – 920 (w); 780 – 715 (m); 710 – 470 (m). The intensities of the absorption bands are indicated as follows: (w) = weak; (m) = medium; and (st) = strong intensity. Measurement of the infrared spectrum likewise took place by means of ATR-IR (Attenuated Total Reflection-Infrared Spectroscopy) using the instrument Spektrum BX from Perkin-Elmer Corp., Beaconsfield, Bucks, England.

The tetrahydrate of the calcium salt of valsartan has the following absorption bands expressed in reciprocal wave numbers (cm^{-1}):

3594 (w); 3306 (w); 3054 (w); 2953 (w); 2870 (w); 1621 (st); 1578 (m); 1458 (m); 1441 (m); 1417 (m); 1364 (m); 1336 (w); 1319 (w); 1274 (w); 1241 (w); 1211 (w); 1180 (w); 1149 (w); 1137 (w); 1106 (w); 1099 (w); 1012 (m); 1002 (w); 974 (w); 966 (w); 955 (w); 941 (w); 863 (w); 855 (w); 844 (w); 824 (w); 791 (w); 784 (w); 758 (m); 738 (m); 696 (m); 666 (m).

The intensities of the absorption bands are indicated as follows: (w) = weak; (m) = medium and (st) = strong intensity.

The most intensive absorption bands of the ATR-IR spectroscopy are shown by the following values expressed in reciprocal wave numbers (cm^{-1}): 3306 (w); 1621 (st); 1578 (m); 1458 (m); 1441 (m); 1417 (m); 1364 (m); 1319 (w); 1274 (w); 1211 (w); 1180 (w); 1137 (w); 1012 (m); 1002 (w); 758 (m); 738 (m); 696 (m); 666 (m).

The error margin for all absorption bands of ATR-IR is ± 2 cm^{-1}.

The water content is in theory 13.2% for the tetrahydrate of the calcium salt of valsartan. Using the thermo-scale TGS-2 (Perkin-Elmer Corp. , Norwalk, CT USA) the water content was determined as 12.9 %. A total formula was calculated from this $(C_{24}H_{27}N_5O_3)^{2-}$ Ca^{2+}• (3.9 ± 0.1) H_2O.

Using thermogravimetry, in a water-free N_2 atmosphere, the weight loss, i.e. the water loss for the tetrahydrate as a function of temperature, was measured at a heating rate of 10 K•min^{-1}. The results are illustrated in table 1.

Table 1

temperature [^{0} C]	weight loss or water loss in %

25	0
50	0
75	0.5
100	3.5
125	10.2
150	12.4
175	12.8
200	12.9
225	12.9
250	13.0
275	13.2

The solubility of the tetrahydrate of the calcium salt of valsartan in water-ethanol mixtures is illustrated in Table 2 for a temperature of 22°C.

Table 2

vol-% ethanol in water	solubility of the tetrahydrate of the calcium salt of valsartan in g/l solution at 22°C
0	9 (pH = 7.4)
10	9
30	14
50	46

A comparison of the solubilities of the two most important salts according to the invention and the free acid in distilled water is illustrated in Table 3.

Table 3

Compound	solubility in g/l solution at 22°C
valsartan	0.17
tetrahydrate of the calcium salt of valsartan	9
hexahydrate of the magnesium salt of valsartan	59

Further characterisation of the tetrahydrate of the calcium salt of valsartan is effected using the interlattice plane intervals determined by a X-ray powder pattern. Measurement of the

X-ray powder patterns was made with a Guinier camera (FR 552 from Enraf Nonius, Delft, NL) on an X-ray film in transmission geometry, using Cu-Ka_1 radiation at room temperature. Evaluation of the films for calculation of the interlattice plane intervals is made both visually and by a Line-Scanner (Johansson Täby, S), and the reflection intensities are determined simultaneously.

The preferred characterisation of the tetrahydrate of the calcium salt of valsartan is obtained from the interlattice plane intervals d of the ascertained X-ray diffraction diagrams, whereby, in the following, average values are indicated with the appropriate error limits.

d in [Å] : 16.1±0.3, 9.9±0.2, 9.4±0.2, 8.03±0.1, 7.71±0.1, 7.03±0.1, 6.50±0.1, 6.33±0.1, 6.20±0.05, 5.87±0.05, 5.74±0.05, 5.67±0.05, 5.20±0.05, 5.05±0.05, 4.95±0.05, 4.73±0.05, 4.55±0.05, 4.33±0.05, 4.15±0.05, 4.12±0.05, 3.95±0.05, 3.91±0.05, 3.87±0.05, 3.35±0.05.

The most intensive reflections in the X-ray diffraction diagram show the following interlattice plane intervals:

d in [Å] : 16.1±0.3, 9.9±0.2, 9.4±0.2, 7.03±0.1, 6.50±0.1, 5.87±0.05, 5.74±0.05, 4.95±0.05, 4.73±0.05, 4.33±0.05, 4.15±0.05, 4.12±0.05, 3.95±0.05.

A preferred method of checking the above-indicated average values of the interlattice plane intervals and intensities measured by experimentation from X-ray diffraction diagrams with a Guinier camera, for a given substance, consists in calculating these intervals and their intensities from the comprehensive single crystal structure determination. This structure determination yields cell constants and atom positions, which enable the X-ray diffraction diagram corresponding to the solid to be calculated by means of computer-aided calculation methods (programme CaRine Crystallography, Université de Compiègne, France). A comparison of these data, namely the interlattice plane intervals and intensities of the most important lines of the tetrahydrate of the calcium salt of valsartan, obtained from measurements with the Guinier camera and from calculating the single crystal data, is illustrated in Table 4.

Table 4

measured		calculated		measured		calculated	
d in [Å]	Intensity	d in [Å]	Intensity	d in [Å]	Intensity	d in [Å]	Intensity
16.10	very strong	16.02	very strong	5.67	very weak	5.658	very weak

9.89	strong	9.88	very strong	5.20	very weak	5.199	very weak
9.38	average	9.37	average	5.05	very weak	5.040	very weak
8.03	weak	8.02	average	4.95	average	4.943	weak
7.71	weak	7.70	weak	4.73	weak	4.724	weak
7.03	average	7.01	average	4.55	weak	4.539	weak
6.50	average	6.49	average	4.33	weak	4.338	weak
6.33	weak	6.33	weak	4.15	strong	4.150	strong
6.20	very weak	6.19	very weak	4.12	weak	4.114	weak
5.87	average	5.862	average	3.95	average	3.941	average
5.74	average	5.738	average	3.35	weak	3.349	weak

The invention relates to the crystalline tetrahydrate of the calcium salt of (S)-N-(1-carboxy-2-methylprop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amine, a crystalline solid which is clearly characterised by the data and parameters obtained from single crystal X-ray analysis and X-ray powder patterns. An in-depth discussion of the theory of the methods of single crystal X-ray diffraction and the definition of the evaluated crystal data and the parameters may be found in Stout & Jensen, X-Ray Structure Determination; A Practical Guide, Mac Millian Co., New York, N.Y. (1968) chapter 3.

The data and parameters of the single crystal X-ray structure determination for the tetrahydrate of the calcium salt of valsartan are contained in Table 5.

Table 5

Crystal data and parameters of the tetrahydrate of the calcium salt of valsartan

Crystal data	
sum formula	$(C_{24}H_{27}N_5O_3)^{2-}Ca^{2+} \cdot 4H_2O$
molecular mass	545.65
crystal colour	colourless
crystal shape	flat prisms

crystal system	monoclinic
space group	$P2_1$
size of the single crystal	0.42 • 0.39 • 0.17 mm^3
dimensions and angle of elementary cell	a = 10.127(2) Å
	b = 8.596(2) Å
	c = 32.214(6) Å
	$\alpha = 90^0$
	$\beta = 95.34(3)^0$
	$\gamma = 90^0$
volume of elementary cell	$V_c = 2792.1(10)$ Å ^{3}
number of molecules in the elementary cell	4
F (000)	1160
measurement range of cell parameters (Θ)	7.47-16.50 ^{0}
calculated density	1.298 ($g \cdot cm^{-3}$)
linear absorption coefficient	0.274 mm^{-1}

X-ray measurement data

diffractometer	Enraf Nonius CAD4
X-radiation (graphite monochromator)	MoKα
wavelength	0.71073
temperature	295 K
scan range (θ)	1.27 - 31.99 ^{0}
scan mode	ω / 2 Θ
reflections collected/unique	19384 / 18562
number of significant reflections ($I > 2\sigma(I)$)	10268
variation in intensity	1.7 %
absorption correction	numeric

Structure refinement

method	full matrix, least squares, F^2
number of parameters	893
agreement index (R)	6.2 %
weighted agreement index (R_W)	14.4 %

S factor (Goodness of fit)	1.085
number of reflections used	18562
treatment of all hydrogen atoms in the molecule, including in the water molecules	all found by difference-Fourier calculation, almost all isotropically refined, a few theoretically fixed (riding)
extinction correction	none
maximum/minimum residual electron density in conclusive difference-Fourier calculation	0.662 / - 0.495 (e•Å^{-3})
absolute structure parameters	0.00 (4)

Computer programmes used
SHELXS 86 (Sheldrick, Göttingen, 1990)
SHELXL 96 (Sheldrick, Göttingen, 1996)
SCHAKAL 86 (Keller, Freiburg 1986)
PLATON (Spek, Acta Cryst., 1990)

The elementary cell is defined by six parameters, namely by the grating constants a, b and c, and by the axial angle, namely by a, β, und γ. In this way, the volume of the elementary cell V_c is determined. A differentiated description of these crystal parameters is illustrated in chapter 3 of Stout & Jensen (see above). The details for the tetrahydrate of the calcium salt of valsartan from the single crystal measurements, especially the atom coordinates, the isotropic thermal parameters, the coordinates of the hydrogen atoms as well as the corresponding isotropic thermal parameters, show that a monoclinic elementary cell exists, its cell content of four formula units Ca^{2+} valsartan^{2-} • 4 H_20 occurring as a result of two crystallographic independent units on two-fold positions.

Given the acentric space group $P2_1$ determined from the single crystal X-ray structure determination, a racemate is ruled out. Thus the enantiomeric purity of the S-configuration for the crystalline tetrahydrate of the calcium salt of (S)-N-(1-carboxy-2-methylprop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amine is verified.

An essential feature for the quality of a pure active substance both for the physical-chemical procedures such as drying, sieving, grinding, and in the galenic processes which are carried

out with pharmaceutical excipients, namely in mixing processes, in granulation, in spray-drying, in tabletting, is the water absorption or water loss of this active substance depending on temperature and the relative humidity of the environment in question. With certain formulations, free and bound water is without doubt introduced with excipients and/or water is added to the process mass for reasons associated with the respective formulation process. In this way, the pharmaceutical active substance is exposed to free water over rather long periods of time, depending on the temperature of the different activity (partial vapour pressure).

A clear characterisation of this property is achieved by means of isothermal measurements over predetermined time intervals and predetermined relative humidity using dynamic vapour sorption (DVS-1 from the company Surface Measurement Systems LTD, Marlow, Buckinghamshire, UK). Table 6 illustrates the mass change, i.e. the water absorption or loss as a function of relative humidity at 25°C for a sample of 9.5 mg of the tetrahydrate of the calcium salt of valsartan and for a period of 4 hours. The following cycles of changes in relative humidity are shown: 40-90; 90-0; 0-90; 90-0 % relative humidity:

Table 6

relative humidity in %	water absorption or loss in %	relative humidity in %	water absorption or Abgabe in %
40	0.04	10	0.00
50	0.04	0	-0.01
60	0.03	10	0.00
70	0.02	20	0.00
80	0.02	30	0.00
90	0.00	40	0.00
80	0.02	50	0.00
70	0.02	60	0.01
60	0.02	70	0.00
50	0.02	80	-0.01
40	0.02	90	-0.02
30	0.01	0	-0.02
20	0.01	(starting value)	0.00

The measurement error of this sorption method based on thermogravimetry is about 0.1%. Therefore, the tetrahydrate of the calcium salt of valsartan under the conditions employed, which are realistic from a pharmaceutical-galenic point of view, shows no measurable water absorption or loss. This is surprising to a large extent, since the tetrahydrate, which has incorporated about 13% of bound water in the crystal structure, is totally indifferent to water even at extreme values of relative humidity. This property is crucial in the final stages of chemical manufacture and also in practice in all galenic process stages of the different dosage forms. This exceptional stability similarly benefits the patients through the constant availability of the active ingredient.

The intrinsic dissolving rates of the calcium salt of valsartan at pH 1, pH 4.5 and pH 6.8 show improved values over those of valsartan.

The exceptional stability of the calcium salt of valsartan, especially the tetrahydrate thereof, towards water may also be shown in stability tests. In these, the water content of the tetrahydrate of the calcium salt of valsartan remains constant both in an open container and in a sealed ampoule after four weeks at 40°C and 75% relative humidity.

Owing to the advantageous crystallinity of the calcium salt, especially the tetrahydrate thereof, this salt is suitable for pressing directly to form corresponding tablet formulations.

In addition, an improved dissolving profile in a tablet can be assured. In studies of the dissolving profile, it was established that the calcium salt, especially the tetrahydrate thereof, is released by 100% from a film-coated tablet within 15 minutes.

Of the group of new-type crystalline solids, a magnesium salt hydrate of valsartan is preferred, in particular the hexahydrate. The thermal behaviour of this salt hydrate in the region of the melting point shows a certain chemical and physical instability. The thermal data are thus dependent on the measurement conditions. In the sealed gold specimen container with an internal free volume of ca. 22 microlitres, with a sample of 2 to 4 mg and with a heating rate of $T_r = 10\ K \cdot min^{-1}$, the melting point of the hexahydrate of the magnesium salt of valsarten is 132 ± 1.5° Celsius and the melting enthalpy is 56 ± 3 kJ·Mol

[1]. The melting enthalpy which is about 5 times higher than the free acid of valsartan, together with the significantly higher melting point of the hexahydrate of the magnesium salt of valsartan is a measure of the stability of the new-type crystal grating at around room temperature.

The optical rotation of the hexahydrate of the magnesium salt of valsartan in methanol as a 1% solution at 20°C is $[\alpha]^{20}_D = -14°$.

A measurement of the infrared absorption spectrum of the hexahydrate of the magnesium salt of valsartan in a potassium bromide compressed tablet shows the following significant bands expressed in reciprocal wave numbers (cm^{-1}): 3800 – 3000 (st); 3000 – 2500 (st); 1800 – 1500 (st); 1500 – 1440 (m); 1440 – 1300 (m); 1280 – 1240 (w); 1240 – 1190 (w); 1190 – 1150 (w); 1120 – 1070 (w); 1050 – 990 (w); 990 – 960 (w); 960 – 920 (w); 920 – 700 (m); 700 – 590 (w); 590 – 550 (w).
The intensities of the absorption bands are indicated as follows: (w) = weak; (m) = medium; and (st) = strong intensity.

Measurement of the infrared spectrum likewise took place by means of ATR-IR (Attenuated Total Reflection-Infrared Spectroscopy) using the instrument Spektrum BX from Perkin-Elmer Corp., Beaconsfield, Bucks, England.

The hexahydrate of the magnesium salt of valsartan has the following absorption bands expressed in reciprocal wave numbers (cm^{-1}):
3378 (m); 3274 (m); 2956 (m); 2871 (w); 2357 (w); 1684 (w); 1619 (st); 1557 (m); 1464 (m); 1419 (m); 1394 (st); 1374 (m); 1339 (w); 1319 (w); 1300 (w); 1288 (w); 1271 (w) 1255 (w); 1223 (w); 1210 (w); 1175 (m); 1140 (w); 1106 (w); 1047 (w); 1024 (w); 1015 (w); 1005 (w); 989 (w); 975 (w); 955 (w); 941 (w); 888 (w); 856 (w); 836 (m); 820 (w); 766 (st); 751 (m); 741 (st); 732 (st).
The intensities of the absorption bands are indicated as follows: (w) = weak; (m) = medium and (st) = strong intensity.

The most intensive absorption bands of the ATR-IR spectroscopy are shown by the following values expressed in reciprocal wave numbers (cm^{-1}): 3378 (m); 3274 (m);

2956 (m); 1619 (st); 1557 (m); 1464 (m); 1419 (m); 1394 (st); 1271 (w); 1175 (m); 1015 (w); 975 (w); 836 (m); 766 (st); 751 (m); 741 (st); 732 (st).
The error margin for all absorption bands of ATR-IR is ± 2 cm^{-1}.

The theoretical water content of the hexahydrate of the magnesium salt of valsartan is 19.1%. Using a coupled instrument based on thermogravimetry-Fourier transformation-infrared-spectroscopy (TG-FTIR, IFS 28 from the companies Netzsch Gerätebau GmbH, Selb, Bayern and Bruker Optik GmbH, Karlsruhe), whilst simultaneously measuring the weight loss and identifying the material component given up, using infrared spectroscopy (release of water), the water content was determined at 18.5 %, conforming well with the theoretical value. For the hexahydrate, this corresponds to a molar ratio of 5.8 ± 0.2 mols H_20 per mol magnesium salt.

Table 7 illustrates the water loss of the hexahydrate of the magnesium salt of valsartan depending on temperature, using the weight loss measured in an N_2 atmosphere on a thermogravimetric thermal analysis instrument for a heating rate of 10 $K°min^{-1}$. From the TG-FTIR measurement, the correlation of the weight loss is assured solely by the release of water.

Table 7

temperature [^{0} C]	weight loss or water release in %
25	0
50	1.2
75	4.2
100	11.0
125	16.7
150	17.7
175	18.3
200	18.5
225	18.7
250	18.9
275	19.3

The hexahydrate of the magnesium salt of valsartan has a solubility in distilled water at 22°C of 59 g per litre of solution for a pH value of 9.3.

The crystalline form of the hexahydrate of the magnesium salt of valsartan is clearly characterised by the interlattice plane intervals calculated from the lines in an X-ray powder pattern. The measurement and analysis methods used are the same as those used for the tetrahydrate of the calcium salt of valsartan.

This preferred characterisation of the hexahydrate of the magnesium salt of valsartan is obtained from the interlattice plane intervals d, whereby, in the following, average values are indicated with the appropriate error limits:
d in [Å]: 19.7±0.3, 10.1±0.2, 9.8±0.2, 7.28±0.1, 6.48±0.1, 6.00±0.1, 5.81±0.1, 5.68±0.1, 5.40±0.05, 5.22 ±0.05, 5.12±0.05, 5.03±0.05, 4.88±0.05, 4.33±0.05, 4.22±0.05, 4.18±0.05, 4.08±0.05, 3.95±0.05, 3.46±0.05, 3.42±0.05.

The most intensive reflections in the X-ray diffraction diagram show the following interlattice plane intervals:
d in [Å] : 19.7±0.3, 10.11±0.2, 9.8±0.2, 7.28±0.1, 5.81±0.05, 5.68±0.05, 5.03±0.05, 4.88±0.05, 4.18±0.05, 4.08±0.05, 3.46 ±0.05.

A preferred method of checking the above-indicated average values of the interlattice plane intervals and intensities measured by experimentation from X-ray diffraction diagrams with a Guinier camera, for a given substance, consists in calculating these intervals and their intensities from the comprehensive single crystal structure determination. This structure determination yields cell constants and atom positions, which enable the X-ray diffraction diagram corresponding to the solid to be calculated by means of computer-aided calculation methods (programme CaRine Crystallography, Université de Compiègne, France). A comparison of these data, namely the interlattice plane intervals and intensities of the most important lines of the hexahydrate of the magnesium salt of valsartan, obtained from measurements with the Guinier camera and from calculating the single crystal data, is illustrated in Table 8.

Table 8

measured		calculated		measured		calculated	
d in [Å]	Intensity	d in [Å]	Intensity	d in [Å]	Intensity	d in [Å]	Intensity
19.7	very strong	19.66	very strong	5.12	weak	5.124	weak
10.11	average	10.09	average	5.03	strong	5.032	very strong
9.83	average	9.84	very strong	4.88	strong	4.878	very strong
7.28	average	7.27	average	4.33	very weak	4.341	weak
6.48	weak	6.46	weak	4.22	weak	4.215	weak
6.00	weak	6.00	weak	4.18	average	4.181	average
5.81	average	5.805	average	4.08	average	4.079	average
5.68	average	5.676	strong	3.95	weak	3.946	weak
5.40	very weak	5.391	very weak	3.46	average	3.463	average
5.22	weak	5.217	weak	3.42	weak	3.428	weak

The invention relates in particular to the crystalline hexahydrate of the magnesium salt of (S)-N-(1-carboxy-2-methylprop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amine, a crystalline solid which is clearly characterised by the data and parameters obtained from single crystal X-ray analysis. An in-depth discussion of the theory of the methods of single crystal X-ray diffraction and the definition of the evaluated crystal data and the parameters may be found in Stout & Jensen, X-Ray Structure Determination; A Practical Guide, Mac Millian Co., New York, N.Y. (1968) chapter 3.

The data and parameters of the single crystal X-ray analysis for the magnesium-valsartan-hexahydrate are given in Table 9.

Table 9

Crystal data and parameters of the hexahydrate of the magnesium salt of valsartan

Crystal data

sum formula	$(C_{24}H_{27}N_5O_3)^{2-}Mg^{2+} \cdot 6\,H_2O$
molecular mass	565.91

crystal colour	colourless
crystal shape	flat prisms
crystal system	monoclinic
space group	C2
size of the single crystal	0.013 • 0.50 • 0.108 mm^3
dimensions and angle of elementary cell	a = 40.075(8) Å
	b = 7.400(1) Å
	c = 10.275(2) Å
	$\alpha = 90^0$
	$\beta = 100.85(3)^0$
	$\gamma = 90^0$
volume of elementary cell	$V_c = 2992.6(9)$ Å ^{3}
number of molecules in the elementary cell	4
F (000)	1208
measurement range of cell parameters (Θ)	2.82 –11.15 ^{0}
calculated density	1.256 ($g \cdot cm^{-3}$)
linear absorption coefficient	0.114 mm^{-1}

X-ray measurement data

diffractometer	Enraf Nonius CAD4
X-radiation (graphite monochromator)	MoKα
wavelength	0.71073
temperature	295 K
scan range (θ)	1.03 – 26.00 ^{0}
scan mode	ω / 2 Θ
reflections collected/unique	5954 / 5868
number of significant reflections (I > 2σ(I))	1341
variation in intensity	<1 %
absorption correction	numeric

Structure refinement

method	full matrix, least squares, F^2

number of parameters	243
agreement index (R)	10.7 %
weighted agreement index (R_W)	13.8 %
S factor (Goodness of fit)	1.001
number of reflections used	5868
determination of hydrogen atoms	majority according to the "riding" model, nine H-atoms from water molecules isotropically refined from difference-Fourier calculation
extinction correction	0.00098 (10)
maximum/minimum residual electron density in final difference-Fourier calculation	0.473 / - 0.614 (e•Å^{-3})
absolute structure parameters	0.0(10)

Computer programmes used
SHELXS 86 (Sheldrick, Göttingen, 1990)
SHELXL 96 (Sheldrick, Göttingen, 1996)
SCHAKAL 86 (Keller, Freiburg 1986)
PLATON (Spek, Acta Cryst., 1990)

The elementary cell is defined by six parameters, namely by the grating constants a, b and c, and by the axial angle, namely by a, β, und γ. In this way, the volume of the elementary cell V_c is determined. A differentiated description of these crystal parameters is illustrated in chapter 3 of Stout & Jensen (see above).

The details for the hexahydrate of the magnesium salt of valsartan from the single crystal measurements, especially the atom coordinates, the isotropic thermal parameters, the coordinates of the hydrogen atoms as well as the corresponding isotropic thermal parameters, show that a monoclinic elementary cell exists, its cell content occurring from four formula units Mg^{2+} Valsartan • 6 H_2O .

Given the acentric space group C2 determined from the single crystal X-ray structure determination, a racemate is ruled out. Thus the enantiomeric purity of the S-configuration for the crystalline hexahydrate of the magnesium salt of valsartan is proved.

Table 10 illustrates the mass change, i.e. the water absorption or loss as a function of relative humidity at 25°C for a sample of 9.5 mg of magnesium-valsartan-hexahydrate and for a period of 4 hours (h). The following cycles of changes in relative humidity are shown: 40-90; 90-0; 0-90; 90-0 % relative humidity:

Table 10

relative humidity in %	water absorption or loss in %	relative humidity in %	water absorption or loss in %
40	0.06	10	-0.12
50	0.14	0	-4.3
60	0.19	10	-0.79
70	0.25	20	-0.14
80	0.41	30	-0.05
90	0.58	40	0.02
80	0.32	50	0.09
70	0.22	60	0.14
60	0.14	70	0.20
50	0.08	80	0.28
40	0.16	90	0.51
30	-0.03	0	-3.68
20	-0.07	(starting value)	-0.01

The measurement error of this sorption method based on thermogravimetry is about 0.1%. Therefore, the hexahydrate of the magnesium salt of valsartan under the conditions employed, which are realistic from a pharmaceutical-galenic point of view, shows weak, reproducible water absorption or water loss in a range of 20 to 80% relative humidity. This is surprising to a large extent, since the hexahydrate, which has incorporated about 19% bound water in the crystal structure, reversibly absorbs or releases water even at extreme values of relative humidity and is relatively insensitive at an average range of relative humidity. This characteristic enables an uncomplicated physical-chemical process to be developed and allows a choice of the best dosage forms for the patients.

The exceptional stability of the magnesium salt of valsartan, especially the hexahydrate thereof, towards water may also be shown in stability tests In these, the water content of the hexahydrate of the magnesium salt of valsartan remains constant both in an open container and in a sealed ampoule after four weeks at 40°C and 75% relative humidity.

Owing to the advantageous crystallinity of the magnesium salt, especially the hexahydrate thereof, this salt is suitable for pressing directly to form corresponding tablet formulations.

In addition, an improved dissolving profile in a tablet can be assured. In studies of the dissolving profile, it was established that the magnesium salt, especially the hexahydrate thereof, is released by 100% from a film-coated tablet within 15 minutes.

In addition, the magnesium salt of valsartan, especially the hexahydrate thereof, shows an advantageous compression hardness profile.

Calcium/magnesium mixed salts of valsartan also have advantageous properties, for example uniform crystal conglomerates may be produced. These may be advantageously used in the galenic formulation.

The intrinsic dissolving rates of the di-potassium salt of valsartan at pH 1, pH 4.5 and pH 6.8 show improved values over those of valsartan.

A further object of the invention is the preparation of the salts according to the invention.

The salts according to the invention, including amorphous or crystalline forms thereof, may be prepared as follows:

To form the salt, the process is carried out in a solvent system, in which the two reactants, namely the acid valsartan and the respective base, are sufficiently soluble. It is expedient to use a solvent or solvent mixture, in which the resulting salt is only slightly soluble or not soluble at all, in order to achieve crystallisation or precipitation. One variant for the salt according to the invention would be to use a solvent in which this salt is very soluble, and to subsequently add an anti-solvent to this solution, that is a solvent in which the resulting salt has only poor solubility. A further variant for salt crystallisation consists in concentrating the

salt solution, for example by heating, if necessary under reduced pressure, or by slowly evaporating the solvent, e.g. at room temperature, or by seeding with the addition of seeding crystals, or by setting up water activity required for hydrate formation.

The solvents that may be used are for example C_1-C_5-alkanols, preferably ethanol and isopropanol, as well as C_1-C_5-dialkylketones, preferably acetone and mixtures thereof with water.

The antisolvents for salt crystallisation may be for example C_3-C_7-alkylnitriles, especially acetonitrile, esters, especially C_2-C_7-alkanecarboxylic acid-C_1-C_5-alkylester, such as ethyl or isopropyl acetate, di-(C_1-C_5-alkyl)-ethers, such as tert.-butylmethylether, furthermore tetrahydrofuran, and C_5-C_8-alkanes, especially pentane, hexane or heptane.

To produce hydrates, a dissolving and crystallising process is used in particular, or a water-equilibrating crystallisation process.

The dissolving and crystallising process is characterised in that
(i) valsartan and the appropriate base are brought to a reaction in a preferably water-containing, organic solvent,
(ii) the solvent system is concentrated, for example by heating, if necessary under reduced pressure and by seeding with seeding crystals or by slowly evaporating, e.g. at room temperature, then crystallisation or precipitation is initiated and
(iii) the salt obtained is isolated.

In the dissolving and crystallising process, the water-containing, organic solvent system employed is advantageously a mixtures of alcohols, such as ethanol, and water, or or alkyl-nitrile, especially acetonitrile, and water.

The equilibrating crystallisation process for producing hydrates is characterised in that
(i) valsartan and the appropriate base are added to a water-containing organic solvent,
(ii) the solvent is concentrated, for example by heating, if necessary under reduced pressure or by slowly evaporating, e.g. at room temperature,
(iii) the residue of evaporation is equilibrated with the required amount of water by

(a) suspending the residue of evaporation, which is advantageously still warm, and which still contains some water, in an appropriate solvent or

(b) by equilibrating the water excess in the solvent;

whereby in a) and b) the existing or added water is present in a quantity in which the water dissolves in the organic solvent and does not form an additional phase; and

(iv) the salt obtained is isolated.

The solvent system used as the water-containing organic solvent advantageously comprises mixtures of suitable alcohols, such as C_1-C_7-alkanols, especially ethanol, and water.

An appropriate solvent for equilibration is, for example, an ester such as C_1-C_7-alkane-carboxylic acid-C_1-C_7-alkylester, especially ethyl acetate, or a ketone such as di-C_1-C_5-alkylketone, especially acetone.

The equilibration process is notable for example for its high yields and outstanding reproducibility.

When producing the mono-alkali metal salts according to the present invention, predominantly amorphous forms are obtained. On the other hand, the di-alkali metal salts and alkaline earth metal salts of the present invention may also be obtained in crystalline form and are in the form of hydrates throughout, from appropriate solvents that are conventionally used in production processes, such as esters, e.g. C_1-C_7-alkanecarboxylic acid-C_1-C_7-alkylesters, especially ethyl acetate, ketones, e.g. di-C_1-C_5-alkylketones, especially acetone, C_3-C_7-alkylnitriles, especially acetonitrile, or ethers, e.g. di-(C_1-C_5-alkyl)-ethers, such as tert.-butylmethylether, also tetrahydrofuran, or mixtures of solvents. By using the dissolving and crystallising process, or the water-equilibrating crystallisation process, the defined hydrates, which are present in crystalline and in polymorphous forms, may be obtained reproducibly.

The preparation of the hydrate-free bis-dialkylammonium salts of the present invention is advantageously effected in one step by using an appropriate solvent which is optionally mixed with an antisolvent. In this way, crystalline salts are obtained.

As a rule, the amino acid salts of the present invention are obtained in amorphous form.

The processes for forming salts are likewise objects of the present invention.

These salts or salt hydrates according to the invention are obtained for example by neutralising the acid valsartan with a base corresponding to the respective cation. This neutralisation is suitably effected in an aqueous medium, e.g. in water or a mixture of water and a solvent in which valsartan is more soluble than in water. Salts with weaker bases may be converted into other salts either by treating with stronger bases or by treating with acids and then neutralising with other bases.

Crystallisation, especially of the alkaline earth salt hydrates, is effected in water or an aqueous medium, which consists of water and at least one solvent that is miscible or partially miscible with water, i.e. not too non-polar, e.g. an alkanol such as methanol, ethanol, propanol, isopropanol, butanol, acetone, methyl ethyl ketone, acetonitrile, DMF, DMSO. The alkanol portion amounts to about 10 to 90, or 20 to 70, advantageously 30 to 50% by volume. For higher alkanols, the less polar solvent may also be present in lower concentrations. Owing to the restricted water-solubility of valsartan, the process frequently takes place in suspensions, or if valsartan is soluble in the other solvent component, in a solution.

In one embodiment, for example to produce the calcium salt of valsartan, an aqueous solution of valsartan is neutralised with a calcium hydroxide solution at room temperature and the solution is left to crystallise. In a preferred procedure, crystallisation is effected from a solvent mixture of water/ethanol, the ethanol proportion amounting to ca. 30 to 50% by volume. In an especially preferred form, crystallisation is effected in a closed system by transporting through a low temperature gradient (especially 1-2°C at 40°C) in 30% by volume of ethanol.

In a preferred variant, crystallisation may be optimised, e.g. accelerated, by adding at least one seed crystal.

The salts according to the invention may be used e.g. in the form of pharmaceutical preparations, which contain the active substance e.g. in a therapeutically effective amount

of the active substance, optionally together with a pharmaceutically acceptable carrier, for example with an inorganic or organic, solid or optionally also liquid pharmaceutically acceptable carrier, which is suitable for enteral, e.g. oral, or parenteral administration.

The invention relates in particular to a pharmaceutical composition, especially in a solid dosage unit, preferably for oral administration, optionally together with a pharmaceutically acceptable carrier.

Pharmaceutical preparations of this kind may be used for example for the prophylaxis and treatment of diseases or conditions which may be inhibited by blocking the AT_1 receptor for example
a disease or condition selected from the group consisting of
(a) hypertension, congestive heart failure, renal failure, especially chronic renal failure, restenosis after percutaneous transluminal angioplasty, and restenosis after coronary artery bypass surgery;
(b) atherosclerosis, insulin resistance and syndrome X, diabetes mellitus type 2, obesity, nephropathy, renal failure, e.g. chronic renal failure, hypothyroidism, survival post myocardial infarction (MI), coronary heart diseases, hypertension in the elderly, familial dyslipidemic hypertension, increase of formation of collagen, fibrosis, and remodeling following hypertension (antiproliferative effect of the combination), all these diseases or conditions associated with or without hypertension;
(c) endothelial dysfunction with or without hypertension,
(d) hyperlipidemia, hyperlipoproteinemia, atherosclerosis and hypercholesterolemia, and
(e) glaucoma.

Primary usages are for the treatment of high blood pressure and congestive heart failure, as well as post-myocardial infarction.

The person skilled in the pertinent art is fully enabled to select a relevant and standard animal test model to prove the hereinbefore and hereinafter indicated therapeutic indications and beneficial effects.

The pharmaceutical activities as effected by administration of representatives of the salts of the present invention or of the combination of active agents used according to the present

invention can be demonstrated e.g. by using corresponding pharmacological models known in the pertinent art. The person skilled in the pertinent art is fully enabled to select a relevant animal test model to prove the hereinbefore and hereinafter indicated therapeutic indications and beneficial effects.

These beneficial effects can, for example, be demonstrated in the test model as disclosed by G. Jeremic et al. in J. Cardovasc. Pharmacol. 27:347-354, 1996.

For example, the valuable potential of the salts or combinations of the present invention for the prevention and treatment of myocardial infarction can be found using the following test model.

Study design

In the study to be performed, permanent coronary artery occlusion (CAO) in rats is used as a model of acute myocardial infarction. The experiments are carried out with 5 treatment groups characterized by following features:

- sham-operated animals
- CAO + vehicle
- CAO + a salt according to the present invention,

optionally

- CAO + a salt according to the present invention + a combination partner.

During the study following variables are measured:

- infarct size
- LV chamber volume
- interstitial and perivascular collagen density in spared LV myocardium
- COL-I and COL-III protein content in spared LV myocardium by Western blot
- cardiomyocytes cross-sectional area and length in sections of LV myocardium
- plasma concentrations of renin and aldosterone
- urine concentration of sodium, potassium and aldosterone
- blood pressure in conscious animals
- LV and carotid blood pressure in anesthetized animals.

Methodology

Infarct size: Six µm-thick transverse histological sections of the left ventricle are stained with nitroblue tetrazolium and acquired by a B/W XC-77CE CCD video camera (Sony). The resulting image is processed on a KS 300 image analysis system (Carl Zeiss Vision) using a software specifically developed (Porzio *et al.,* 1995). A single operator blinded to treatment interactively defines the boundaries of the interventricular septum, and the infarcted area on each section is semiautomatically identified as the area of unstained ventricular tissue. The software automatically calculates for each component of the ventricular section defined as the chamber, septum, infarcted area, infarcted LV wall and viable LV wall, a set of geometric parameters (Porzio *et al.,* 1995).

Histology: Hearts are fixed in situ, by retrograde perfusion with buffered 4% formaldehyde after arrest in diastole by i.v. injection of 0.5 M KCl. After fixation, the left ventricle (LV) and the free wall of the right ventricle are separately weighed; LV longer diameter is measured with a caliper. LV histological sections are stained with hematoxylin & eosin for qualitative examination and to quantify cardiomyocytes cross-sectional area with a semi-automated image analysis routine. Interstitial collagen deposition in LV is evaluated on Sirius red stained sections with a semi-automated image analysis routine (Masson *et al.,* 1998).

Collagen content in LV spared myocardium: LV tissue in the spared myocardium is homogenized, subjected to PAGE-SDS electrophoresis and electroblotted onto nitrocellulose membrane. The blots are exposed to primary antibodies, i.e. rabbit anti-rat collagen type I or type III antiserum (Chemicon). The primary antibodies are recognized by secondary antibodies conjugated to alkaline phosphatase (for colagen type I) or peroxidase (collagen type III).

Left ventricular chamber volume: LV chamber volume is determined in hearts arrested in diastole (KCl) and fixed in formalin under a hydrostatic pressure equivalent to the measured LV end-diastolic pressure. A metric rod is inserted into the LV to measure LV inner length. The transverse diameters of the LV chamber are measured in two 1-mm thick transverse sections near to the base and the apex of the ventricle (Jeremic *et al.,* 1996). The chamber volume is computed from an equation integrating transverse diameters and inner length.

Systemic and Left ventricular hemodynamics: A microtip pressure transducer (Millar SPC-320) connected to a recorder (Windograf, Gould Electronics) is inserted into the right carotid artery to record systolic and diastolic blood pressures. The pressure transducer is advanced into the LV to measure LV systolic (LVSP) and end-diastolic (LVEDP) pressures, the first derivative of LV pressure over time (+dP/dt) and heart rate.

Non-invasive blood pressure: Systolic blood pressure and heart rate are measured by the tail-cuff method (Letica LE 5002) in conscious rats.

Urine electrolytes, hormones: Rats are individually housed in metabolic cages and 24-h urine collected on 1 ml HCl 6N. Water intake is measured. Urine catecholamines are extracted on Bondelut C_{18} columns (Varian), separated by HPLC (Apex-II C18, 3 µm, 50x4.5 mm analytical column, Jones Chromatography) and quantified with an electrochemical detector (Coulochem II, ESA) (Goldstein *et al.,* 1981). Plasma and urine aldosterone, and plasma angiotensin II is determined with specific radioimmunoassays (Aldoctk-2, DiaSorin and Angiotensin II, Nichols Diagnostics). Urine sodium and potassium are measured by flamme photometry.

<u>Sample size</u>

10 animals analyzable in each treatment groups are sufficient to detect biologically significant differences. Only rats with an infarct size of at least 10% of the LV section area are included in the final analysis.

Endothelial dysfunction is being acknowledged as a critical factor in vascular diseases. The endothelium plays a bimodal role as the source of various hormones or by-products with opposing effects: vasodilation and vasoconstriction, inhibition or promotion of growth, fibrinolysis or thrombogenesis, production of anti-oxidants or oxidising agents. Genetically predisposed hypertensive animals with endothelial dysfunction constitute a valid model for assessing the efficacy of a cardiovascular therapy.

Endothelial disfunction is characterized by, for example, increased oxidative stress, causing decreased nitric oxide, increased factors involved in coagulation or fibrinolysis such as plasminogen activating inhibitor-1 (PAI-1), tissue factor (TF), tissue plasminogen activator (tPA), increased adhesion molecules such as ICAM and VCAM, increased growth factors

such as bFGF, TGFb, PDGF, VEGF, all factors causing cell growth inflammation and fibrosis.

The treatment e.g. of endothelian dysfunction can be demonstrated in the following pharmacological test:

Material and methods
Male 20-24 week-old SHR, purchased from RCC Ldt (Füllingsdorf, Switzerland), are maintained in a temperature- and light-controlled room with free access to rat chow (Nafag 9331, Gossau, Switzerland) and tap water. The experiment is performed in accordance with the NIH guidelines and approved by the Canton Veterinary office (Bew 161, Kantonales Veterinäramt, Liestal, Switzerland). All rats are treated with the NO synthesis inhibitor L-NAME (Sigma Chemicals) administered in drinking water (50 mg/l) for 12 weeks. The average daily dose of L-NAME calculated from the water consumed was 2.5 mg/kg/d (range 2.1-2.7).

The rats can be divided into 2 or 3 groups: group 1, control (n = e.g. 40); Group 2, a salt according to the present invention; n = e.g. 40); for testing combinations Group 3, combination partner;(n = e.g. 30). The drugs are administered in drinking fluid. The pressure effect of Ang II at 1 mg/kg obtained in controls normotensive rats can be reduced after treatment with a salt according to the present invention (Gervais et al. 1999).

Body weight is measured every week. Systolic blood pressure and heart rate are recorded by tail cuff plethysmography 3 and 2 weeks before starting the study and at 2 weeks after drug administration. Urine is collected over a 24 hour period from rats kept in individual (metabolic) cages the week before starting treatment and at weeks 4 and 12 for volume measurement and protein, creatinine, sodium and potassium determination using standard laboratory methods. At the same time points, blood samples are withdrawn from the retro-orbital plexus (maximum 1 ml) for creatinine, Na^+ and K^+ assays.

Ten rats from each group are sacrificed at 4 weeks for collection of kidney and heart for morphological analysis. The remaining rats are sacrificed at 12 weeks. Cardiac and kidney weight is recorded. Terminal blood sampling is performed in 5 % EDTA at 4 (morphometry

study) and 12 (end of the study) weeks for aldosterone, determination by radioimmunoassay using a DPC coat-a-count aldosterone-RIA kit (Bühlmann, Switzerland).

Statistical analysis:

All data are expressed as mean ± SEM. Statistical analysis is performed using a one-way ANOVA, followed by a Duncan's multiple range test and a Newman-Keuls test, 7for comparison between the different groups. Results with a probability value of less than 0.05 are deemed statistically significant.

An improvement of regression of artherosclerosis without effecting the serum lipid levels can, for example, be demonstrated by using the animal model as disclosed by H. Kano et al. in Biochemical and Biophysical Research Communications 259, 414-419 (1999).

That the salts or combinations according to the present invention can be used for the regression of a cholesterol diet-induced atherosclerosis, can be demonstrated using the test model described, e.g., by C. Jiang et al. in Br. J. Pharmacol. (1991), 104, 1033-1037.

That the salts or combinations according to the present invention can be used for the treatment of renal failure, especially chronic renal failure, can be demonstrated using the test model described, e.g., by D. Cohen et al. in Journal of Cardiovascular Pharmacology, 32: 87-95 (1998).

The present pharmaceutical preparations which, if so desired, may contain further pharmacologically active substances, are prepared in a manner known *per se*, for example by means of conventional mixing, granulating, coating, dissolving or lyophilising processes, and contain from about 0.1% to 100%, especially from about 1% to about 50%, of lyophilisates up to 100% of the active substance.

The invention similarly relates to compositions containing the salts according to the invention.

The invention similarly relates to the use of the salts according to the invention preferably for the production of pharmaceutical preparations, especially for the prophylaxis and also for the treatment of diseases or conditions which may be inhibited by blocking the AT_1

receptor. Primary usages are for the treatment of high blood pressure and congestive heart failure, as well as post-myocardial infarction.

The invention similarly relates to the use for the prophylaxis and treatment of diseases or conditions which may be inhibited by blocking the AT_1 receptor, characterised in that a patient, including a human patient, requiring such treatment is administered with a therapeutically effective amount of a salt according to the invention, optionally in combination with at least one composition for the treatment of cardiovascular diseases and related conditions and diseases listed hereinbefore or hereinafter.

The invention similarly relates to combinations, e.g. pharmaceutical combinations, containing a salt of the present invention or in each case a pharmaceutically acceptable salt thereof in combination with at least one composition for the treatment of cardiovascular diseases and related conditions and diseases as listed hereinbefore or hereinafter, or in each case a pharmaceutically acceptable salt thereof. Combinations with other compositions for the treatment of cardiovascular diseases and related conditions and diseases as listed hereinbefore or hereinafter, or in each case a pharmaceutically acceptable salt thereof, are likewise objects of the present invention.

The combination may be made for example with the following compositions, selected from the group consisting of a:

(i) HMG-Co-A reductase inhibitor or a pharmaceutically acceptable salt thereof,

(ii) angiotensin converting enzyme (ACE) Inhibitor or a pharmaceutically acceptable salt thereof,

(iii) calcium channel blocker or a pharmaceutically acceptable salt thereof,

(iv) aldosterone synthase inhibitor or a pharmaceutically acceptable salt thereof,

(v) aldosterone antagonist or a pharmaceutically acceptable salt thereof,

(vi) dual angiotensin converting enzyme/neutral endopeptidase (ACE/NEP) inhibitor or a pharmaceutically acceptable salt thereof,

(vii) endothelin antagonist or a pharmaceutically acceptable salt thereof,

(viii) renin inhibitor or a pharmaceutically acceptable salt thereof, and

(ix) diuretic or a pharmaceutically acceptable salt thereof.

HMG-Co-A reductase inhibitors (also called β-hydroxy-β-methylglutaryl-co-enzyme-A reductase inhibitors) are understood to be those active agents that may be used to lower the lipid levels including cholesterol in blood.

The class of HMG-Co-A reductase inhibitors comprises compounds having differing structural features. For example, mention may be made of the compounds that are selected from the group consisting of atorvastatin, cerivastatin, compactin, dalvastatin, dihydrocompactin, fluindostatin, fluvastatin, lovastatin, pitavastatin, mevastatin, pravastatin, rivastatin, simvastatin, and velostatin, or, in each case, a pharmaceutically acceptable salt thereof.

Preferred HMG-Co-A reductase inhibitors are those agents which have been marketed, most preferred is fluvastatin and pitavastatin or, in each case, a pharmaceutically acceptable salt thereof.

The interruption of the enzymatic degradation of angiotensin I to angiotensin II with so-called ACE-inhibitors (also called angiotensin converting enzyme inhibitors) is a successful variant for the regulation of blood pressure and thus also makes available a therapeutic method for the treatment of congestive heart failure.

The class of ACE inhibitors comprises compounds having differing structural features. For example, mention may be made of the compounds which are selected from the group consisting alacepril, benazepril, benazeprilat, captopril, ceronapril, cilazapril, delapril, enalapril, enaprilat, fosinopril, imidapril, lisinopril, moveltopril, perindopril, quinapril, ramipril, spirapril, temocapril, and trandolapril, or, in each case, a pharmaceutically acceptable salt thereof.

Preferred ACE inhibitors are those agents that have been marketed, most preferred are benazepril and enalapril.

The class of CCBs essentially comprises dihydropyridines (DHPs) and non-DHPs such as diltiazem-type and verapamil-type CCBs.

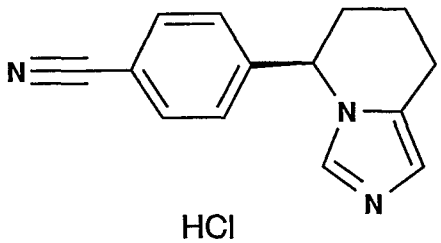
A CCB useful in said combination is preferably a DHP representative selected from the group consisting of amlodipine, felodipine, ryosidine, isradipine, lacidipine, nicardipine, nifedipine, niguldipine, niludipine, nimodipine, nisoldipine, nitrendipine, and nivaldipine, and is preferably a non-DHP representative selected from the group consisting of flunarizine, prenylamine, diltiazem, fendiline, gallopamil, mibefradil, anipamil, tiapamil and verapamil, and in each case, a pharmaceutically acceptable salt thereof. All these CCBs are therapeutically used, e.g. as anti-hypertensive, anti-angina pectoris or anti-arrhythmic drugs. Preferred CCBs comprise amlodipine, diltiazem, isradipine, nicardipine, nifedipine, nimodipine, nisoldipine, nitrendipine, and verapamil, or, e.g. dependent on the specific CCB, a pharmaceutically acceptable salt thereof. Especially preferred as DHP is amlodipine or a pharmaceutically acceptable salt, especially the besylate, thereof. An especially preferred representative of non-DHPs is verapamil or a pharmaceutically acceptable salt, especially the hydrochloride, thereof.

Aldosterone synthase inhibitor is an enzyme that converts corticosterone to aldosterone to by hydroxylating cortocosterone to form 18-OH-corticosterone and 18-OH-corticosterone to aldosterone. The class of aldosterone synthase inhibitors is known to be applied for the treatment of hypertension and primary aldosteronism comprises both steroidal and non-steroidal aldosterone synthase inhibitors, the later being most preferred.

Preference is given to commercially available aldosterone synthase inhibitors or those aldosterone synthase inhibitors that have been approved by the health authorities.

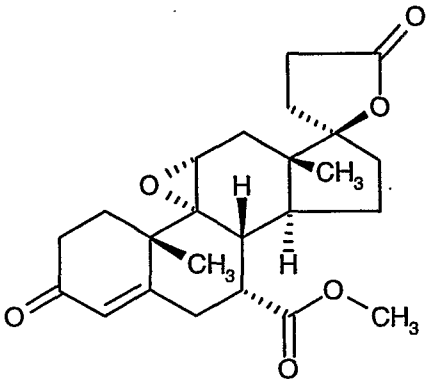
The class of aldosterone synthase inhibitors comprises compounds having differing structural features. For example, mention may be made of the compounds which are selected from the group consisting of the non-steroidal aromatase inhibitors anastrozole, fadrozole (including the (+)-enantiomer thereof), as well as the steroidal aromatase inhibitor exemestane, or, in each case where applicable, a pharmaceutically acceptable salt thereof.

The most preferred non-steroidal aldosterone synthase inhibitor is the (+)-enantiomer of the hydrochloride of fadrozole (US patents 4617307 and 4889861) of formula



HCl

A preferred steroidal aldosterone antagonist is eplerenone of the formula



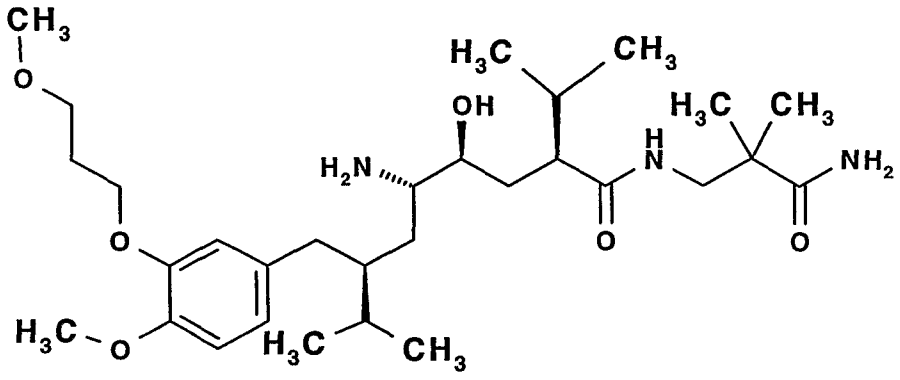
or

spironolactone.

A preferred dual angiotensin converting enzyme/neutral endopetidase (ACE/NEP) inhibitor is, for example, omapatrilate (cf. EP 629627), fasidotril or fasidotrilate, or, if appropriable, a pharmaceutically acceptable salt thereof.

A preferred endothelin antagonist is, for example, bosentan (cf. EP 526708 A), furthermore, tezosentan (cf. WO 96/19459), or in each case, a pharmaceutically acceptable salt thereof.

A renin inhibitor is, for example, a non-peptidic renin inhibitor such as the compound of formula



chemically defined as 2(S),4(S),5(S),7(S)-N-(3-amino-2,2-dimethyl-3-oxopropyl)-2,7-di(1-methylethyl)-4-hydroxy-5-amino-8-[4-methoxy-3-(3-methoxy-propoxy)phenyl]-octanamide. This representative is specifically disclosed in EP 678503 A. Especially preferred is the hemi-fumarate salt thereof.

A diuretic is, for example, a thiazide derivative selected from the group consisting of chlorothiazide, hydrochlorothiazide, methylclothiazide, and chlorothalidon. The most preferred is hydrochlorothiazide.

Preferably, the jointly therapeutically effective amounts of the active agents according to the combination of the present invention can be administered simultaneously or sequentially in any order, separately or in a fixed combination.

The structure of the active agents identified by generic or tradenames may be taken from the actual edition of the standard compendium "The Merck Index" or from databases, e.g. Patents International (e.g. IMS World Publications). The corresponding content thereof is hereby incorporated by reference. Any person skilled in the art is fully enabled to identify the active agents and, based on these references, likewise enabled to manufacture and test the pharmaceutical indications and properties in standard test models, both in vitro and in vivo.

The corresponding active ingredients or a pharmaceutically acceptable salts thereof may also be used in form of a solvate, such as a hydrate or including other solvents, used for crystallization.

The compounds to be combined can be present as pharmaceutically acceptable salts. If these compounds have, for example, at least one basic center, they can form acid addition salts. Corresponding acid addition salts can also be formed having, if desired, an additionally present basic center. The compounds having an acid group (for example COOH) can also form salts with bases.

In a variation thereof, the present invention likewise relates to a "kit-of-parts", for example, in the sense that the components to be combined according to the present invention can be dosed independently or by use of different fixed combinations with distinguished amounts of the components, i.e. simultaneously or at different time points. The parts of the kit of parts can then e.g. be administered simultaneously or chronologically staggered, that is at different time points and with equal or different time intervals for any part of the kit of parts. Preferably, the time intervals are chosen such that the effect on the treated disease or condition in the combined use of the parts is larger than the effect that would be obtained by use of only any one of the components.

The invention furthermore relates to a commercial package comprising the combination according to the present invention together with instructions for simultaneous, separate or sequential use.

Dosaging may depend on various factors, such as mode of application, species, age and/or individual condition. For oral application, the doses to be administered daily are between ca. 0.25 and 10 mg/kg, and for warm-blooded animals with a body weight of ca. 70 kg, preferably between ca. 20 mg and 500 mg, especially 40mg, 80mg, 160mg and 320mg based on the free acid.

The invention is illustrated in particular by the examples and also relates to the new compounds named in the examples and to their usage and to methods for the preparation thereof.

The following examples serve to illustrate the invention without limiting the invention in any way.

For example, the di-potassium salt of valsartan is formed, especially a hydrate thereof. The di-potassium salt is noted in particular for its marked water solubility. The crystalline tetrahydrate of the di-potassium salt of valsartan, with a melting point of 135.0°C, may be mentioned in particular. According to elementary analysis, a certain sample of this hydrate has a water content of 3.72 mols of water per mol of di-potassium salt. For high relative humidity at room temperature, the tetrahydrate is formed and for low values of relative humidity, the anhydrate of the di-potassium salt is formed.

A magnesium salt of valsartan is similarly produced, in this instance as an amorphous solid with 3.4% H_2O. The temperature of glass transition, as a mean value of the stage of the specific heat of 0.85 J • [g • ^{0} C]$^{-1}$ is 167 °C. No melting point is observed. Both facts, namely the glass transition and the absence of a melting point, together with the measured value of the change in specific heat, confirm that this magnesium salt of valsartan is practically 100% amorphous. According to a stereo-specific chromatography method, the enantiomer purity of this amorphous magnesium salt has been determined as 83%.

Example 1:

Production of the calcium salt as the tetrahydrate *in situ* of (S)-N-(1-carboxy-2-methyl-prop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-amine

21.775 g of (S)-N-(1-carboxy-2-methyl-prop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-amine are dissolved at room temperature in 300 ml of ethanol. By careful addition of 300 ml of water, the ethanol concentration is reduced to 50% by volume. Using a magnetic stirrer, 3.89 g of $Ca(OH)_2$ are added slowly in small portions to this clear, slightly acidic (pH 4) solution, so that the pH value temporarily does not exceed a value of ca. 8. Because it absorbs CO_2 from the air, the $Ca(OH)_2$ used contains traces of $CaCO_3$; therefore the added amount includes an excess of 5%. After adding the stoichiometric amount of $Ca(OH)_2$, the pH is ca. 6, and after adding the excess it rises to 7. The solution becomes turbid through the small amount of finely divided $CaCO_3$, which is removed through a folded filter. The product contained in the solution crystallises continuously upon removal of the alcohol content by allowing to stand at room temperature. The procedure can be accelerated by using a flat dish in a recirculating air drier at 40°C. After concentrating to ca. one half, the alcohol content of the solution drops to ca. 10% by

volume and most of the product crystallises. It is filtered, rinsed for a short time with 10% by volume ethanol and dried at 40°C until reaching a constant weight. (S)-N-(1-carboxy-2-methyl-prop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-amine calcium salt tetrahydrate is obtained.

The melting point for the tetrahydrate of the calcium salt of valsartan, produced according to example 1, for a heating rate of 10 $K \cdot min^{-1}$ and in a closed specimen container with a small internal volume is determined as 205°C and the melting enthalpy as 92 $kJ \cdot Mol^{-1}$.
The density of the crystals of the calcium-valsartan-tetrahydrate produced according to example 1, determined by a helium pycnometer, is 1.297 $g \cdot cm^{-3}$. This value conforms to the theoretically calculated value of 1.298 $g \cdot cm^{-3}$ calculated from the single crystal structure.
The optical rotation of the tetrahydrate of the calcium salt of valsartan according to example 1 is measured in methanol as a 1% solution $[a]^{20}_D = +1^\circ$.
The enantiomer purity of the salt hydrate produced according to example 1 is determined by a stereo-specific HPLC method. The stereo-specific separation is achieved by a chiral column (Chiral AGP). The enantiomer purity is determined as ee = 100%.

Calculation of the interlattice plane intervals from the X-ray powder pattern taken with a Guinier camera is as follows for the most important lines for this batch of the tetrahydrate of the calcium salt of valsartan:
d in [Å] : 16.27, 9.90, 9.39, 8.04, 7.71, 7.05, 6.49, 6.34, 6.2, 5.87, 5.75, 5.66, 5.20, 5.05, 4.95, 4.73, 4.55, 4.33, 4.15, 4.12, 3.95, 3.91, 3.87, 3.35.

Elementary analysis gives the following measured values of the elements present in calcium-valsartan-tetrahydrate and of water. The water evaluation was carried out at 130°C after expulsion. The findings of the elementary analysis, within the error limits, correspond to the sum formula $(C_{24}H_{27}N_5O_3)^{2-} Ca^{2+} \cdot 4 H_2O$.

	% found	% calculated
C	52.82	52.83
H	6.42	6.47
N	12.91	12.83
O	20.20	20.53
water	13.25	13.21

Ca	7.03	7.35

Example 2:

Production of the magnesium salt as the hexahydrate *in situ* of (S)-N-(1-carboxy-2-methyl-prop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-amine

43.55 g of valsartan [(S)-N-(1-carboxy-2-methyl-prop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-amine] are dissolved at room temperature in 600 ml of 50% by volume ethanol (from absolute ethanol - see Merck and quarz-bidistilled water). The slightly turbid solution becomes clear after adding a further 50 ml of 50% ethanol. Using a magnetic stirrer, 4.03 g or 0.1 M MgO (Merck p.a.) are slowly added in small portions to this slightly acidic solution with a pH value of 4. The pH value hereby rises to ca. 6. The process is effected with an excess of 10%, i.e. a further 0.40 g of MgO are added. This excess is not fully dissolved, and the pH value rises to ca. 7.5. The small residue is filtered from the solution through a folded filter and washed with 50 ml of 50% ethanol.

The combined clear solution is carefully concentrated at 40°C whilst stirring with a magnetic stirrer in a large crystallisation dish. Towards the end of this procedure, the solution has a tendency to harden into a glassy gel. Scratching with a glass rod induces the *in situ* crystallisation in this phase, which may be recognised by the white colour of the crystalline solid thus formed. The product is dried at 50°C in a recirculating air drier until reaching a constant weight. The yield of magnesium-valsartan-hexahydrate is 53.7 g or 95% based on the valsartan employed as the free acid.

The melting point for the salt hydrate produced according to example2, namely the magnesium-valsartan-hexahydrate, for a heating rate of 10 $K \cdot min^{-1}$ in a sealed sample container with a small internal volume, in an amount of 2.24 mg, was measured at 132°C and the melting enthalpy at 64 $kJ \cdot Mol^{-1}$.

The density of the crystals of the hexahydrate of the magnesium salt of valsartan produced according to example 2, determined by a helium pycnometer, is 1.273 $g \cdot cm^{-3}$. This value conforms to the theoretically calculated value of 1.256 $g \cdot cm^{-3}$ calculated from the single crystal structure.

The optical rotation of the magnesium-valsartan-hexahydrate produced according to example 2 is measured in methanol as a 1% solution $[a]^{20}_D = -14°$.
The enantiomer purity of the salt hydrate produced according to example 2 is determined by a stereo-specific HPLC method. The stereo-specific separation is achieved by a chiral column (Chiral AGP). The enantiomer purity is determined as ee = 99.6 %.

Calculation of the interlattice plane intervals from the X-ray powder pattern taken with a Guinier camera is as follows for the most important lines for this batch of the magnesium valsartan hexahydrate:
d in [Å] : 19.78, 10.13, 9.84, 7.28, 6.00, 5.81, 5.67, 5.21, 5.04, 4.88, 4.21, 4.18, 4.08, 3.95, 3.46, 3.42.

Elementary analysis gives the following measured values of the elements present in the hexahydrate of the magnesium salt of valsartan and of water. The water evaluation is carried out at 130°C after expulsion. The findings of the elementary analysis, within the error limits, correspond to the sum formula ($C_{24}H_{27}N_5O_3)^{2-}Mg^{2+} \cdot 6\ H_2O$.

	% found	% calculated
C	51.03	50.94
H	7.00	6.95
N	12.45	12.38
O	25.02	25.44
water	19.08	19.10
Mg	4.35	4.29

Example 3:
Production of the hydrate of di-potassium salt of (S)-N-(1-carboxy-2-methyl-prop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-amine (3.5 ± 1.0 mole H_2O)

5 g of (S)-N-(1-carboxy-2-methyl-prop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-amine are dissolved whilst heating gently in 11.5 ml of 2 normal potassium hydroxide solution and mixed with 320 ml of acetonitrile. The mixture is heated for 5 minutes to reflux (turbid solution), left without stirring for 3 days at room temperature (seeding) and then left for 24 hours at 0°C. The mother liquor is decanted. The

crystallisate is washed twice with acetonitrile and then dried in the air for 36 hours until reaching a constant weight. (S)-N-(1-carboxy-2-methyl-prop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-amine dipotassium salt hydrate is obtained (3.7 mols water per mol dipotassium salt). The melting point in a closed specimen container is 135°C.

Elementary analysis: C_{24} H_{27} N_5 O_3 K_2, 3.72 H_2O, molar mass 578.72

	% found	% calculated
C	49.90	49.81
H	5.92	6.00
N	12.14	12.10
O	18.55	18.58
water	11.58	11.58
K	13.50	13.51

X-ray diffraction diagram measured with the diffractometer Scintag Inc., Cupertino, CA 95014, US, using CuKα radiation.
Reflection lines and intensities of the most important lines of the hydrate of the di-potassium salt of valsartan, values given in 2θ in °:

2θ in °	Intensity
4.6	strong
8.8	medium
9.2	strong
11.1	weak
12.5	weak
14.8	strong
15.3	weak
16.4	medium
17.8	strong
18.2	medium
18.4	medium
18.9	medium

20.4	medium
21.1	weak
21.3	medium
22.3	weak
22.5	strong
23.1	medium
23.9	strong
25.6	weak
26.6	strong
26.9	medium
28.1	medium

Preferred are hydrates comprising the medium and strong intensity peaks.

Table 11:
Crystal data and parameters of the hydrate of the di-potassium salt of valsartan

Crystal data	
sum formula	$(C_{24}H_{27}N_5O_3)^{2-}2K^+ . x\ H_2O$ (x=3.5±1.0)
molecular mass	574.78
crystal system	orthorhombic
space group	$P2_12_12$
a (Å)	38.555(2)
b (Å)	7.577(1)
c (Å)	10.064(1)
V ($Å^3$)	2940.0(5)
Z	4
F(000)	1212
$D_{calc.}$ ($g.cm^{-3}$)	1.286
number of reflections for cell parameters	25
θ range for cell parameters (°)	30-38
μ (mm^{-1})	3.24
Temperature (°C)	23
crystal shape	prisms

crystal size (mm)	0.63x0.20x0.14
crystal colour	colourless
Data collection	
diffractometer	Enraf Nonius CAD4
radiation (graphite monochromator)	CuKα
wave length (Å)	1.54178
scan mode	ω/2θ
scan range (θ)	3-74
absorption correction	none
number of measured reflections	3450
number of observed reflections (I>2σ(I))	2867
h range	-48→0
k range	-9→0
l range	-12→0
number of standard reflections	3 every 120 mins
variation in intensity	±5%
Structure refinement	
refinement method	refinement on F^2, complete matrix
number of parameters	341
R	0.069
R_W	0.182
S	1.57
number of reflections used	2867
treatment of H-atoms	"riding", apart from those of the water molecules ,which were ignored
Δ/σ_{max}	0.24
extinction correction	0.0010(5)
maximum/minimum residual electron density in final difference-Fourier calculation	0.815/-0.676(eÅ^{-3})
absolute structure parameters	-0.02(4)

Programmes used

SHELXS86 (Sheldrick, Göttingen),
XHELXL93 (Sheldrick, Göttingen),
SCHAKAL92 (Keller, Freiburg)

Example 4:

Production of the di-potassium salt of (S)-N-(1-carboxy-2-methyl-prop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-amine

25 g of (S)-N-(1-carboxy-2-methyl-prop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-amine are dissolved in 200 ml of ethanol. 50 ml of water are added, the solution cooled to 0°C and then mixed with 57.4 ml of 2 normal potassium hydroxide solution. The mixture is concentrated by evaporation on a rotary evaporator, evaporated again with each of toluene and acetonitrile, and dried in a high vacuum for 15 minutes at 50°C. The product is dissolved in 290 ml of a hot mixture of acetonitrile/water (95:5), mixed with an additional 110 ml of acetonitrile, allowed to cool and seeded at ca. 30°C. The mixture is left to stand for 4 days at room temperature and filtered by suction. The residue is washed with acetonitrile/water (95:5) and dried in a high vacuum at 80°C. (S)-N-(1-carboxy-2-methyl-prop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-amine dipotassium salt is obtained as a white powder. Melting point >300°C.

Elementary analysis: The material obtained is hygroscopic and can be equilibrated in the air (C_{24} H_{27} N_5 O_3 K_2, 3.96 mols H_2O).

	% found	% calculated
C	49.15	49.44
H	6.02	6.04
N	11.91	12.01
O	19.18	19.1
water	12.23	12.24
K	13.4	13.41

Example 5:

Production of the di-sodium salt of (S)-N-(1-carboxy-2-methyl-prop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-amine

1 g of (S)-N-(1-carboxy-2-methyl-prop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-amine is dissolved in 50 ml of ethanol, mixed with 2.3 ml of 2 normal sodium hydroxide solution and concentrated by evaporation, and the residue is evaporated with each of ethanol and ethyl acetate. The white residue is stirred in hot acetonitrile and filtered by suction at room temperature. Drying in a high vacuum at 80°C over night yields (S)-N-(1-carboxy-2-methyl-prop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-amine disodium salt as a white powder. Melting point from 260°C, brownish discolouration at 295°C.

Elementary analysis: The material obtained (hygroscopic) can be equilibrated in the air (C_{24} H_{27} N_5 O_3 Na_2, 5.36 mols H_2O, molar mass 576.05)

	% found	% calculated
C	49.79	50.04
H	6.51	6.60
N	12.00	12.16
O	23.44	23.22
water	16.75	16.76
Na	8.09	7.98

Example 6:

Production of the magnesium salt of (S)-N-(1-carboxy-2-methyl-prop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-amine

5 g of (S)-N-(1-carboxy-2-methyl-prop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-amine are added to a suspension of 0.666 g of magnesium hydroxide in 20 ml of water. 40 ml of methanol are added, then the mixture is stirred for 2 hours at room temperature and concentrated. The residue is dissolved in methanol, filtered through a hard filter, concentrated and evaporated with acetonitrile. The product is stirred with hot

acetonitrile, filtered by suction at room temperature and dried in a high vacuum at 90°C over night. (S)-N-(1-carboxy-2-methyl-prop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-amine magnesium salt is obtained as a white powder. Melting point: The sample becomes brownish upon heating and vitrifies towards 300°C.

Elementary analysis: C_{24} H_{27} N_5 O_3 Mg, 0.89 mols H_2O, molar mass: 473.85

	% found	% calculated
C	61.26	60.83
H	6.13	6.12
N	14.88	14.78
O		13.13
water	3.39	3.38
Mg	4.74	5.13

Example 7:

Production of the calcium salt of (S)-N-(1-carboxy-2-methyl-prop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-amine

5 g of (S)-N-(1-carboxy-2-methyl-prop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-amine are added to a suspension of 0.851 g of calcium hydroxide in 20 ml of water and then mixed with 200 ml of ethanol. The mixture is stirred for one hour at room temperature, concentrated by evaporation to dryness (re-evaporation with acetonitrile), stirred in hot acetonitrile (with a trace each of ethanol and water) and filtered by suction at room temperature.

0.95 g of the salt are heated to reflux in 20 ml of acetonitrile/water (1:1), whereby the mixture almost dissolves. The mixture is allowed to cool to room temperature, mixed with 20 ml of acetonitrile, filtered by suction and washed twice with acetonitrile/water (1:1) and dried over night in a high vacuum at 80°C. Melting point: from 300°C (decomposition).

Elementary analysis: C_{24} H_{27} N_5 O_3 Ca, 1.71 mols H_2O, molar mass 504.39 (water evaluation carried out after expulsion at 150°C).

	% found	% calculated
C	56.88	57.15
H	6.13	6.08
N	13.89	13.88
O		14.94
water	6.12	6.11
Ca	7.94	7.95

Example 8:

Production of the mono-potassium salt of (S)-N-(1-carboxy-2-methyl-prop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-amine

2 g of (S)-N-(1-carboxy-2-methyl-prop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-amine are suspended in 20 ml of water and mixed with 2.296 ml of a 2 normal potassium hydroxide solution. The mixture is stirred for 30 minutes and mixed with 50 ml of ethanol, whereupon a colourless solution is obtained. The mixture is concentrated by evaporation, evaporated once more with acetonitrile and lyophilised from tert.-butanol (with a trace of water).

Elementary analysis (after equilibration in the air). C_{24} H_{27} N_5 O_3 Ca, 1.69 mols H_2O, molar mass 504.06 (water evaluation carried out after expulsion at 150°C).

	% found	% calculated
C	57.30	57.19
H	6.35	6.27
N	13.61	13.89
O	14.58	14.89
water	6.04	6.04
K	7.72	7.76

Example 9:

Production of the magnesium salt as the hexahydrate of valsartan by a water-equilibrating process.

1600 g of valsartan and 6820 g of isopropanol are stirred to form a suspension in a mixing container at room temperature, and added to an 80 litre glass receptacle with a stirrer. The mixing container is rinsed with 3919 g of isopropanol in portions and the rinsing solution added to the main mixture. After adding 3800 g of deionised water, the mixture is transformed into a homogeneous solution by stirring. Then, 156.3 g of magnesium oxide, suspended in 1520 g of deionised water, are added and the suspension supplemented with 1000 g of deionised water. By slowly stirring at room temperature, the magnesium oxide goes into solution. The pH value of the resulting solution is ca. 7.2. By adding a further 2.5 g of magnesium oxide in small portions, the pH value is raised to ca. 8.3. The resulting mixture is turbid owing to undissolved particles of unknown type in the magnesium oxide.

This mixture is transferred through a candle filter to a 35 litre enamel boiler and the glass receptacle and the transfer tube are rinsed with 885 g of isopropanol and 1122 g of deionised water. For mild concentration, a vacuum is created in the boiler to an initial theoretical value of 89-100 mbar. With a temperature of the heating medium of 45-50°C and a boiling temperature of the mixture of 37-40°C, a total of 13.66 kg of aqueous isopropanol is distilled. By lowering the distillation pressure to a final value of 10 mbar and simultaneously raising the heating medium temperature to 65°C, the amount of distillate is increased to a total of 17.12 kg. 9300 g of ethyl acetate, followed by 14.9 g of valsartan Mg salt hexahydrate as seeding crystals, are added to the boiler content whilst stirring. Finally, a further 6680 g of ethyl acetate are dispensed in and cooling is effected to room temperature whilst stirring. The stirring procedure is maintained for at least 24 hours. The suspension is then filtered through Büchner filters. A moist filter cake is thus obtained. The boiler is rinsed with 1171 g of ethyl acetate and the rinsing mixture is used to wash the filter cake. Drying of a partial amount on metal sheets in a vacuum drying chamber at 50 mbar pressure and 40°C oven temperature for 6.5 hours until reaching a constant weight yields a dry substance.

The physical data, especially the X-ray powder pattern, correspond to the magnesium hexahydrate salt of example 2.

Example 10:

Production of the calcium salt of valsartan as the tetrahydrate.

1600 g of valsartan and 7000 g of ethanol are stirred to form a suspension in a mixing container at room temperature, and added to a 35 litre enamel boiler with a stirrer. The mixing container is rinsed with 2000 g of ethanol in portions and the rinsing solution added to the main mixture. After adding 9000 g of deionised water, the mixture is transformed into a homogeneous solution by stirring. Then, 272 g of calcium hydroxide, suspended in 1500 g of deionised water, are added and the suspension supplemented with 1300 g of deionised water. By slowly stirring at room temperature, the calcium hydroxide goes into solution. The pH value of the resulting solution is ca. 6.9. By adding a further 9.6 g of calcium hydroxide, the pH value is raised to ca. 10.6. The resulting mixture is turbid owing to undissolved particles (calcium carbonate) in the calcium hydroxide. This mixture is transferred through a candle filter to a 35 litre enamel boiler and the glass receptacle and the transfer tube are rinsed with a solution of 1048 g of ethanol and 1000 g of deionised water. For mild concentration, a vacuum is created in the boiler to a theoretical value of 100-120 mbar. With a temperature of the heating medium of ca. 50°C and a boiling temperature of the mixture of max. 44°C, a total of 11.32 kg of aqueous ethanol is distilled. The dissolved salt crystallises spontaneously during the course of distillation. The suspension present at the end of distillation is cooled to ca. 5°C whilst stirring, and is stirred for ca. 16 hours at 5°C. The suspension is then filtered through Büchner filters. The boiler is rinsed with a mixture of 3600 ml of deionised water and 400 ml of ethanol, the mixture being cooled to 5°C, and the rinsing mixture is used to wash the filter cake. A moist filter cake is thus obtained. Drying of a partial amount on metal sheets in a vacuum drying chamber at 50 mbar pressure and 40°C oven temperature for 24 hours until reaching a constant weight yields a dry substance.

The physical data, especially the X-ray powder pattern, correspond to the calcium tetrahydrate salt of example 1.

Example 11:

Hydrate of valsartan disodium salt (2.4 ± 1.0 mole H_2O):

50 ml of 2N sodium hydroxide solution are added dropwise at ca. 25°C to a solution of 21.5 g of valsartan in 200 ml of isopropanol. The clear solution (pH ca. 7.2) is concentrated under vacuum at ca. 40°C. The amorphous residue of the disodium salt is suspended in 100 ml of isopropanol, and water is removed by concentrating under vacuum once more at ca. 40°C and degassing. The amorphous residue is suspended in 75 ml of acetone and 2 ml of water at ca. 40°C. At ca. 25-30°C, 200 ml of tert.-butylmethylether are added, whereby constituents that are initially smeary are gradually transformed into a crystalline suspension. After stirring over night at ca. 25°C, the suspension is cooled to 10°C and after ca. 1 hour is filtered by suction whilst excluding atmospheric moisture. Washing then takes place with 20 ml of tert.-butylmethylether. The moist filter cake is dried over night at ca. 30 mbar and at 30°C. A colourless, slightly hygroscopic crystal powder is obtained.

Elementary analysis: C_{24} H_{27} N_5 O_3 Na_2, 2.44 mols H_2O

	% found	% calculated
C	55.03	55.07
H	6.16	6.14
N	13.38	13.38
O		16.63
water	8.40	8.41
Na	8.67	8.78

X-ray diffraction diagram (reflection lines and intensities of the most important lines) of the crystalline hydrate of the disodium salt of valsartan measured with the diffractometer Scintag Inc. Cupertino, CA 95014, US, using CuKα radiation:

2θ	Intensity
4.7	strong
9.1	strong
13.3	weak
13.7	weak
15.6	medium
16.4	medium

17.2	medium
17.9	medium
18.7	medium
19.6	medium
21.3	medium
21.9	medium
22.8	strong
24.0	weak
24.8	weak
25.5	weak
26.5	medium
26.8	weak
27.3	weak
27.8	weak
28.6	weak
29.4	weak
29.9	medium

Example 12:

Hydrate of the valsartan dipotassium salt (3.4 ± 1.0 mole H_2O):

6.9 g of potassium carbonate are added at ca. 25°C to the solution of 21.7 g of valsartan in 150 ml of acetone and 20 ml of water. After stirring for 2 hours at ca. 25°C, an almost clear solution is obtained, which is concentrated in a vacuum at ca. 50°C bath temperature. 55 ml of acetone are added to the residue (29.3 g) which contains residual water, and at ca. 35°C, over the course of ca. two hours, a total of 250 ml of tert.-butylmethylether is dispensed in. After stirring at ca. 25°C, the easily stirrable crystal suspension is cooled to 10°C, stirred for at least one hour, filtered by suction and washed with 20 ml of tert.butylmethylether. The moist filter cake is dried over night at ca. 30 mbar and at 30°C. A colourless, slightly hygroscopic crystal powder is obtained.

Elementary analysis: C_{24} H_{27} N_5 O_3 K_2, 3.42 mols H_2O

	% found	% calculated
C	50.37	50.28
H	5.87	5.95
N	12.24	12.22
O		17.92
water	10.76	10.75
K	13.4	13.64

X-ray diffraction diagram measured with the diffractometer Scintag Inc., Cupertino, CA 95014, US using a CuKα radiation.

Reflection lines and intensities of the most important lines of the hydrate of the di-potassium salt of valsartan, values given in 2θ in °:

2θ in °	Intensity
4.9	strong
9.4	strong
11.4	weak
12.8	weak
14.0	weak
15.0	weak
15.6	weak
16.6	medium
18.0	weak
18.5	weak
18.9	weak
20.7	weak
21.5	weak
22.0	weak
22.7	medium
23.3	weak
24.1	medium
25.6	weak
25.8	weak

27.1	medium
29.4	weak

Preferred are hydrates comprising medium and strong intensity peaks.

Example 13:

Valsartan calcium/magnesium mixed salt:

21.5 g of valsartan in 200 ml of isopropanol and 100 ml of water are stirred for ca. 3 hours at ca. 25°C with 1.5 g of magnesium hydroxide and 1.9 g of calcium hydroxide. The practically clear solution is concentrated in a vacuum at ca. 50°C. A total of 240 ml of ethyl acetate is added with stirring to the still warm, semi-solid residue which contains residual water. Upon stirring over night at ca. 25°C, initially sticky constituents are transformed into a homogeneous suspension. The suspension is filtered by suction and washed with 20 ml of ethyl acetate. The moist filter cake is dried in a vacuum at 30-40°C. A colourless crystal powder is obtained.

The X-ray diffraction diagram corresponds to a conglomerate of calcium tetrahydrate and magnesium hexahydrate from example 1 and 2.

Example 14:

Valsartan bis-diethylammonium salt:

1.5 g of diethylamine are added dropwise at ca. 25°C to the solution of 4.35 g of valsartan in 60 ml of acetone. After a short time, crystallisation slowly sets in. After stirring over night, the crystallisate is filtered by suction at ca. 20°C, washed with cold acetone and dried in a vacuum at ca. 50°C. A colourless crystal powder is obtained.

Elementary analysis: C_{32} H_{51} N_7 O_3, 0.1 mols H_2O

	% found	% calculated
C	65.82	65.84
H	8.90	8.84
N	16.84	16.80

O		8.52
water	0.34	0.34

X-ray diffraction diagram (reflection lines and intensities of the most important lines) of the crystalline bis-diethylammonium salt

2θ	Intensity
4.7	weak
8.5	strong
9.3	strong
10.8	strong
11.3	weak
13.4	strong
14.0	medium
14.3	weak
14.9	medium
17.1	medium
17.4	medium
17.6	medium
18.3	weak
19.0	medium
20.0	weak
21.2	medium
21.6	weak
22.4	medium
22.7	weak
24.9	medium
25.2	weak
27.0	weak

Example 15:

Valsartan bis-dipropylammonium salt:

2.1 g of dipropylamine are added dropwise at 25°C to the solution of 4.35 g of valsartan in 60 ml of acetone. When crystallisation has set in, the temperature is raised for a brief

period to 40°C and is allowed to drop to room temperature over ca. 2 hours. After stirring over night, the crystallisate is filtered by suction, washed twice with 15 ml of acetone and dried in a vacuum at ca. 40°C. Granular crystals are obtained.

Elementary analysis: C_{36} H_{69} N_7 O_3, 0.05 mols H_2O

	% found	% calculated
C	67.74	67.69
H	9.32	9.33
N	15.36	15.35
O		7.64
water	0.13	0.14

X-ray diffraction diagram (reflection lines and intensities of the most important lines) of the crystalline bis-dipropylammonium salt

2θ	Intensity
8.5	strong
8.9	weak
9.4	strong
10.0	medium
11.2	weak
11.6	weak
12.5	weak
13.2	strong
13.9	strong
14.3	weak
14.7	weak
15.1	weak
15.6	weak
16.0	weak
17.0	medium
17.9	medium
18.7	strong
19.9	weak

20.4	weak
20.6	weak
21.0	strong
21.7	weak
22.3	medium
23.1	strong
24.5	weak
25.5	medium
25.8	weak
26.7	weak
28.6	weak

Example 16:

Bis-dibutylammonium salt of valsartan:

A solution of 2.15 g of valsartan in 30 ml of acetone is mixed with 1.4 g of dibutylamine at ca. 25°C. Crystallisation sets in after a short time, and the thick suspension is gradually diluted with 20 ml of isopropyl acetate over ca. 1 hour. After stirring for 4 hours at ca. 25°C, the crystals are removed by suction, washed twice with 10 ml of isopropyl acetate and dried in a vacuum at 50°C. A colourless, slightly hygroscopic crystal powder is obtained.

Elementary analysis: C_{40} H_{67} N_7 O_3, 0.5 mols H_2O

	% found	% calculated
C	68.25	68.30
H	9.79	9.75
N	13.89	13.94
O		8.01
water	1.33	1.33

X-ray diffraction diagram (reflection lines and intensities of the most important lines) of the crystalline bis-dibutylammonium salt

2θ	Intensity
7.5	very strong
8.5	medium
9.7	strong
12.7	strong
13.3	weak
14.1	strong
15.1	medium
16.4	strong
17.7	weak
18.2	weak
19.5	strong
19.9	medium
20.5	medium
21.4	medium
21.9	medium
22.2	medium
22.6	medium
23.0	strong
23.7	weak
24.2	weak
24.7	medium
25.7	medium
26.0	weak
26.5	weak
28.8	weak

Formulation example 1:

Directly compressed tablet:

No.	Ingredient	proportion per batch [g]	proportion per tablet core [mg]
1	valsartan calcium salt tetrahydrate	134.24	80

2	Avicel PH 102 (microcrystalline cellulose)	60.408	36
3	lactose (crystalline)	96.1494	57.3
4	crospovidone	7.551	4.5
5	aerosil 200 (silica, colloidal anhydrous)	0.839	0.5
6	magnesium stearate (vegetable)	6.2086	3.7

Ingredient no. 1 is sieved through a 0.5 mm sieve and mixed for 15 minutes in a Turbula with ingredients 1-6. Tablets are compress using a single punch tablet press with punches of a diameter of 8mm.

Formulation example 2:

Tablet produced by roller compaction:

No.	Ingredient	proportion per batch [g]	proportion per tablet core [mg]
1	valsartan magnesium salt hexahydrate	400	80
2	Avicel PH 102 (microcrystalline cellulose)	270	54
3	crospovidone	75	15
4	aerosil 200 (silica, colloidal anhydrous)	7.5	1.5
5	magnesium stearate	15	3
6	magnesium stearate	7.5	1.5

Ingredients no. 1-5 are mixed for 50 minutes and compacted on a Freund roller compactor. The band is milled and after admixing ingredient no 6, compressed into tablets using a single punch tablet press with punches of a diameter of 8mm.

What we claim is:

1. A salt of valsartan, selected from the group consisting of the monosodium salt, the monopotassium salt, the disodium salt, the dipotassium salt, the magnesium salt, the calcium salt, the bis-diethylammonium salt, the bis-dipropylammonium salt, the bis-dibutylammonium salt, the mono-L-arginine salt, the bis-L-arginine salt, the mono-L-lysine salt and the bis-L-lysine salt, as well as salt mixtures thereof.

2. A salt according to claim 1 in crystalline, partially crystalline or amorphous form.

3. The calcium salt or the magnesium salt of valsartan according to claim 1.

4. The tetrahydrate of the calcium salt of valsartan according to claim 3.

5. The tetrahydrate according to claim 4, characterised by
(i) an X-ray powder pattern taken with a Guinier camera comprising the following interlattice plane intervals:
d in [Å]: 16.1±0.3, 9.9±0.2, 9.4±0.2, 7.03±0.1, 6.50±0.1, 5.87±0.05, 5.74±0.05, 4.95±0.05, 4.73±0.05, 4.33±0.05, 4.15±0.05, 4.12±0.05, 3.95±0.05; or
(ii) an ATR-IR spectrum having the following absorption bands expressed in reciprocal wave numbers (cm^{-1}):
1621 (st); 1578 (m); 1458 (m); 1441 (m); 1417 (m); 1364 (m); 1012 (m); 758 (m); 738 (m); 696 (m); 666 (m).

6. The hexahydrate of the magnesium salt of valsartan according to claim 1.

7. The hexahydrate according to claim 6, characterised by
(i) an X-ray powder pattern taken with a Guinier camera comprising the following interlattice plane intervals:
d in [Å] : 19.7±0.3, 10.11±0.2, 9.8±0.2, 7.28±0.1, 5.81±0.05, 5.68±0.05, 5.03±0.05, 4.88±0.05, 4.18±0.05, 4.08±0.05, 3.46 ±0.05; or

(ii) an ATR-IR spectrum having the following absorption bands expressed in reciprocal wave numbers (cm^{-1}):
3378 (m); 3274 (m); 2956 (m); 1619 (st); 1557 (m); 1464 (m); 1419 (m); 1394 (st); 1374 (m); 1175 (m); 836 (m); 820 (s); 766 (st); 751 (m); 741 (st); 732 (st).

8. A salt according to one of claims 1-7 in the form of a solvate.

9. A salt according to one of claims 1-8 in the form of a hydrate.

10. A salt according to one of claims 1-9 in a form selected from the group consisting of
(i) a crystalline form;
(ii) a partly crystalline form;
(iii) an amorphous form; and
(iv) a polymorphous form.

11. Pharmaceutical preparation containing a compound according to one of claims 1 to 10 and a pharmaceutically acceptable excipient or additive.

12. Pharmaceutical preparation according to claim 11, containing a salt according to one of claims 1-9 in combination with at least one composition selected from the group consisting of a:
(i) HMG-Co-A reductase inhibitor or a pharmaceutically acceptable salt thereof,
(ii) angiotensin converting enzyme (ACE) inhibitor or a pharmaceutically acceptable salt thereof,
(iii) calcium channel blocker or a pharmaceutically acceptable salt thereof,
(iv) aldosterone synthase inhibitor or a pharmaceutically acceptable salt thereof,
(v) aldosterone antagonist or a pharmaceutically acceptable salt thereof,
(vi) dual angiotensin converting enzyme/neutral endopeptidase (ACE/NEP) inhibitor or a pharmaceutically acceptable salt thereof,
(vii) endothelin antagonist or a pharmaceutically acceptable salt thereof,
(viii) renin inhibitor or a pharmaceutically acceptable salt thereof, and
(ix) diuretic or a pharmaceutically acceptable salt thereof.

13. Use of a compound according to one of claims 1 to 10 in the preparation of a medicament for the prophylaxis or treatment of diseases and conditions which can be inhibited by blocking the AT_1 receptor.

14. Process for the manufacture of a salt according to claim 1, characterised in that

(i) valsartan and the appropriate base are added to a water-containing organic solvent,

(ii) the solvent is concentrated, for example by heating, if necessary under reduced pressure or by slowly evaporating, e.g. at room temperature,

(iii) the residue of evaporation is equilibrated with the required amount of water by

(a) suspending the residue of evaporation, which is advantageously still warm, and which still contains some water, in an appropriate solvent or

(b) by equilibrating the water excess in the solvent;

whereby in a) and b) the existing or added water is present in a quantity in which the water dissolves in the organic solvent and does not form an additional phase; and

(iv) the salt obtained is isolated.

INTERNATIONAL SEARCH REPORT

onal Application No PCT/EP 01/08253

192

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D257/04 A61K31/41 A61P9/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 071 931 A (HUMKE ULRICH) 6 June 2000 (2000-06-06) column 5, line 38-65	1-9
Y	WO 99 67231 A (NICOX SA ;DEL SOLDATO PIERO (IT)) 29 December 1999 (1999-12-29) page 2 -page 5; example 4	1-9
Y	EP 0 443 983 A (CIBA GEIGY AG) 28 August 1991 (1991-08-28) cited in the application page 17, line 47,48; example 16	1-9
P,Y	WO 00 59475 A (LIPOCINE INC) 12 October 2000 (2000-10-12) page 8, line 23 page 14 -page 15	1-9

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 November 2001	04/12/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Lauro, P

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	SPURLOCK C H: "INCREASING SOLUBILITY OF ENOXACIN AND NORFLOXACIN BY MEANS OF SALT FORMATION" JOURNAL OF PARENTERAL SCIENCE AND TECHNOLOGY, vol. 40, no. 2, 1 March 1986 (1986-03-01), pages 70-72, XP000577919 ISSN: 0279-7976 the whole document ---	1-9
Y	BERGE S M ET AL: "PHARMACEUTICALS SALTS" JOURNAL OF PHARMACEUTICAL SCIENCES,US,AMERICAN PHARMACEUTICAL ASSOCIATION. WASHINGTON, vol. 66, no. 1, 1977, pages 1-19, XP000562636 ISSN: 0022-3549 the whole document -----	1-9

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 01/08253

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US 6071931 A	06-06-2000	AU	7213296 A	30-04-1997
		BR	9611007 A	13-07-1999
		CA	2232663 A1	17-04-1997
		WO	9713513 A1	17-04-1997
		EP	0853477 A1	22-07-1998
		JP	11513395 T	16-11-1999
		ZA	9608378 A	07-04-1997
WO 9967231 A	29-12-1999	IT	MI981408 A1	20-12-1999
		AU	4513999 A	10-01-2000
		BR	9911305 A	23-10-2001
		CN	1315945 T	03-10-2001
		WO	9967231 A1	29-12-1999
		EP	1087953 A1	04-04-2001
EP 0443983 A	28-08-1991	AT	134624 T	15-03-1996
		AU	644844 B2	23-12-1993
		AU	7115191 A	22-08-1991
		CA	2036427 A1	20-08-1991
		CA	2232775 A1	20-08-1991
		CY	1978 A	05-09-1997
		DE	59107440 D1	04-04-1996
		DK	443983 T3	18-03-1996
		EP	0443983 A1	28-08-1991
		ES	2084801 T3	16-05-1996
		FI	910747 A	20-08-1991
		FI	980787 A	06-04-1998
		GR	3019155 T3	31-05-1996
		HK	219996 A	03-01-1997
		HU	61271 A2	28-12-1992
		HU	220073 B	28-10-2001
		IE	910548 A1	28-08-1991
		IL	97219 A	08-12-1995
		JP	2749458 B2	13-05-1998
		JP	4235149 A	24-08-1992
		KR	171409 B1	01-02-1999
		LU	90100 A9	25-09-1997
		LU	90362 A9	10-05-1999
		LV	5773 A4	20-12-1996
		MX	24598 A	28-02-1994
		NO	304023 B1	12-10-1998
		NZ	237126 A	25-11-1994
		PH	30484 A	28-05-1997
		PT	96799 A ,B	31-10-1991
		US	5965592 A	12-10-1999
		US	5399578 A	21-03-1995
		ZA	9101179 A	27-11-1991
WO 0059475 A	12-10-2000	AU	3763700 A	23-10-2000
		WO	0059475 A1	12-10-2000

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
16 September 2004 (16.09.2004)

PCT

(10) International Publication Number
WO 2004/078163 A2

(51) International Patent Classification[7]: A61K 9/14, C07C 233/00, C07D 233/00, A61K 31/00

(21) International Application Number: PCT/US2004/006288

(22) International Filing Date: 26 February 2004 (26.02.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/451,213	28 February 2003 (28.02.2003)	US
PCT/US03/06662	3 March 2003 (03.03.2003)	US
60/456,027	18 March 2003 (18.03.2003)	US
60/463,962	18 April 2003 (18.04.2003)	US
10/449,307	30 May 2003 (30.05.2003)	US
PCT/US03/19574	20 June 2003 (20.06.2003)	US
10/601,092	20 June 2003 (20.06.2003)	US
60/487,064	11 July 2003 (11.07.2003)	US
PCT/US03/27772	4 September 2003 (04.09.2003)	US
10/660,202	11 September 2003 (11.09.2003)	US
60/508,208	2 October 2003 (02.10.2003)	US
PCT/US03/41273	24 December 2003 (24.12.2003)	US
60/542,752	6 February 2004 (06.02.2004)	US

(71) Applicants *(for all designated States except US)*: **TRANSFORM PHARMACEUTICALS, INC.** [US/US]; 29 Hartwell Avenue, Lexington, MA 2421 (US). **UNIVERSITY OF SOUTH FLORIDA** [US/US]; Division of Patents and Licensing, 4202 East Flower Avenue, FAO 126, Tampa, FL 33620-7900 (US). **THE REGENTS OF THE UNIVERSITY OF MICHIGAN** [US/US]; Office of Technology Transfer, Wolverine Tower, 3003 South State St., Suite 2071, Ann Arbor, MI 48109-1280 (US). **ZAWOROTKO, Michael, J.** [CA/US]; 4202 E. Fowler Ave (USF30244), Tampa, FL 33620 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **ALMARSSON, Örn** [IS/US]; 22 Farmington Drive, Shrewsbury, MA 01545 (US). **HICKEY, Magali, Bourghol** [US/US]; 342 Malden Street, Medford, MA 02155 (US). **PETERSON, Matthew** [US/US]; 60 Linda Avenue, Framingham, MA 01701 (US). **MOULTON, Brian** [CA/US]; 324 Brook Street, Box H, Providence, RI 02912 (US). **RODRIGUEZ-HORNEDO, Nair** [US/US]; 1690 Northbrook Dr., Ann Arbor, MI 48103 (US).

(74) Agent: **EISENSCHENK, Frank, C.**; Saliwanchik, Lloyd & Saliwanchik, A Professional Association, 2421 N.W. 41 st Street, Suite A-1, Gainesville, FL 32606-6669 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PHARMACEUTICAL CO-CRYSTAL COMPOSITIONS

(57) Abstract: A pharmaceutical composition comprising a co-crystal of an API and a co-crystal former; wherein the API has at least one functional group selected from ether, thioether, alcohol, thiol, aldehyde, ketone, thioketone, nitrate ester, phosphate ester, thiophosphate ester, ester, thioester, sulfate ester, carboxylic acid, phosphinic acid, phosphonic acid, sulfonic acid, amide, primary amine, secondary amine, ammonia, tertiary amine, imine, thiocyanate, cyanamide, oxime, nitrile diazo, organohalide, nitro, S-heterocyclic ring, thiophene, N-heterocyclic ring, pyrrole, 0-heterocyclic ring, furan, epoxide, peroxide, hydroxamic acid, imidazole, pyridine and the co-crystal former has at least one functional group selected from amine, amide, pyridine, imidazole, indole, pyrrolidine, carbonyl, carboxyl, hydroxyl, phenol, sulfone, sulfonyl, mercapto and methyl thio, such that the API and co-crystal former are capable of co-crystallizing from a solution phase under crystallization conditions.

WO 2004/078163 A2

PHARMACEUTICAL CO-CRYSTAL COMPOSITIONS

Cross-Reference to Related Applications

This application is a continuation-in-part of United States Patent Application 10/660,202, filed September 11, 2003 (which claims the benefit of US Provisional Patent Application No. 60/451,213 filed on February 28, 2003; U.S. Provisional Patent Application No. 60/463,962, filed on April 18, 2003; and U.S. Provisional Application No. 60/487,064, filed on July 11, 2003 each of which incorporated herein by reference in its entirety for all purposes.

This application is also a continuation-in-part of PCT US03/27772, filed on September 4, 2003 which is a continuation-in-part of U.S. Patent Application No. 10/378,956, filed March 1, 2003, which claims the benefit of U.S. Provisional Application No. 60/360,768, filed March 1, 2002; said PCT US03/27772 also claims the benefit of US Provisional Patent Application No. 60/451,213 filed on February 28, 2003; U.S. Provisional Patent Application No. 60/463,962, filed on April 18, 2003; and U.S. Provisional Application No. 60/487,064, filed on July 11, 2003 each of which are hereby incorporated by reference in its entirety for all purposes.

Said 10/660,202 and PCT US03/27772 are also continuations-in-part of U.S. Patent Application No. 10/637,829, filed August 8, 2003, which is a divisional of U.S. Patent Application No. 10/295,995, filed November 18, 2002, which is a continuation of U.S. Patent Application No.10/232,589, filed September 3, 2002, which claims the benefit of US Provisional Patent Application No. 60/406,974, filed August 30, 2002 and US Provisional Patent Application No.60/380,288, filed May 15, 2002 and US Provisional Patent Application No. 60/356,764, filed February 15, 2002 each of which are hereby incorporated by reference in its entirety for all purposes.

Said 10/660,202 and PCT US03/27772 are also continuations-in-part of US Patent Application No. 10/449,307, filed May 30, 2003 which claims the benefit of US Provisional Patent Application No. 60/463,962 filed April 18, 2003 and US Provisional Patent Application No. 60/444,315, filed January 31, 2003 and US Provisional Patent Application No. 60/439,282 filed January 10, 2003 and US Provisional Patent Application No. 60/384,152, filed May 31, 2002 each of which are hereby incorporated by reference in its entirety for all purposes.

Said 10/660,202 and PCT US03/27772 are also continuations-in-part of US Patent Application No. 10/601,092, filed June 20, 2003, which claims the benefit of US Provisional Patent Application No. 60/451,213, filed February 28, 2003 each of which are hereby incorporated by reference in its entirety for all purposes.

This application is also a continuation-in-part of U.S. Patent Application No. 10/637,829, filed August 8, 2003, which is a divisional of U.S. Patent Application No. 10/295,995, filed

November 18, 2002, which is a continuation of U.S. Patent Application No.10/232,589, filed September 3, 2002, which claims the benefit of US Provisional Patent Application No. 60/406,974, filed August 30, 2002 and US Provisional Patent Application No.60/380,288, filed May 15, 2002 and US Provisional Patent Application No. 60/356,764, filed February 15, 2002 each of which are hereby incorporated by reference in its entirety for all purposes.

This application is also a continuation-in-part of US Patent Application No. 10/449,307, filed May 30, 2003 which claims the benefit of US Provisional Patent Application No. 60/463,962 filed April 18, 2003 and US Provisional Patent Application No. 60/444,315, filed January 31, 2003 and US Provisional Patent Application No. 60/439,282 filed January 10, 2003 and US Provisional Patent Application No. 60/384,152, filed May 31, 2002 each of which are hereby incorporated by reference in its entirety for all purposes.

This application is also a continuation-in-part of US Patent Application No. 10/601,092, filed June 20, 2003, which claims the benefit of US Provisional Patent Application No. 60/451,213, filed February 28, 2003 each of which are hereby incorporated by reference in its entirety for all purposes.

This application claims benefit of United States Provisional Patent Application 60/508,208, filed October 2, 2003 and United States Provisional Patent Application 60/542,752, filed February 6, 2004 (Entitled: "Modafinil Compositions"; having Docket TPIP044A+; Magali B. Hickey, Matthew Peterson, Orn Almarsson, and Mark Oliveira) each of which are hereby incorporated by reference in its entirety for all purposes.

This application is also a continuation-in-part of PCT/US03/41273, filed December 24, 2003, which is a continuation in part of PCT/03/19584, filed June 20, 2003, which claims the benefit of U.S. Provisional Application No. 60/390,881, filed on June 21, 2002, U.S. Provisional Application No. 60/426,275, filed on November 14, 2002; U.S. Provisional Application No. 60/427,086 filed on November 15, 2002; U.S. Provisional Application No. 60/429,515 filed on November 26, 2002; U.S. Provisional Application No. 60/437,516 filed on December 30, 2002; and U.S. Provisional Application No. 60/456,027 filed on March 18, 2003 each which are hereby incorporated by reference in its entirety for all purposes.

This application is also a continuation-in-part of United States Patent Application 10/601,092, filed June 20, 2003 which claims the benefit of U.S. Provisional Application No. 60/390,881, filed on June 21, 2002, U.S. Provisional Application No. 60/426,275, filed on November 14, 2002; U.S. Provisional Application No. 60/427,086 filed on November 15, 2002; U.S. Provisional Application No. 60/429,515 filed on November 26, 2002; U.S. Provisional Application No. 60/437,516 filed on December 30, 2002; and U.S. Provisional Application No.

60/456,027 filed on March 18, 2003 each of which are hereby incorporated by reference in its entirety for all purposes.

FIELD OF THE INVENTION

The present invention relates to co-crystal API-containing compositions, pharmaceutical compositions comprising such APIs, and methods for preparing the same.

BACKGROUND OF THE INVENTION

Active pharmaceutical ingredients (API or APIs (plural)) in pharmaceutical compositions can be prepared in a variety of different forms. Such APIs can be prepared so as to have a variety of different chemical forms including chemical derivatives or salts. Such APIs can also be prepared to have different physical forms. For example, the APIs may be amorphous, may have different crystalline polymorphs, or may exist in different solvation or hydration states. By varying the form of an API, it is possible to vary the physical properties thereof. For example, crystalline polymorphs typically have different solubilities from one another, such that a more thermodynamically stable polymorph is less soluble than a less thermodynamically stable polymorph. Pharmaceutical polymorphs can also differ in properties such as shelf-life, bioavailability, morphology, vapour pressure, density, colour, and compressibility. Accordingly, variation of the crystalline state of an API is one of many ways in which to modulate the physical properties thereof.

It would be advantageous to have new forms of these APIs that have improved properties, in particular, as oral formulations. Specifically, it is desirable to identify improved forms of APIs that exhibit significantly improved properties including increased aqueous solubility and stability. Further, it is desirable to improve the processability, or preparation of pharmaceutical formulations. For example, needle-like crystal forms or habits of APIs can cause aggregation, even in compositions where the API is mixed with other substances, such that a non-uniform mixture is obtained. It is also desirable to increase or decrease the dissolution rate of API-containing pharmaceutical compositions in water, increase or decrease the bioavailability of orally-administered compositions, and provide a more rapid or more delayed onset to therapeutic effect. It is also desirable to have a form of the API which, when administered to a subject, reaches a peak plasma level faster or slower, has a longer lasting therapeutic plasma concentration, and higher or lower overall exposure when compared to equivalent amounts of the API in its presently-known form. The improved properties discussed above can be altered in a way which is most beneficial to a specific API for a specific therapeutic effect.

SUMMARY OF THE INVENTION

It has now been found that new co-crystalline forms of APIs can be obtained which improve the properties of APIs as compared to such APIs in a non-co-crystalline state (free acid, free base, zwitter ions, salts, etc.).

Accordingly, in a first aspect, the present invention provides a co-crystal pharmaceutical composition comprising an API compound and a co-crystal former, such that the API and co-crystal former are capable of co-crystallizing from a solid or solution phase under crystallization conditions.

Another aspect of the present invention provides a process for the production of a pharmaceutical composition, which process comprises:

(1) providing an API which has at least one functional group selected from ether, thioether, alcohol, thiol, aldehyde, ketone, thioketone, nitrate ester, phosphate ester, thiophosphate ester, ester, thioester, sulfate ester, carboxylic acid, phosphonic acid, phosphinic acid, sulfonic acid, amide, primary amine, secondary amine, ammonia, tertiary amine, imine, thiocyanate, cyanamide, oxime, nitrile, diazo, organohalide, nitro, S-heterocyclic ring, thiophene, N-heterocyclic ring, pyrrole, O-heterocyclic ring, furan, epoxide, peroxide, hydroxamic acid, imidazole, and pyridine;

(2) providing a co-crystal former which has at least one functional group selected from ether, thioether, alcohol, thiol, aldehyde, ketone, thioketone, nitrate ester, phosphate ester, thiophosphate ester, ester, thioester, sulfate ester, carboxylic acid, phosphonic acid, phosphinic acid, sulfonic acid, amide, primary amine, secondary amine, ammonia, tertiary amine, imine, thiocyanate, cyanamide, oxime, nitrile, diazo, organohalide, nitro, S-heterocyclic ring, thiophene, N-heterocyclic ring, pyrrole, O-heterocyclic ring, furan, epoxide, peroxide, hydroxamic acid, imidazole, and pyridine;

(3) grinding, heating, co-subliming, co-melting, or contacting in solution the API with the co-crystal former under crystallization conditions;

(4) isolating co-crystals formed thereby; and

(5) incorporating the co-crystals into a pharmaceutical composition.

A further aspect of the present invention provides a process for the production of a pharmaceutical composition, which comprises:

(1) grinding, heating, co-subliming, co-melting, or contacting in solution an API compound with a co-crystal former, under crystallization conditions, so as to form a solid phase;

(2) isolating co-crystals comprising the API and the co-crystal former; and

(3) incorporating the co-crystals into a pharmaceutical composition.

In a further aspect, the present invention provides a process for the production of a pharmaceutical composition, which comprises:

(1) providing (*i*) an API or a plurality of different APIs, and (*ii*) a co-crystal former or a plurality of different co-crystal formers, wherein at least one of the APIs and the co-crystal formers is provided as a plurality thereof;

(2) isolating co-crystals comprising the API and the co-crystal former; and

(3) incorporating the co-crystals into a pharmaceutical composition.

Solubility Modulation

In a further aspect, the present invention provides a process for modulating the solubility of an API, which process comprises:

(1) grinding, heating, co-subliming, co-melting, or contacting in solution the API with a co-crystal former under crystallization conditions, so as to form a co-crystal of the API and the co-crystal former; and

(2) isolating co-crystals comprising the API and the co-crystal former.

Dissolution Modulation

In a further aspect, the present invention provides a process for modulating the dissolution of an API, whereby the aqueous dissolution rate or the dissolution rate in simulated gastric fluid or in simulated intestinal fluid, or in a solvent or plurality of solvents is increased or decreased, which process comprises:

(1) grinding, heating, co-subliming, co-melting, or contacting in solution the API with a co-crystal former under crystallization conditions, so as to form a co-crystal of the API and the co-crystal former; and

(2) isolating co-crystals comprising the API and the co-crystal former.

In one embodiment, the dissolution of the API is increased.

Bioavailability Modulation

In a further aspect, the present invention provides a process for modulating the bioavailability of an API, whereby the AUC is increased, the time to T_{max} is reduced, the length of time the concentration of the API is above ½ T_{max} is increased, or C_{max} is increased, which process comprises:

(1) grinding, heating, co-subliming, co-melting, or contacting in solution the API with a co-crystal former under crystallization conditions, so as to form a co-crystal of the API and the co-crystal former; and

(2) isolating co-crystals comprising the API and the co-crystal former.

Dose Response Modulation

In a further aspect the present invention provides a process for improving the linearity of a dose response of an API, which process comprises:

(1) grinding, heating, co-subliming, co-melting, or contacting in solution an API with a co-crystal former under crystallization conditions, so as to form a co-crystal of the API and the co-crystal former; and

(2) isolating co-crystals comprising the API and the co-crystal former.

Increased Stability

In a still further aspect the present invention provides a process for improving the stability of a pharmaceutical salt, which process comprises:

(1) grinding, heating, co-subliming, co-melting, or contacting in solution the pharmaceutical salt with a co-crystal former under crystallization conditions, so as to form a co-crystal of the API and the co-crystal former; and

(2) isolating co-crystals comprising the API and the co-crystal former.

Difficult to Salt or Unsaltable Compounds

In a still further aspect the present invention provides a process for making co-crystals of difficult to salt or unsaltable APIs, which process comprises:

(1) grinding, heating, co-subliming, co-melting, or contacting in solution the API with a co-crystal former under crystallization conditions, so as to form a co-crystal of the API and the co-crystal former; and

(2) isolating co-crystals comprising the API and the co-crystal former.

Decreasing Hygroscopicity

In a still further aspect the present invention provides a method for decreasing the hygroscopicity of an API, which method comprises:

(1) grinding, heating, co-subliming, co-melting, or contacting in solution the API with a co-crystal former under crystallization conditions, so as to form a co-crystal of the API and the co-crystal former; and

(2) isolating co-crystals comprising the API and the co-crystal former.

Crystallizing Amorphous Compounds

In a still further embodiment aspect the present invention provides a process for crystallizing an amorphous compound, which process comprises:

(1) grinding, heating, co-subliming, co-melting, or contacting in solution the API with a co-crystal former under crystallization conditions, so as to form a co-crystal of the API and the co-crystal former; and

(2) isolating co-crystals comprising the API and the co-crystal former.

Decreasing Form Diversity

In a still further embodiment aspect the present invention provides a process for reducing the form diversity of an API, which process comprises:

(1) grinding, heating, co-subliming, co-melting, or contacting in solution the API with a co-crystal former under crystallization conditions, so as to form a co-crystal of the API and the co-crystal former; and

(2) isolating co-crystals comprising the API and the co-crystal former.

Morphology Modulation

In a still further embodiment aspect the present invention provides a process for modifying the morphology of an API, which process comprises:

(1) grinding, heating, co-subliming, co-melting, or contacting in solution the API with a co-crystal former under crystallization conditions, so as to form a co-crystal of the API and the co-crystal former; and

(2) isolating co-crystals comprising the API and the co-crystal former.

In a further aspect, the present invention provides a co-crystal composition comprising a co-crystal, wherein said co-crystal comprises an API compound and a co-crystal former. In further embodiments the co-crystal has an improved property as compared to the free form (including a free acid, free base, zwitter ion, hydrate, solvate, etc.) or a salt (which includes salt hydrates and solvates). In further embodiments, the improved property is selected from the group consisting of: increased solubility, increased dissolution, increased bioavailability, increased dose

response, decreased hygroscopicity, a crystalline form of a normally amorphous compound, a crystalline form of a difficult to salt or unsaltable compound, decreased form diversity, more desired morphology, or other property described herein.

BRIEF DESCRIPTION OF THE DRAWINGS

Figs. 1A-B PXRD diffractograms of a co-crystal comprising celecoxib and nicotinamide, with the background removed and as collected, respectively.

Fig. 2 DSC thermogram for a co-crystal comprising celecoxib and nicotinamide.

Fig. 3 TGA thermogram for a co-crystal comprising celecoxib and nicotinamide.

Fig. 4 Raman spectrum for a co-crystal comprising celecoxib and nicotinamide.

Figs. 5A-B PXRD diffractograms of a co-crystal comprising celecoxib and 18-crown-6, with the background removed and as collected, respectively.

Fig. 6 DSC thermogram for a co-crystal comprising celecoxib and 18-crown-6.

Fig. 7 TGA thermogram for a co-crystal comprising celecoxib and 18-crown-6.

Figs. 8A-B PXRD diffractograms of a co-crystal comprising topiramate and 18-crown-6, with the background removed and as collected, respectively.

Fig. 9 DSC thermogram for a co-crystal comprising topiramate and 18-crown-6.

Figs. 10A-B PXRD diffractograms of a co-crystal comprising olanzapine and nicotinamide (Form I), with the background removed and as collected, respectively.

Fig. 11 DSC thermogram for a co-crystal comprising olanzapine and nicotinamide (Form I).

Fig. 12 PXRD diffractogram of a co-crystal comprising olanzapine and nicotinamide (Form II).

Figs. 13A-B PXRD diffractograms of a co-crystal comprising olanzapine and nicotinamide (Form III), with the background removed and as collected, respectively.

Figs. 14A-D Packing diagrams and crystal structure of a co-crystal comprising olanzapine and nicotinamide (Form III).

Fig. 15 PXRD diffractogram of a co-crystal comprising *cis*-itraconazole and succinic acid.

Fig. 16 DSC thermogram for a co-crystal comprising *cis*-itraconazole and succinic acid.

Fig. 17 PXRD diffractogram of a co-crystal comprising *cis*-itraconazole and fumaric acid.

Fig. 18 DSC thermogram for a co-crystal comprising *cis*-itraconazole and fumaric acid.

Fig. 19 PXRD diffractogram of a co-crystal comprising *cis*-itraconazole and L-tartaric acid.

Fig. 20 DSC thermogram for a co-crystal comprising *cis*-itraconazole and L-tartaric acid.

Fig. 21 PXRD diffractogram of a co-crystal comprising *cis*-itraconazole and L-malic acid.

Fig. 22 DSC thermogram for a co-crystal comprising *cis*-itraconazole and L-malic acid.

Fig. 23 PXRD diffractogram of a co-crystal comprising *cis*-itraconazoleHCl and DL-tartaric acid.

Fig. 24 DSC thermogram for a co-crystal comprising *cis*-itraconazoleHCl and DL-tartaric acid.

Fig. 25 PXRD diffractogram of a co-crystal comprising modafinil and malonic acid (Form I).

Fig. 26 DSC thermogram for a co-crystal comprising modafinil and malonic acid (Form I).

Fig. 27 Raman spectrum for a co-crystal comprising modafinil and malonic acid (Form I).

Fig. 28 PXRD diffractogram of a co-crystal comprising modafinil and malonic acid (Form II).

Figs. 29A-B PXRD diffractograms of a co-crystal comprising modafinil and glycolic acid, with the background removed and as collected, respectively.

Figs. 30A-B PXRD diffractograms of a co-crystal comprising modafinil and maleic acid, with the background removed and as collected, respectively.

Figs. 31A-B PXRD diffractograms of a co-crystal comprising 5-fluorouracil and urea, with the background removed and as collected, respectively.

Fig. 32 DSC thermogram for a co-crystal comprising 5-fluorouracil and urea.

Fig. 33 TGA thermogram for a co-crystal comprising 5-fluorouracil and urea.

Fig. 34 Raman spectrum for a co-crystal comprising 5-fluorouracil and urea.

Figs. 35A-B PXRD diffractograms of a co-crystal comprising hydrochlorothiazide and nicotinic acid, with the background removed and as collected, respectively.

Figs. 36A-B PXRD diffractograms of a co-crystal comprising hydrochlorothiazide and 18-crown-6, with the background removed and as collected, respectively.

Figs. 37A-B PXRD diffractograms of a co-crystal comprising hydrochlorothiazide and piperazine, with the background removed and as collected, respectively.

Figs. 38A-B An acetaminophen 1-D polymeric chain and a co-crystal of acetaminophen and 4,4'-bipyridine, respectively.

Figs. 39A-B Pure phenytoin and a co-crystal with phenytoin and pyridone, respectively.

Figs. 40A-D Pure aspirin and the corresponding crystal structure are shown in Figures 40A and 40B, respectively. Figures 40C and 40D show the supramolecular entity containing the synthon and corresponding co-crystal of aspirin and 4,4'-bipyridine, respectively.

Figs. 41A-D Pure ibuprofen and the corresponding crystal structure are shown in Figures 41A and 41B, respectively. Figures 41C and 41D show the supramolecular entity containing the synthon and corresponding co-crystal of ibuprofen and 4,4'-bipyridine, respectively.

Figs. 42A-D Pure flurbiprofen and the corresponding crystal structure are shown in Figures 42A and 42B, respectively. Figures 42C and 42D show the supramolecular synthon and corresponding co-crystal of flurbiprofen and 4,4'-bipyridine, respectively..

Figs. 43A-B The supramolecular entity containing the synthon and the corresponding co-crystal

structure of flurbiprofen and trans-1,2-bis(4-pyridyl)ethylene, respectively.

Figs. 44A–B The crystal structure of pure carbamazepine and the co-crystal structure of carbamazepine and *p*-phthalaldehyde, respectively.

Fig. 45 A packing diagram of the co-crystal structure of carbamazepine and nicotinamide.

Fig. 46 PXRD diffractogram of a co-crystal comprising carbamazepine and nicotinamide.

Fig. 47 DSC thermogram for a co-crystal comprising carbamazepine and nicotinamide.

Fig. 48 A packing diagram of the co-crystal structure of carbamazepine and saccharin.

Fig. 49 PXRD diffractogram of a co-crystal comprising carbamazepine and saccharin.

Fig. 50 DSC thermogram for a co-crystal comprising carbamazepine and saccharin.

Figs. 51A-B The crystal structure of carbamazepine and the co-crystal structure of carbamazepine and 2,6-pyridinedicarboxylic acid, respectively.

Figs. 52A-B The crystal structure of carbamazepine and the co-crystal structure of carbamazepine and 5-nitroisophthalic acid, respectively.

Figs. 53A-B The crystal structure of carbamazepine and the co-crystal structure of carbamazepine and 1,3,5,7-adamantanetetracarboxylic acid, respectively.

Figs. 54A-B The crystal structure of carbamazepine and the co-crystal structure of carbamazepine and benzoquinone, respectively.

Figs. 55A-B The crystal structure of carbamazepine and the co-crystal structure of carbamazepine and trimesic acid, respectively.

Fig. 56 PXRD diffractogram of a co-crystal comprising carbamazepine and trimesic acid.

Fig. 57 Dissolution profile for a co-crystal of celecoxib:nicotinamide vs. celecoxib free acid.

Fig. 58 Dissolution profile for co-crystals of itraconazole:succinic acid, itraconazle:tartaric acid and itraconazole:malic acid vs. itraconazole free base.

Fig. 59 Hygroscopicity profile for a co-crystal of celecoxib:nicotinamide vs. celecoxib sodium.

Fig. 60 Hydrogen-bonding motifs observed in co-crystals.

Fig. 61 Dissolution profile of several formulations of modafinil free form and modafinil:malonic acid (Form I).

DETAILED DESCRIPTION OF THE INVENTION

The term "co-crystal" as used herein means a crystalline material comprised of two or more unique solids at room temperature, each containing distinctive physical characteristics, such as structure, melting point and heats of fusion, with the exception that, if specifically stated, the API may be a liquid at room temperature. The co-crystals

of the present invention comprise a co-crystal former H-bonded to an API. The co-crystal former may be H-bonded directly to the API or may be H-bonded to an additional molecule which is bound to the API. The additional molecule may be H-bonded to the API or bound ionically or covalently to the API. The additional molecule could also be a different API. Solvates of API compounds that do not further comprise a co-crystal former are not co-crystals according to the present invention. The co-crystals may however, include one or more solvate molecules in the crystalline lattice. That is, solvates of co-crystals, or a co-crystal further comprising a solvent or compound that is a liquid at room temperature, is included in the present invention, but crystalline material comprised of only one solid and one or more liquids (at room temperature) are not included in the present invention, with the previously noted exception of specifically stated liquid APIs. The co-crystals may also be a co-crystal between a co-crystal former and a salt of an API, but the API and the co-crystal former of the present invention are constructed or bonded together through hydrogen bonds. Other modes of molecular recognition may also be present including, pi-stacking, guest-host complexation and van der Waals interactions. Of the interactions listed above, hydrogen-bonding is the dominant interaction in the formation of the co-crystal, (and a required interaction according to the present invention) whereby a non-covalent bond is formed between a hydrogen bond donor of one of the moieties and a hydrogen bond acceptor of the other. Hydrogen bonding can result in several different intermolecular configurations. For example, hydrogen bonds can result in the formation of dimers, linear chains, or cyclic structures. These configurations can further include extended (two-dimensional) hydrogen bond networks and isolated triads (Fig. 60). An alternative embodiment provides for a co-crystal wherein the co-crystal former is a second API. In another embodiment, the co-crystal former is not an API. In another embodiment the co-crystal comprises two co-crystal formers. For purposes of the present invention, the chemical and physical properties of an API in the form of a co-crystal may be compared to a reference compound that is the same API in a different form. The reference compound may be specified as a free form, or more specifically, a free acid, free base, or zwitterion; a salt, or more specifically for example, an inorganic base addition salt such as sodium, potassium, lithium, calcium, magnesium, ammonium, aluminum salts or organic base

addition salts, or an inorganic acid addition salts such as HBr, HCl, sulfuric, nitric, or phosphoric acid addition salts or an organic acid addition salt such as acetic, propionic, pyruvic, malanic, succinic, malic, maleic, fumaric, tartaric, citric, benzoic, methanesulfonic, ethanesulforic, stearic or lactic acid addition salt; an anhydrate or hydrate of a free form or salt, or more specifically, for example, a hemihydrate, monohydrate, dihydrate, trihydrate, quadrahydrate, pentahydrate, sesquihydrate; or a solvate of a free form or salt. For example, the reference compound for an API in salt form co-crystallized with a co-crystal former can be the API salt form. Similarly, the reference compound for a free acid API co-crystallized with a co-crystal former can be the free acid API. The reference compound may also be specified as crystalline or amorphous.

According to the present invention, the co-crystals can include an acid addition salt or base addition salt of an API. Acid addition salts include, but are not limited to, inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, and phosphoric acid, and organic acids such as acetic acid, propionic acid, hexanoic acid, heptanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartatic acid, citric acid, benzoic acid, o-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, madelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, *p*-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, *p*-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo[2.2.2]oct-2-ene-1-carboxylic acid, glucoheptonic acid, 4,4'-methylenebis(3-hydroxy-2-ene-1-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutaric acid, hydroxynaphthoic acid, salicylic acid, stearic acid, and muconic acid. Base addition salts include, but are not limited to, inorganic bases such as sodium, potassium, lithium, ammonium, calcium and magnesium salts, and organic bases such as primary, secondary and tertiary amines (e.g. isopropylamine, trimethyl amine, diethyl amine, tri(iso-propyl) amine, tri(n-propyl) amine, ethanolamine, 2-dimethylaminoethanol, tromethamine, lysine, arginine, histidine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, N-alkylglucamines, theobromine, purines, piperazine, piperidine,

morpholine, and N-ethylpiperidine).

The ratio of API to co-crystal former may be stoichiometric or non-stoichiometric according to the present invention. For example, 1:1, 1.5:1, 1:1.5, 2:1 and 1:2 ratios of API:co-crystal former are acceptable.

It has surprisingly been found that when an API and a selected co-crystal former are allowed to form co-crystals, the resulting co-crystals give rise to improved properties of the API, as compared to the API in a free form (including free acids, free bases, and zwitterions, hydrates, solvates, etc.), or an acid or base salt thereof particularly with respect to: solubility, dissolution, bioavailability, stability, Cmax, Tmax, processability, longer lasting therapeutic plasma concentration, hygroscopicity, crystallization of amorphous compounds, decrease in form diversity (including polymorphism and crystal habit), change in morphology or crystal habit, etc. For example, a co-crystal form of an API is particularly advantageous where the original API is insoluble or sparingly soluble in water. Additionally, the co-crystal properties conferred upon the API are also useful because the bioavailability of the API can be improved and the plasma concentration and/or serum concentration of the API can be improved. This is particularly advantageous for orally-administrable formulations. Moreover, the dose response of the API can be improved, for example by increasing the maximum attainable response and/or increasing the potency of the API by increasing the biological activity per dosing equivalent.

Accordingly, in a first aspect, the present invention provides a pharmaceutical composition comprising a co-crystal of an API and a co-crystal former, such that the API and co-crystal former are capable of co-crystallizing from a solution phase under crystallization conditions or from the solid-state, for example, through grinding, heating, or through vapor transfer (e.g., co-sublimation). In another aspect, the API has at least one functional group selected from ether, thioether, alcohol, thiol, aldehyde, ketone, thioketone, nitrate ester, phosphate ester, thiophosphate ester, ester, thioester, sulfate ester, carboxylic acid, phosphonic acid, phosphinic acid, sulfonic acid, amide, primary amine, secondary amine, ammonia, tertiary amine, imine, thiocyanate, cyanamide, oxime, nitrile, diazo, organohalide, nitro, S-heterocyclic ring, thiophene, N-heterocyclic ring, pyrrole, O-heterocyclic ring, furan, epoxide, peroxide, hydroxamic acid, imidazole, and

pyridine and a co-crystal former which has at least one functional group selected from ether, thioether, alcohol, thiol, aldehyde, ketone, thioketone, nitrate ester, phosphate ester, thiophosphate ester, ester, thioester, sulfate ester, carboxylic acid, phosphonic acid, phosphinic acid, sulfonic acid, amide, primary amine, secondary amine, ammonia, tertiary amine, imine, thiocyanate, cyanamide, oxime, nitrile, diazo, organohalide, nitro, S-heterocyclic ring, thiophene, N-heterocyclic ring, pyrrole, O-heterocyclic ring, furan, epoxide, peroxide, hydroxamic acid, imidazole, and pyridine, or a functional group in a Table herein, such that the API and co-crystal former are capable of co-crystallizing from a solution phase under crystallization conditions.

The co-crystals of the present invention are formed where the API and co-crystal former are bonded together through hydrogen bonds. Other non-covalent interactions, including pi-stacking and van der Waals interactions, may also be present.

In one embodiment, the co-crystal former is selected from the co-crystal formers of Table I and Table II. In other embodiments, the co-crystal former of Table I is specified as a Class 1, Class 2, or Class 3 co-crystal former (see column labeled "class" Table I). In another embodiment, the difference in pK_a value of the co-crystal former and the API is less than 2. In other embodiments, the difference in pK_a values of the co-crystal former and API is less than 3, less than 4, less than 5, between 2 and 3, between 3 and 4, or between 4 and 5. Table I lists multiple pK_a values for co-crystal formers having multiple functionalities. It is readily apparent to one skilled in the art the particular functional group corresponding to a particular pK_a value.

In another embodiment the particular functional group of a co-crystal former interacting with the API is specified (see for example Table I, columns labeled "Functionality" and "Molecular Structure" and the column of Table II labeled "Co-Crystal Former Functional Group"). In a further embodiment the functional group of the API interacting with the co-crystal former functional group is specified (see, for example, Tables II and III).

In another embodiment, the co-crystal comprises more than one co-crystal former. For example, two, three, four, five, or more co-crystal formers can be incorporated in a co-crystal with an API. Co-crystals which comprise two or more co-crystal formers and an API are bound together via hydrogen bonds. In one embodiment, incorporated co-

crystal formers are hydrogen bonded to the API molecules. In another embodiment, co-crystal formers are hydrogen bonded to either the API molecules or the incorporated co-crystal formers.

In a further embodiment, several co-crystal formers can be contained in a single compartment, or kit, for ease in screening an API for potential co-crystal species. The co-crystal kit can comprise 5, 10, 15, 20, 25, 30, 40, 50, 60, 70, 80, 90, 100, or more of the co-crystal formers in Tables I and II. The co-crystal formers are in solid form or in solution and in an array of individual reaction vials such that individual co-crystal formers can be tested with one or more APIs by one or more crystallization methods or multiple co-crystal formers can be easily tested against one or more compounds by one or more crystallization methods. The crystallization methods include, but are not limited to, melt recrystallization, grinding, milling, standing, co-crystal formation from solution by evaporation, thermally driven crystallization from solution, co-crystal formation from solution by addition of anti-solvent, co-crystal formation from solution by vapor-diffusion, co-crystal formation from solution by drown-out, co-crystal formation from solution by any combination of the above mentioned techniques, co-crystal formation by co-sublimation, co-crystal formation by sublimation using a Knudsen cell apparatus, co-crystal formation by standing the desired components of the co-crystal in the presence of solvent vapor, co-crystal formation by slurry conversion of the desired components of the co-crystal in a solvent or mixtures of solvents, or co-crystal formation by any combination of the above techniques in the presence of additives, nucleates, crystallization enhancers, precipitants, chemical stabilizers, or anti-oxidants. The co-crystallization kits can be used alone or as part of larger crystallization experiments. For example, kits can be constructed as single co-crystal former single well kits, single co-crystal former multi-well kits, multi-co-crystal former single well kits, or multi-co-crystal former multi-well kits. High-throughput crystallization (e.g., the CrystalMax™ platform) can be used to construct and customize co-crystal former kits. Multi-well plates (e.g., 96 wells, 384 wells, 1536 wells, etc.), for example, can be used to store or employ an array of co-crystal formers.

In a further embodiment, the API is selected from an API of Table IV or elsewhere herein. For pharmaceuticals listed in Table IV, co-crystals can comprise such

APIs in free form (i.e. free acid, free base, zwitter ion), salts, solvates, hydrates, or the like. For APIs in Table IV listed as salts, solvates, hydrates, and the like, the API can either be of the form listed in Table IV or its corresponding free form, or of another form that is not listed. Table IV includes the CAS number, chemical name, or a PCT or patent reference (each incorporated herein in their entireties). In further embodiments, the functional group of the particular API interacting with the co-crystal former is specified. A specific functional group of a co-crystal former, a specific co-crystal former, or a specified functional group or a specific co-crystal former interacting with the particular API may also be specified. It is noted that for Table II, the co-crystal former, and optionally the specific functionality, and each of the listed corresponding interacting groups are included as individual species of the present invention. Thus, each specific combination of a co-crystal former and one of the interacting groups in the same row may be specified as a species of the present invention. The same is true for other combinations as discussed in the Tables and elsewhere herein.

In another embodiment of the present invention, the co-crystal comprises an API wherein the API forms a dimeric primary amide structure via hydrogen bonds with an R^2_2 (8) motif. In such a structure, the NH_2 moiety can also participate in a hydrogen bond with a donor or an acceptor moiety from, for example, a co-crystal former or an additional (third) molecule, and the C=O moiety can participate in a hydrogen bond with a donor moiety from the co-crystal former or the additional molecule. In a further embodiment, the dimeric primary amide structure further comprises one, two, three, or four hydrogen bond donors. In a further embodiment, the dimeric primary amide structure further comprises one or two hydrogen bond acceptors. In a further embodiment, the dimeric primary amide structure further comprises a combination of hydrogen bond donors and acceptors. For example, the dimeric primary amide structure can further comprise one hydrogen bond donor and one hydrogen bond acceptor, one hydrogen bond donor and two hydrogen bond acceptors, two hydrogen bond donors and one hydrogen bond acceptor, two hydrogen bond donors and two hydrogen bond acceptors, or three hydrogen bond donors and one hydrogen bond acceptor. Two non-limiting examples of APIs which form a dimeric primary amide co-crystal structure include modafinil and carbamazepine. Some examples of APIs which include a primary

amide functional group include, but are not limited to, arotinolol, atenolol, carpipramine, cefotetan, cefsulodin, docapromine, darifenacin, exalamide, fidarestat, frovatriptan, silodosin, levetiracetam, MEN-10700, mizoribine, oxiracetam, piracetam, protirelin, TRH, ribavirin, valrecemide, temozolomide, tiazofurin, antiPARP-2, levovirin, N-benzyloxycarbonyl glycinamide, and UCB-34714.

In each process according to the invention, there is a need to contact the API with the co-crystal former. This may involve grinding or milling the two solids together or melting one or both components and allowing them to recrystallize. The use of a granulating liquid may improve or may impede co-crystal formation. Non-limiting examples of tools useful for the formation of co-crystals may include, for example, an extruder or a mortar and pestle. Further, contacting the API with the co-crystal former may also involve either solubilizing the API and adding the co-crystal former, or solubilizing the co-crystal former and adding the API. Crystallization conditions are applied to the API and co-crystal former. This may entail altering a property of the solution, such as pH or temperature and may require concentration of the solute, usually by removal of the solvent, typically by drying the solution. Solvent removal results in the concentration of both API and co-crystal former increasing over time so as to facilitate crystallization. For example, evaporation, cooling, co-sublimation, or the addition of an antisolvent may be used to crystallize co-crystals. In another embodiment, a slurry comprising an API and a co-crystal former is used to form co-crystals. Once the solid phase comprising any crystals is formed, this may be tested as described herein.

The manufacture of co-crystals on a large and/or commercial scale may be successfully completed using one or more of the processes and techniques described herein. For example, crystallization of co-crystals from a solvent and grinding or milling are conceivable non-limiting processes.

In another embodiment, the use of an excess (more than 1 molar equivalent for a 1:1 co-crystal) of a co-crystal former has been shown to drive the formation of stoichiometric co-crystals. For example, co-crystals with stoichiometries of 1:1, 2:1, or 1:2 can be produced by adding co-crystal former in an amount that is 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 50, 75, 100 times or more than the stoichiometric amount for a given co-crystal. Such an excessive use of a co-crystal former to form a co-crystal can be

employed in solution or when grinding an API and a co-crystal former to drive co-crystal formation.

In another embodiment, the present invention provides for the use of an ionic liquid as a medium for the formation of a co-crystal, and can also be used to crystallize other forms in addition to co-crystals (e.g., salts, solvates, free acid, free base, zwitterions, etc.). This medium is useful, for example, where the above methods do not work or are difficult or impossible to control. Several non-limiting examples of ionic liquids useful in co-crystal formation are: 1-butyl-3-methylimidazolium lactate, 1-ethyl-3-methylimidazolium lactate, and 1-butylpyridinium hexafluorophosphate.
The co-crystals obtained as a result of one or more of the above processes or techniques may be readily incorporated into a pharmaceutical composition by conventional means. Pharmaceutical compositions in general are discussed in further detail below and may further comprise a pharmaceutically-acceptable diluent, excipient or carrier.

In a further aspect, the present invention provides a process for the production of a pharmaceutical composition, which process comprises:

(1) providing an API which has at least one functional group selected from ether, thioether, alcohol, thiol, aldehyde, ketone, thioketone, nitrate ester, phosphate ester, thiophosphate ester, ester, thioester, sulfate ester, carboxylic acid, phosphonic acid, phosphinic acid, sulfonic acid, amide, primary amine, secondary amine, ammonia, tertiary amine, imine, thiocyanate, cyanamide, oxime, nitrile diazo, organohalide, nitro, S-heterocyclic ring, thiophene, N-heterocyclic ring, pyrrole, O-heterocyclic ring, furan, epoxide, peroxide, hydroxamic acid, imidazole, and pyridine or of Table II or III;

(2) providing a co-crystal former which has at least one functional group selected from ether, thioether, alcohol, thiol, aldehyde, ketone, thioketone, nitrate ester, phosphate ester, thiophosphate ester, ester, thioester, sulfate ester, carboxylic acid, phosphonic acid, phosphinic acid, sulfonic acid, amide, primary amine, secondary amine, ammonia, tertiary amine, imine, thiocyanate, cyanamide, oxime, nitrile, diazo, organohalide, nitro, S-heterocyclic ring, thiophene, N-heterocyclic ring, pyrrole, O-heterocyclic ring, furan, epoxide, peroxide, hydroxamic acid, imidazole, and pyridine or of Table I, II, or III;

(3) grinding, heating or contacting in solution the API with the co-crystal former under crystallization conditions;

(4) isolating co-crystals formed thereby; and

(5) incorporating the co-crystals into a pharmaceutical composition.

In a still further aspect the present invention provides a process for the production of a pharmaceutical composition, which comprises:

(1) grinding, heating or contacting in solution an API with a co-crystal former, under crystallization conditions, so as to form a solid phase;

(2) isolating co-crystals comprising the API and the co-crystal former; and

(3) incorporating the co-crystals into a pharmaceutical composition.

Assaying the solid phase for the presence of co-crystals of the API and the co-crystal former may be carried out by conventional methods known in the art. For example, it is convenient and routine to use powder X-ray diffraction techniques to assess the presence of co-crystals. This may be affected by comparing the spectra of the API, the crystal former and putative co-crystals in order to establish whether or not true co-crystals had been formed. Other techniques, used in an analogous fashion, include differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), solid state NMR spectroscopy, and Raman spectroscopy. Single crystal X-ray diffraction is especially useful in identifying co-crystal structures.

In a further aspect, the present invention therefore provides a process of screening for co-crystal compounds, which comprises:

(1) providing (*i*) an API compound, and (*ii*) a co-crystal former; and

(2) screening for co-crystals of APIs with co-crystal formers by subjecting each combination of API and co-crystal former to a step comprising:

(a) grinding, heating, co-subliming, co-melting, or contacting in solution the API with the co-crystal former under crystallization conditions so as to form a solid phase; and

(b) isolating co-crystals comprising the API and the co-crystal former.

An alternative embodiment is drawn to a process of screening for co-crystal compounds, which comprises:

(1) providing (*i*) an API or a plurality of different APIs, and (*ii*) a co-crystal former or a plurality of different co-crystal formers, wherein at least one of the API and the co-crystal former is provided as a plurality thereof; and

(2) screening for co-crystals of APIs with co-crystal formers by subjecting each combination of API and co-crystal former to a step comprising

(a) grinding, heating, co-subliming, co-melting, or contacting in solution the API with the co-crystal former under crystallization conditions so as to form a solid phase; and

(b) isolating co-crystals comprising the API and the co-crystal former.

Some of the APIs and co-crystal formers of the present invention have one or more chiral centers and may exist in a variety of stereoisomeric configurations. As a consequence of these chiral centers, several APIs and co-crystal formers of the present invention occur as racemates, mixtures of enantiomers and as individual enantiomers, as well as diastereomers and mixtures of diastereomers. All such racemates, enantiomers, and diastereomers are within the scope of the present invention including, for example, *cis*- and *trans*-isomers, R- and S-enantiomers, and (D)- and (L)-isomers. Co-crystals of the present invention can include isomeric forms of either the API or the co-crystal former or both. Isomeric forms of APIs and co-crystal formers include, but are not limited to, stereoisomers such as enantiomers and diastereomers. In one embodiment, a co-crystal can comprise a racemic API and/or co-crystal former. In another embodiment, a co-crystal can comprise an enantiomerically pure API and/or co-crystal former. In another embodiment, a co-crystal can comprise an API or a co-crystal former with an enantiomeric excess of about 50 percent, 55 percent, 60 percent, 65 percent, 70 percent, 75 percent, 80 percent, 85 percent, 90 percent, 95 percent, 96 percent, 97 percent, 98 percent, 99 percent, greater than 99 percent, or any intermediate value. Several non-limiting examples of stereoisomeric APIs include modafinil, *cis*-itraconazole, ibuprofen, and flurbiprofen. Several non-limiting examples of stereoisomeric co-crystal formers

include tartaric acid and malic acid.

Co-crystals comprising enantiomerically pure components (e.g., API or co-crystal former) can give rise to chemical and/or physical properties which are modulated with respect to those of the corresponding co-crystal comprising a racemic component. For example, the modafinil:malonic acid co-crystal from Example 10 comprises racemic modafinil. Enantiomerically pure R-modafinil:malonic acid can conceivably be synthesized via the same or another method of the present invention and is therefore included in the scope of the invention. Likewise, enantiomerically pure S-modafinil:malonic acid can conceivably be synthesized via a method of the present invention and is therefore included in the scope of the invention. A co-crystal comprising an enantiomerically pure component can give rise to a modulation of, for example, activity, bioavailability, or solubility, with respect to the corresponding co-crystal comprising a racemic component. As an example, the co-crystal R-modafinil:malonic acid can have modulated properties as compared to the racemic modafinil:malonic acid co-crystal.

As used herein and unless otherwise noted, the term "racemic co-crystal" refers to a co-crystal which is comprised of an equimolar mixture of two enantiomers of the API, the co-crystal former, or both. For example, a co-crystal comprising a stereoisomeric API and a non-stereoisomeric co-crystal former is a "racemic co-crystal" when there is present an equimolar mixture of the API enantiomers. Similarly, a co-crystal comprising a non-stereoisomeric API and a stereoisomeric co-crystal former is a "racemic co-crystal" when there is present an equimolar mixture of the co-crystal former enantiomers. In addition, a co-crystal comprising a stereoisomeric API and a stereoisomeric co-crystal former is a "racemic co-crystal" when there is present an equimolar mixture of the API enantiomers and of the co-crystal former enantiomers.

As used herein and unless otherwise noted, the term "enantiomerically pure co-crystal" refers to a co-crystal which is comprised of a stereoisomeric API or a stereoisomeric co-crystal former or both where the enantiomeric excess of the stereoisomeric species is greater than or equal to about 90 percent *ee*.

In another embodiment, the present invention includes a pharmaceutical composition comprising a co-crystal with an enantiomerically pure API or co-crystal

former wherein the bioavailability is modulated with respect to the racemic co-crystal. In another embodiment, the present invention includes a pharmaceutical composition comprising a co-crystal with an enantiomerically pure API or co-crystal former wherein the activity is modulated with respect to the racemic co-crystal. In another embodiment, the present invention includes a pharmaceutical composition comprising a co-crystal with an enantiomerically pure API or co-crystal former wherein the solubility is modulated with respect to the racemic co-crystal.

As used herein, the term "enantiomerically pure" includes a composition which is substantially enantiomerically pure and includes, for example, a composition with greater than or equal to about 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99 percent enantiomeric excess.

Solubility Modulation

In a further aspect, the present invention provides a process for modulating the solubility of an API, which process comprises:

(1) grinding, heating, co-subliming, co-melting, or contacting in solution the API with a co-crystal former under crystallization conditions, so as to form a co-crystal of the API and the co-crystal former; and

(2) isolating co-crystals comprising the API and the co-crystal former.

In one embodiment, the solubility of the API is modulated such that the aqueous solubility is increased. Solubility of APIs may be measured by any conventional means such as chromatography (e.g., HPLC) or spectroscopic determination of the amount of API in a saturated solution of the API, such as UV-spectroscopy, IR-spectroscopy, Raman spectroscopy, quantitative mass spectroscopy, or gas chromatography.

In another aspect of the invention, the API may have low aqueous solubility. Typically, low aqueous solubility in the present application refers to a compound having a solubility in water which is less than or equal to 10 mg/mL, when measured at 37 degrees C, and preferably less than or equal to 5 mg/mL or 1 mg/mL. Low aqueous solubility can further be specifically defined as less than or equal to 900, 800, 700, 600, 500, 400, 300, 200 150 100, 90, 80, 70, 60, 50, 40, 30, 20 micrograms/mL, or further 10,

5 or 1 micrograms/mL, or further 900, 800, 700, 600, 500, 400, 300, 200 150, 100 90, 80, 70, 60, 50, 40, 30, 20, or 10 ng/mL, or less than 10 ng/mL when measured at 37 degrees C. Aqueous solubility can also be specified as less than 500, 400, 300, 200, 150, 100, 75, 50 or 25 mg/mL. As embodiments of the present invention, solubility can be increased 2, 3, 4, 5, 7, 10, 15, 20, 25, 50, 75, 100, 200, 300, 500, 750, 1000, 5000, or 10,000 times by making a co-crystal of the reference form (e.g., crystalline or amorphous free acid, free base or zwitter ion, hydrate or solvate), or a salt thereof. Further aqueous solubility can be measured in simulated gastric fluid (SGF) or simulated intestinal fluid (SIF) rather than water. SGF (non-diluted) of the present invention is made by combining 1 g/L Triton X-100 and 2 g/L NaCl in water and adjusting the pH with 20 mM HCl to obtain a solution with a final pH=1.7 (SIF is 0.68% monobasic potassium phosphate, 1% pancreatin, and sodium hydroxide where the pH of the final solution is 7.5). The pH of the solvent used may also be specified as 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, 11.5, 12, 12.5, 13, 13.5, or 14 or any pH in between successive values.

Examples of embodiments includes: co-crystal compositions with an aqueous solubility, at 37 degrees C and a pH of 7.0, that is increased at least 5 fold over the reference form, co-crystal compositions with a solubility in SGF that is increased at least 5 fold over the reference form, co-crystal compositions with a solubility in SIF that is increased at least 5 fold over the reference form.

Dissolution Modulation

In another aspect of the present invention, the dissolution profile of the API is modulated whereby the aqueous dissolution rate or the dissolution rate in simulated gastric fluid or in simulated intestinal fluid, or in a solvent or plurality of solvents is increased. Dissolution rate is the rate at which API solids dissolve in a dissolution medium. For APIs whose absorption rates are faster than the dissolution rates (e.g., steroids), the rate-limiting step in the absorption process is often the dissolution rate. Because of a limited residence time at the absorption site, APIs that are not dissolved before they are removed from intestinal absorption site are considered useless. Therefore, the rate of dissolution has a major impact on the performance of APIs that are poorly

soluble. Because of this factor, the dissolution rate of APIs in solid dosage forms is an important, routine, quality control parameter used in the API manufacturing process.

$$\text{Dissolution rate} = K\,S\,(C_s\text{-}C)$$

where K is dissolution rate constant, S is the surface area, C_s is the apparent solubility, and C is the concentration of API in the dissolution medium. For rapid API absorption, C_s-C is approximately equal to C_s. The dissolution rate of APIs may be measured by conventional means known in the art.

The increase in the dissolution rate of a co-crystal, as compared to the reference form (e.g., free form or salt), may be specified, such as by 10, 20, 30, 40, 50, 60, 70, 80, 90, or 100%, or by 2, 3, 4, 5 ,6, 7, 8, 9, 10, 15, 20, 25, 30, 40, 50, 75, 100, 125, 150, 175, 200, 250, 300, 350, 400, 500, 1000, 10,000, or 100,000 fold greater than the reference form (e.g., free form or salt form) in the same solution. Conditions under which the dissolution rate is measured is the same as discussed above The increase in dissolution may be further specified by the time the composition remains supersaturated before reaching equilibrium solubility.

Examples of above embodiments include: co-crystal compositions with a dissolution rate in aqueous solution, at 37 degrees C and a pH of 7.0, that is increased at least 5 fold over the reference form, co-crystal compositions with a dissolution rate in SGF that is increased at least 5 fold over the reference form, co-crystal compositions with a dissolution rate in SIF that is increased at least 5 fold over the reference form.

Bioavailability Modulation

The methods of the present invention are used to make a pharmaceutical API formulation with greater solubility, dissolution, and bioavailability. Bioavailability can be improved via an increase in AUC, reduced time to T_{max}, (the time to reach peak blood serum levels), or increased C_{max},. The present invention can result in higher plasma concentrations of API when compared to the neutral form or salt alone (reference form). AUC is the area under the plot of plasma concentration of API (not logarithm of the concentration) against time after API administration. The area is conveniently determined by the "trapezoidal rule": The data points are connected by straight line segments, perpendiculars are erected from the abscissa to each data point, and the sum of the areas

of the triangles and trapezoids so constructed is computed. When the last measured concentration (C_n, at time t_n) is not zero, the AUC from t_n to infinite time is estimated by C_n/k_{el}.

The AUC is of particular use in estimating bioavailability of APIs, and in estimating total clearance of APIs (Cl_T). Following single intravenous doses, AUC = D/Cl_T, for single compartment systems obeying first-order elimination kinetics, where D is the dose; alternatively, AUC = C_0/k_{el}, where k_{el} is the API elimination rate constant. With routes other than the intravenous, for such systems, AUC = $F \cdot D/Cl_T$, where F is the absolute bioavailability of the API.

Thus, in a further aspect, the present invention provides a process for modulating the bioavailability of an API when administered in its normal and effective dose range as a co-crystal, whereby the AUC is increased, the time to T_{max} is reduced, or C_{max} is increased, as compared to a reference form, which process comprises:

(1) grinding, heating, co-subliming, co-melting, or contacting in solution the API with a co-crystal former under crystallization conditions, so as to form a co-crystal of the API and the co-crystal former; and

(2) isolating co-crystals comprising the API and the co-crystal former.

Examples of the above embodiments include: co-crystal compositions with a time to T_{max} that is reduced by at least 10% as compared to the reference form, co-crystal compositions with a time to T_{max} that is reduced by at least 20% over the reference form, co-crystal compositions with a time to T_{max} that is reduced by at least 40% over the reference form, co-crystal compositions with a time to T_{max} that is reduced by at least 50% over the reference form, co-crystal compositions with a T_{max} that is reduced by at least 60% over the reference form, co-crystal compositions with a T_{max} that is reduced by at least 70% over the reference form, co-crystal compositions with a T_{max} that is reduced by at least 80% over the reference form, co-crystal compositions with a T_{max} that is reduced by at least 90% over the reference form, co-crystal compositions with a C_{max} that is increased by at least 20% over the reference form, co-crystal compositions with a C_{max} that is increased by at least 30% over the reference form, co-crystal compositions with a C_{max} that is increased by at least 40% over the reference form, co-crystal compositions

with a C_{max} that is increased by at least 50% over the reference form, co-crystal compositions with a C_{max} that is increased by at least 60% over the reference form, co-crystal compositions with a C_{max} that is increased by at least 70% over the reference form, co-crystal compositions with a C_{max} that is increased by at least 80% over the reference form, co-crystal compositions with a Cmax that is increased by at least 2 fold, 3 fold, 5 fold, 7.5 fold, 10 fold, 25 fold, 50 fold or 100 fold, co-crystal compositions with an AUC that is increased by at least 10% over the reference form, co-crystal compositions with an AUC that is increased by at least 20% over the reference form, co-crystal compositions with an AUC that is increased by at least 30% over the reference form, co-crystal compositions with an AUC that is increased by at least 40% over the reference form, co-crystal compositions with an AUC that is increased by at least 50% over the reference form, co-crystal compositions with an AUC that is increased by at least 60% over the reference form, co-crystal compositions with an AUC that is increased by at least 70% over the reference form, co-crystal compositions with an AUC that is increased by at least 80% over the reference form or co-crystal compositions with an AUC that is increased by at least 2 fold, 3 fold, 4 fold, 5 fold, 6 fold, 7 fold, 8 fold, 9 fold, or 10 fold. Other examples include wherein the reference form is crystalline, wherein the reference form is amorphous, wherein the reference form is an anhydrous crystalline sodium salt, or wherein the reference form is an anhydrous crystalline HCl salt.

Dose Response Modulation

In a further aspect the present invention provides a process for improving the dose response of an API, which process comprises:

(1) grinding, heating, co-subliming, co-melting, or contacting in solution an API with a co-crystal former under crystallization conditions, so as to form a co-crystal of the API and the co-crystal former; and

(2) isolating co-crystals comprising the API and the co-crystal former.

Dose response is the quantitative relationship between the magnitude of response and the dose inducing the response and may be measured by conventional means known in the art. The curve relating effect (as the dependent variable) to dose (as the

independent variable) for an API-cell system is the "dose-response curve". Typically, the dose-response curve is the measured response to an API plotted against the dose of the API (mg/kg) given. The dose response curve can also be a curve of AUC against the dose of the API given.

In an embodiment of the present invention, a co-crystal of the present invention has an increased dose response curve or a more linear dose response curve than the corresponding reference compound.

Increased Stability

In a still further aspect the present invention provides a process for improving the stability of an API (as compared to a reference form such as its free form or a salt thereof), which process comprises:

(1) grinding, heating, co-subliming, co-melting, or contacting in solution the pharmaceutical salt with a co-crystal former under crystallization conditions, so as to form a co-crystal of the API and the co-crystal former; and

(2) isolating co-crystals comprising the API and the co-crystal former.

In a preferred embodiment, the compositions of the present invention, including the API or active pharmaceutical ingredient (API) and formulations comprising the API, are suitably stable for pharmaceutical use. Preferably, the API or formulations thereof of the present invention are stable such that when stored at 30 degrees C for 2 years, less than 0.2 % of any one degradant is formed. The term degradant refers herein to product(s) of a single type of chemical reaction. For example, if a hydrolysis event occurs that cleaves a molecule into two products, for the purpose of the present invention, it would be considered a single degradant. More preferably, when stored at 40 degrees C for 2 years, less than 0.2 % of any one degradant is formed. Alternatively, when stored at 30 degrees C for 3 months, less than 0.2% or 0.15 %, or 0.1 % of any one degradant is formed, or when stored at 40 degrees C for 3 months, less than 0.2 % or 0.15 %, or 0.1 % of any one degradant is formed. Further alternatively, when stored at 60 degrees C for 4 weeks, less than 0.2 % or 0.15 %, or 0.1 % of any one degradant is formed. The relative humidity (RH) may be specified as ambient (RH), 75 % (RH), or as any single integer between 1 to 99 %.

Difficult to Salt or Unsaltable Compounds

In a still further aspect the present invention provides a process for making co-crystals of unsaltable or difficult to salt APIs which process comprises:

(1) grinding, heating, co-subliming, co-melting, or contacting in solution an API with a co-crystal former under crystallization conditions, so as to form a co-crystal of the API and the co-crystal former; and

(2) isolating co-crystals comprising the API and the co-crystal former.

Difficult to salt compounds include bases with a pKa less than 3 or acids with a pKa greater than 10. Zwitter ions are also difficult to salt or unsaltable compounds according to the present invention.

Decreasing Hygroscopicity

In a still further aspect, the present invention provides a method for decreasing the hygroscopicity of an API, which method comprises:

(1) grinding, heating, co-subliming, co-melting, or contacting in solution the API with a co-crystal former under crystallization conditions, so as to form a co-crystal of the API and the co-crystal former; and

(2) isolating co-crystals comprising the API and the co-crystal former.

An aspect of the present invention provides a pharmaceutical composition comprising a co-crystal of an API that is less hygroscopic than amorphous or crystalline, free form or salt (including metal salts such as sodium, potassium, lithium, calcium, magnesium) or another reference compound. Hygroscopicity can be assessed by dynamic vapor sorption analysis, in which 5-50 mg of the compound is suspended from a Cahn microbalance. The compound being analyzed should be placed in a non-hygroscopic pan and its weight should be measured relative to an empty pan composed of identical material and having nearly identical size, shape, and weight. Ideally, platinum pans should be used. The pans should be suspended in a chamber through which a gas, such as air or nitrogen, having a controlled and known percent relative humidity (%RH) is flowed until eqilibrium criteria are met. Typical equilibrium criteria include weight

changes of less than 0.01 % over 3 minutes at constant humidity and temperature. The relative humidity should be measured for samples dried under dry nitrogen to constant weight (<0.01 % change in 3 minutes) at 40 degrees C unless doing so would de-solvate or otherwise convert the material to an amorphous compound. In one aspect, the hygroscopicity of a dried compound can be assessed by increasing the RH from 5 to 95 % in increments of 5 % RH and then decreasing the RH from 95 to 5 % in 5 % increments to generate a moisture sorption isotherm. The sample weight should be allowed to equilibrate between each change in % RH. If the compound deliquesces or becomes amorphous above 75 % RH, but below 95 % RH, the experiment should be repeated with a fresh sample and the relative humidity range for the cycling should be narrowed to 5-75 % RH or 10-75 % RH, instead of 5-95 %RH. If the sample cannot be dried prior to testing due to lack of form stability, than the sample should be studied using two complete humidity cycles of either 10-75 % RH or 5-95 % RH, and the results of the second cycle should be used if there is significant weight loss at the end of the first cycle. Hygroscopicity can be defined using various parameters. For purposes of the present invention, a non-hygroscopic molecule should not gain or lose more than 1.0 %, or more preferably, 0.5 % weight at 25 degrees C when cycled between 10 and 75 % RH (relative humidity at 25 degrees C). The non-hygroscopic molecule more preferably should not gain or lose more than 1.0 %, or more preferably, 0.5 % weight when cycled between 5 and 95 % RH at 25 degrees C, or more than 0.25 % of its weight between 10 and 75 % RH. Most preferably, a non-hygroscopic molecule will not gain or lose more than 0.25 % of its weight when cycled between 5 and 95 % RH.

Alternatively, for purposes of the present invention, hygroscopicity can be defined using the parameters of Callaghan et al., "Equilibrium moisture content ofpharmaceutical excipients", in Api Dev. Ind. Pharm., Vol. 8, pp. 335-369 (1982). Callaghan et al. classified the degree of hygroscopicity into four classes.

Class 1: Non-hygroscopic Essentially no moisture increases occur at relative humidities below 90 %.

Class 2: Slightly hygroscopic Essentially no moisture increases occur at relative humidities below 80%.

Class 3: Moderately hygroscopic Moisture content does not increase more than 5 % after storage for 1 week at relative humidities below 60 %.

Class 4: Very hygroscopic Moisture content increase may occur at relative humidities as low as 40 to 50 %.

Alternatively, for purposes of the present invention, hygroscopicity can be defined using the parameters of the European Pharmacopoeia Technical Guide (1999, p. 86) which has defined hygrospocity, based on the static method, after storage at 25 degrees C for 24 hours at 80 % RH:

Slightly hygroscopic: Increase in mass is less than 2 percent m/m and equal to or greater than 0.2 percent m/m.

Hygroscopic: Increase in mass is less than 15 percent m/m and equal to or greater than 0.2 percent m/m.

Very Hygroscopic: Increase in mass is equal to or greater than 15 percent m/m.

Deliquescent: Sufficient water is absorbed to form a liquid.

Co-crystals of the present invention can be set forth as being in Class 1, Class 2, or Class 3, or as being Slightly hygroscopic, Hygroscopic, or Very Hygroscopic. Co-crystals of the present invention can also be set forth based on their ability to reduce hygroscopicity. Thus, preferred co-crystals of the present invention are less hygroscopic than a reference compound. The reference compound can be specified as the API in free form (free acid, free base, hydrate, solvate, etc.) or salt (e.g., especially metal salts such as sodium, potassium, lithium, calcium, or magnesium). Further included in the present invention are co-crystals that do not gain or lose more than 1.0 % weight at 25 degrees C when cycled between 10 and 75 % RH, wherein the reference compound gains or loses more than 1.0 % weight under the same conditions. Further included in the present invention are co-crystals that do not gain or lose more than 0.5 % weight at 25 degrees C when cycled between 10 and 75 % RH, wherein the reference compound gains or loses more than 0.5 % or more than 1.0 % weight under the same conditions. Further included

in the present invention are co-crystals that do not gain or lose more than 1.0 % weight at 25 degrees C when cycled between 5 and 95 % RH, wherein the reference compound gains or loses more than 1.0 % weight under the same conditions. Further included in the present invention are co-crystals that do not gain or lose more than 0.5 % weight at 25 degrees C when cycled between 5 and 95 % RH, wherein the reference compound gains or loses more than 0.5 % or more than 1.0 % weight under the same conditions. Further included in the present invention are co-crystals that do not gain or lose more than 0.25 % weight at 25 degrees C when cycled between 5 and 95 % RH, wherein the reference compound gains or loses more than 0.5 % or more than 1.0 % weight under the same conditions.

Further included in the present invention are co-crystals that have a hygroscopicity (according to Callaghan et al.) that is at least one class lower than the reference compound or at least two classes lower than the reference compound. Included are a Class 1 co-crystal of a Class 2 reference compound, a Class 2 co-crystal of a Class 3 reference compound, a Class 3 co-crystal of a Class 4 reference compound, a Class 1 co-crystal of a Class 3 reference compound, a Class 1 co-crystal of a Class 4 reference compound, or a Class 2 co-crystal of a Class 4 reference compound.

Further included in the present invention are co-crystals that have a hygroscopicity (according to the European Pharmacopoeia Technical Guide) that is at least one class lower than the reference compound or at least two classes lower than the reference compound. Non-limiting examples include; a slightly hygroscopic co-crystal of a hygroscopic reference compound, a hygroscopic co-crystal of a very hygroscopic reference compound, a very hygroscopic co-crystal of a deliquescent reference compound, a slightly hygroscopic co-crystal of a very hygroscopic reference compound, a slightly hygroscopic co-crystal of a deliquescent reference compound, and a hygroscopic co-crystal of a deliquescent reference compound.

Crystallizing Amorphous Compounds

In a further aspect, the present invention provides a process for crystallizing an amorphous compound, which process comprises:

(1) grinding, heating, co-subliming, co-melting, or contacting in solution the API with a co-crystal former under crystallization conditions, so as to form a co-crystal of the API and the co-crystal former; and

(2) isolating co-crystals comprising the API and the co-crystal former.

An amorphous compound includes compounds that do not crystallize using routine methods in the art.

Decreasing Form Diversity

In a still further embodiment aspect the present invention provides a process for reducing the form diversity of an API, which process comprises:

(1) grinding, heating, co-subliming, co-melting, or contacting in solution the API with a co-crystal former under crystallization conditions, so as to form a co-crystal of the API and the co-crystal former; and

(2) isolating co-crystals comprising the API and the co-crystal former.

For purposes of the present invention, the number of forms of a co-crystal is compared to the number of forms of a reference compound (e.g. the free form or a salt of the API) that can be made using routine methods in the art.

Morphology Modulation

In a still further aspect the present invention provides a process for modifying the morphology of an API, which process comprises:

(1) grinding, heating, co-subliming, co-melting, or contacting in solution the API with a co-crystal former under crystallization conditions, so as to form a co-crystal of the API and the co-crystal former; and

(2) isolating co-crystals comprising the API and the co-crystal former.

In an embodiment the co-crystal comprises or consists of a co-crystal former and a pharmaceutical wherein the interaction between the two, e.g., H-bonding, occurs between a functional group of Table III of an API with a corresponding interacting group of Table III. In a further embodiment, the co-crystal comprises a co-crystal former of

Table I or II and an API with a corresponding interacting group of Table III. In a further embodiment the co-crystal comprises an API from Table IV and a co-crystal former with a functional group of Table III. In a further embodiment, the co-crystal is from Table I or II. In an aspect of the invention, only co-crystals having an H-bond acceptor on the first molecule and an H-bond donor on the second molecule, where the first and second molecules are either co-crystal former and API respectively or API and co-crystal former respectively, are included in the present invention. Table IV includes the CAS number, chemical name or a PCT or patent reference (each incorporated herein in their entireties). Thus, whether a particular API contains an H-bond donor, acceptor or both is readily apparent.

In another embodiment, the co-crystal former and API each have only one H-bond donor/acceptor. In another aspect, the molecular weight of the API is less than 2000, 1500, 1000, 750, 500, 350, 200, or 150 Daltons. In another embodiment, the molecular weight of the API is between 100-200, 200-300, 300-400, 400-500, 500-600, 600-700, 700-800, 800-900, 900-1000, 1000-1200, 1200-1400, 1400-1600, 1600-1800, or 1800-2000. APIs with the above molecular weights may also be specifically excluded from the present invention.

The hydrogen bond donor moieties of a co-crystal can include, but are not limited to, any one, any two, any three, any four, or more of the following: amino-pyridine, primary amine, secondary amine, sulfonamide, primary amide, secondary amide, alcohol, and carboxylic acid. The hydrogen bond acceptor moieties of a co-crystal can include, but are not limited to, any one, any two, any three, any four, or more of the following: amino-pyridine, primary amine, secondary amine, sulfonamide, primary amide, secondary amide, alcohol, carboxylic acid, carbonyl, cyano, dimethoxyphenyl, sulfonyl, aromatic nitrogen (6 membered ring), ether, chloride, organochloride, bromide, organobromide, and organoiodide. Hydrogen bonds are known to form many supramolecular structures including, but not limited to, a catemer, a dimer, a trimer, a tetramer, or a higher order structure. Tables V-XXI list specific hydrogen bond donor and acceptor moieties and their approximate interaction distances from the electromagnetic donor atom through the hydrogen atom to the electromagnetic acceptor atom. For example, Table V lists functional groups that are known to hydrogen bond

with amino-pyridines. Amino-pyridines comprise two distinct sites of hydrogen bond donation/acceptance. Both the aromatic nitrogen atom (Npy) and the amine group (NH_2) can participate in hydrogen bonds. The ability of a given functional group to participate in a hydrogen bond as a donor or as an acceptor or both can be determined by inspection by those skilled in the art.

The data included in Tables V-XXI are taken from an analysis of solid-state structures as reported in the Cambridge Structural Database (CSD). These data include a number of hydrogen bonding interactions between many functional groups and their associated interaction distances.

Table V- Hydrogen bonding functional groups with amino-pyridines and associated interaction distances

Functional Group	Interaction Distances (angstroms)	Mean	Standard Deviation
Primary Amide (to NH_2)	3.07	N/A	N/A
Primary Amide (to Npy)	2.97	N/A	N/A
Secondary Amide (to NH_2)	2.75-3.17	N/A	N/A
Secondary Amide (to Npy)	2.70-3.20	2.92	0.07
Carboxylic Acid (to NH_2)	2.72-3.07	2.89	0.08
Carboxylic Acid (to Npy)	2.54-2.82	2.67	0.05
Water (to NH_2)	2.72-3.15	2.94	0.09
Water (to Npy)	2.65-3.15	2.87	0.10
Alcohol (to NH_2)	2.78-3.14	2.96	0.08
Alcohol (to Npy)	2.63-3.06	2.79	0.07
Primary Amine	2.85-3.25	3.05	0.07
Secondary Amine	2.83-3.25	2.93	0.05
Carbonyl	2.87-3.10	2.95	0.07
Sulfoxo	2.70-3.10	2.90	0.08
Ether	2.84-3.20	3.05	0.07
Ester (C-O-C)	3.09	N/A	N/A
Ester (C=O)	2.85-3.16	3.00	0.08
Aromatic N	2.78-3.25	3.04	0.07
Cyano	2.83-3.30	3.09	0.12
Nitro	2.85-3.28	3.08	0.11
Chloride	3.10-3.45	3.25	0.08
Bromide	3.27-3.48	3.39	0.05

Table VI- Hydrogen bonding functional groups with primary amines and associated interaction distances

Functional Group	Interaction Distances (angstroms)	Mean	Standard Deviation
Primary Amide	2.73-3.20	2.98	0.13
Secondary Amide	2.65-3.20	2.97	0.09
Carboxylic Acid (O=C)	2.74-3.15	2.94	0.09

Carboxylic Acid (OH)	2.72-3.12	2.95	0.11
Amino-pyridine	3.10-3.24	3.22	0.02
Sulfonamide	2.86-3.17	3.02	0.11
Water	2.65-3.17	2.95	0.10
Alcohol	2.63-3.26	2.98	0.15
Carbonyl	2.64-3.15	2.95	0.09
Sulfoxo	2.70-3.10	2.92	0.09
Sulfonyl	2.93-3.12	3.13	0.12
Ether	2.75-3.25	3.05	0.11
Ester (C-O-C)	2.90-3.20	3.11	0.07
Ester (O=C)	2.74-3.27	3.04	0.12
Aromatic N	2.92-3.26	3.07	0.07
Cyano	2.83-3.30	3.02	0.06
Nitro	2.75-3.17	3.05	0.08
Chloride	3.07-3.50	3.28	0.09
Bromide	3.23-3.60	3.43	0.08

Table VII- Hydrogen bonding functional groups with primary sulfonamides and associated interaction distances

Functional Group	**Interaction Distances (angstroms)**	**Mean**	**Standard Deviation**
Water	2.87	N/A	N/A
Alcohol	2.85-3.07	2.94	0.06
Primary Amine	2.85-3.20	3.02	0.10
Secondary Amine	2.85-3.20	3.03	0.10
Sulfonyl	2.85-3.20	3.03	0.12
Ether	2.90-3.20	3.07	0.08
Ester	2.85-3.12	2.99	0.07
Cyano	3.00	N/A	N/A
Nitro	3.00-3.20	3.12	0.07
Chloride	3.20-3.32	3.26	0.03

Table VIII- Hydrogen bonding functional groups with primary amides and associated interaction distances

Functional Group	**Interaction Distances (angstroms)**	**Mean**	**Standard Deviation**
Secondary Amide	2.70-3.15	2.935	0.07
Carboxylic Acid (OH)	2.40-2.80	2.560	0.06
Carboxylic Acid (C=O)	2.80-3.25	2.961	0.09
Amino-pyridine (NH_2)	2.90-3.20	3.069	0.00
Amino-pyridine (Aromatic N)	2.80-3.10	2.972	0.00
Aromatic N	2.90-3.21	3.069	0.07
Water (to C=O)	2.60-3.00	2.813	0.08
Water (to NH_2)	2.70-3.07	2.945	0.07
Alcohol (to C=O)	2.50-3.00	2.753	0.07
Alcohol (to NH_2)	2.70-3.10	2.965	0.06
Secondary Amine (to C=O)	2.80-3.10	2.967	0.07
Secondary Amine (to NH_2)	3.00-3.15	3.079	0.03
Carbonyl	2.80-3.15	2.993	0.08
Sulfonyl	2.90-3.00	2.920	0.00
Ether	2.80-3.10	2.960	0.07

Ester (C=O)	2.70-3.05	2.932	0.05
Cyano	3.00-3.30	3.117	0.07
Nitro	2.90-3.07	3.020	0.03
Chloride	3.10-3.60	3.340	0.08
Bromide	3.30-3.80	3.550	0.11

Table IX- Hydrogen bonding functional groups with secondary amides and associated interaction distances

Functional Group	**Interaction Distances (angstroms)**	**Mean**	**Standard Deviation**
Primary Amide	2.70-3.15	2.935	0.07
Carboxylic Acid (C=O)	2.70-3.10	2.920	0.09
Carboxylic Acid (OH)	2.40-3.05	2.606	0.05
Amino-pyridine (Aromatic N)	2.70-3.20	2.920	0.07
Amino-pyridine (NH_2)	2.75-3.17	2.920	0.08
Sulfonamide (S=O)	2.80-3.20	3.110	0.16
Sulfonamide (NH_2)	2.70-3.00	2.916	0.05
Aromatic N	2.60-3.15	2.955	0.09
Water (to C=O)	2.40-3.10	2.840	0.09
Water (to NH_2)	2.60-3.10	2.887	0.10
Alcohol (to C=O)	2.50-3.04	2.773	0.09
Alcohol (to NH_2)	2.50-3.20	2.933	0.11
Primary Amine	2.65-3.20	2.970	0.09
Secondary Amine	2.60-3.15	2.932	0.11
Carbonyl	2.70-3.07	2.937	0.08
Sulfonyl	2.60-3.25	3.080	0.09
Ether	2.70-3.16	2.992	0.09
Ester	2.80-3.16	2.986	0.09
Cyano	2.90-3.30	3.120	0.09
Nitro	2.80-3.10	2.993	0.08
Chloride	2.90-3.40	3.261	0.15
Bromide	3.10-3.50	3.394	0.11

Table X- Hydrogen bonding functional groups with alcohols and associated interaction distances

Functional Group	**Interaction Distances (angstroms)**	**Mean**	**Standard Deviation**
Primary Amide (C=O)	2.50-3.00	2.753	0.07
Primary Amide (NH_2)	2.70-3.10	2.965	0.06
Secondary Amide (C=O)	2.50-3.04	2.773	0.09
Secondary Amide (NH_2)	2.50-3.20	2.933	0.11
Carboxylic Acid (C=O)	2.50-3.00	2.792	0.08
Carboxylic Acid (OH)	2.40-2.90	2.649	0.05
Amino-pyridine (Aromatic N)	2.60-3.06	2.790	0.07
Amino-pyridine (NH_2)	2.75-3.15	2.960	0.08
Sulfonamide	2.80-3.07	2.940	0.06
Aromatic N	2.50-3.00	2.777	0.08
Water	2.40-3.03	2.787	0.10
Primary Amine	2.60-3.15	2.897	0.13
Secondary Amine	2.60-3.15	2.888	0.13
Carbonyl	2.40-3.05	2.805	0.11
Sulfonyl	2.40-3.15	2.870	0.10
Ether	2.40-3.00	2.841	0.08

Ester	2.50-3.10	2.852	0.10
Cyano	2.40-3.10	2.873	0.09
Nitro	2.45-3.05	2.935	0.08
Chloride	2.60-3.30	3.093	0.07
Bromide	3.00-3.50	3.258	0.07

Table XI- Hydrogen bonding functional groups with carboxylic acids and associated interaction distances

Functional Group	Interaction Distances (angstroms)	Mean	Standard Deviation
Primary Amide (NH_2)	2.80-3.25	2.961	0.09
Primary Amide (C=O)	2.40-2.80	2.560	0.07
Secondary Amide (NH)	2.70-3.10	2.920	0.09
Secondary Amide (C=O)	2.40-3.05	2.606	0.05
Amino-pyridine (Aromatic N)	2.50-2.80	2.670	0.05
Amino-pyridine (NH_2)	2.70-3.00	2.890	0.08
Aromatic N	2.54-2.94	2.658	0.06
Water (to C=O)	2.50-3.00	2.830	0.07
Water (to OH)	2.40-3.00	2.626	0.11
Alcohol (to C=O)	2.50-3.00	2.792	0.08
Alcohol (to OH)	2.50-2.90	2.649	0.05
Primary Amine (to C=O)	2.70-3.10	2.959	0.09
Primary Amine (to OH)	2.70-3.10	2.828	0.12
Secondary Amine (to C=O)	2.70-3.10	2.909	0.11
Secondary Amine (to OH)	2.70-3.10	2.727	0.12
Carbonyl	2.40-3.00	2.696	0.08
Ether	2.50-3.00	2.751	0.12
Ester (C=O)	2.40-3.05	2.672	0.07
Ester (C-O-C)	2.40-3.10	2.990	N/A
Cyano	2.50-2.80	2.746	0.09
Nitro	2.70-3.05	2.942	0.10
Chloride	2.80-3.20	3.001	0.05
Bromide	3.00-3.30	3.150	0.05

Table XII- Hydrogen bonding functional groups with carbonyls and associated interaction distances

Functional Group	Interaction Distances (angstroms)	Mean	Standard Deviation
Primary Amide	2.83-3.15	3.96	0.06
Secondary Amide	2.70-3.07	2.93	0.08
Carboxylic Acid	2.40-3.00	2.70	0.08
Amino-pyridine	2.87-3.10	2.95	0.07
Secondary Sulfonamide	2.76-3.22	2.949	0.12
Water	2.55-3.05	2.82	0.10
Alcohol	2.40-3.05	2.80	0.01
Primary Amine	2.64-3.15	2.959	0.09
Secondary Amine	2.64-3.15	2.87	0.01

Table XIII- Hydrogen bonding functional groups with cyano groups and associated interaction distances

Functional Group	Interaction Distances (angstroms)	Mean	Standard Deviation
Primary Amide	3.01-3.30	3.15	0.09
Secondary Amide	2.90-3.30	3.13	N/A
Carboxylic Acid	2.57-3.00	2.75	0.09
Amino-pyridine	2.84-3.33	3.10	0.12
Primary Sulfonamide	2.99	N/A	N/A
Secondary Sulfonamide	2.83-3.00	2.90	0.07
Water	2.78-3.20	2.98	0.01
Alcohol	2.72-3.13	2.89	0.09
Primary Amine	2.84-3.27	3.08	0.09
Secondary Amine	2.84-3.30	3.09	0.12

Table XIV- Hydrogen bonding functional groups with sulfonyl groups and associated interaction distances

Functional Group	Interaction Distances (angstroms)	Mean	Standard Deviation
Primary Amide	2.92	N/A	N/A
Secondary Amide	2.95-3.25	3.08	0.09
Primary Sulfonamide	2.85-3.10	3.00	0.10
Secondary Sulfonamide	2.85-3.20	3.04	N/A
Water	2.84-3.00	2.90	0.05
Alcohol	2.65-3.15	2.87	0.1
Primary Amine	2.93-3.32	3.13	0.12
Secondary Amine	2.75-3.32	3.05	0.12

Table XV- Hydrogen bonding functional groups with aromatic N and associated interaction distances

Functional Group	Interaction Distances (angstroms)	Mean	Standard Deviation
Primary Amide	2.90-3.21	3.07	0.07
Secondary Amide	2.60-3.15	2.96	0.09
Carboxylic Acid	2.54-2.94	2.66	0.06
Amino-pyridine	2.70-3.20	3.04	0.07
Water	2.60-3.15	2.91	0.09
Alcohol	2.50-3.00	2.78	0.08
Primary Amine	2.92-3.26	3.07	0.07
Secondary Amine	2.73-3.25	3.02	0.10

Table XVI- Hydrogen bonding functional groups with ethers and associated interaction distances

Functional Group	Interaction Distances (angstroms)	Mean	Standard Deviation
Primary Amide	2.80-3.10	2.97	0.08
Secondary Amide	2.70-3.16	2.99	0.09
Carboxylic Acid	2.50-3.02	2.75	0.12
Amino-pyridine	2.80-3.20	3.05	0.07
Sulfonamide	0-3.20	3.07	0.08
Water	2.40-3.15	2.94	0.12
Alcohol	2.40-3.00	2.84	0.08
Primary Amine	2.75-3.25	3.05	0.11
Secondary Amine	2.60-3.25	3.05	0.13

Table XVII- Hydrogen bonding functional groups with chlorides and associated interaction distances

Functional Group	Interaction Distances (angstroms)	Mean	Standard Deviation
Primary Amide	3.10-3.60	3.34	0.08
Secondary Amide	2.90-3.30	3.18	0.06
Carboxylic Acid	2.80-3.30	3.00	0.05
Amino-pyridine	3.10-3.45	3.25	0.08
Sulfonamide	0-3.35	3.26	0.03
Water	2.70-3.30	3.17	0.06
Alcohol	2.50-3.30	3.09	0.07
Primary Amine	3.00-3.50	3.28	0.09
Secondary Amine	2.90-3.40	3.20	0.10

Table XVIII- Hydrogen bonding functional groups with organochlorides and associated interaction distances

Functional Group	Interaction Distances (angstroms)	Mean	Standard Deviation
Primary Amide	3.18-3.21	3.20	0.02
Secondary Amide	3.20-3.27	3.25	0.03
Carboxylic Acid	2.90-3.23	3.17	0.07
Amino-pyridine	3.28-3.33	3.31	0.03
Sulfonamide	0-3.50	N/A	N/A
Water	2.79-3.26	3.14	0.15
Alcohol	2.90-3.29	3.17	0.09
Primary Amine	3.21-3.29	3.25	0.05
Secondary Amine	3.26-3.30	3.28	0.02

Table XIX- Hydrogen bonding functional groups with bromides and associated interaction distances

Functional Group	Interaction Distances (angstroms)	Mean	Standard Deviation
Primary Amide	3.30-3.80	3.55	0.11
Secondary Amide	3.10-3.80	3.39	0.11
Carboxylic Acid	3.00-3.30	3.15	0.05
Amino-pyridine	3.20-3.50	3.39	0.05
Alcohol	3.00-3.50	3.26	0.07
Primary Amine	3.20-3.60	3.43	0.08
Secondary Amine	3.10-3.60	3.38	0.10

Table XX- Hydrogen bonding functional groups with organobromides and associated interaction distances

Functional Group	Interaction Distances (angstroms)	Mean	Standard Deviation
Primary Amide	0-3.50	3.24	N/A
Secondary Amide	0-3.50	N/A	N/A
Carboxylic Acid	3.01-3.31	3.20	0.16
Amino-pyridine	0-3.50	3.38	N/A
Sulfonamide	0-3.50	N/A	N/A
Water	3.14-3.27	3.21	0.09
Alcohol	2.90-3.36	3.21	0.12
Primary Amine	0-3.50	3.38	N/A
Secondary Amine	3.20-3.39	3.30	0.12

Table XXI- Hydrogen bonding functional groups with organoiodides and associated interaction distances

Functional Group	Interaction Distances (angstroms)	Mean	Standard Deviation
Primary Amide	0-3.80	N/A	N/A
Secondary Amide	0-3.80	N/A	N/A
Carboxylic Acid	0-3.80	3.59	0.16
Amino-pyridine	0-3.80	3.42	N/A
Aromatic N	2.70-3.23	2.95	0.11
Alcohol	2.90-3.48	3.20	0.20
Primary Amine	3.25-3.42	3.34	0.11
Secondary Amine	2.71-2.87	2.79	0.08

In another embodiment, peptides, proteins, nucleic acids or other biological APIs are excluded from the present invention. In another embodiment, all non-pharmaceutically acceptable co-crystal formers are excluded from the present invention. In another embodiment, organometalic APIs are excluded from the present invention. In another embodiment, a co-crystal former comprising any one or more of the functional groups of Table III may be specifically excluded from the present invention. In another embodiment, any one or more of the co-crystal formers of Table I or II may be specifically excluded from the present invention. Any APIs currently known in the art may also be specifically excluded from the present invention. For example, carbamazepine, itraconazole, nabumetone, fluoxetine, acetaminophen and theophylline can each be specifically excluded from the present invention. In another embodiment, the API is not a salt, is not a non-metal salt, or is not a metal salt, e.g., sodium, potassium, lithium, calcium or magnesium. In another embodiment, the API is a salt, is a non-metal salt, or is a metal salt, e.g., sodium, potassium, lithium, calcium, magnesium. In one embodiment, the API does not contain a halogen. In one embodiment, the API does contain a halogen.

In another embodiment, any one or more of the APIs of Table IV may be specifically excluded from the present invention. Any APIs currently known in the art may also be specifically excluded from the present invention. For example, nabumetone:2,3-naphthalenediol, fluoxetine HCl:benzoic acid, fluoxetine HCl:succinic acid, acetaminophen:piperazine, acetaminophen:theophylline, theophylline:salicylic acid, theophylline:p-hydroxybenzoic acid, theophylline:sorbic acid, theophylline:1-hydroxy-2-naphthoic acid, theophylline:glycolic acid, theophylline:2,5-dihydroxybenzoic acid, theophylline:chloroacetic acid, bis(diphenylhydantoin):9-ethyladenine acetylacetone

solvate, bis(diphenylhydantoin):9-ethyladenine 2,4-pentanedione solvate, 5,5-diphenylbarbituric acid:9-ethyladenine, bis(diphenylhydantoin):9-ethyladenine, 4-aminobenzoic acid:4-aminobenzonitrile, sulfadimidine:salicylic acid, 8-hydroxyquinolinium 4-nitrobenzoate:4-nitrobenzoic acid, sulfaproxyline:caffeine, retro-inverso-isopropyl (2R,3S)-4-cyclohexyl-2-hydroxy-3-(N-((2R)-2-morpholinocarbonylmethyl-3-(1-naphthyl)propionyl)-L-histidylamino)butyrate:cinnamic acid monohydrate, benzoic acid:isonicotinamide, 3-(2-N',N'-(dimethylhydrazino)-4-thiazolylmethylthio)-N''-sulfamoylpropionamidine:maleic acid, diglycine hydrochloride ($C_2H_5NO_2$:$C_2H_6NO_2^+Cl^-$), octadecanoic acid:3-pyridinecarboxamide, *cis*-N-(3-methyl-1-(2-(1,2,3,4-tetrahydro)naphthyl)-piperidin-4-yl)-N-phenylpropanamide hydrochloride:oxalic acid, trans-N-(3-methyl-1-(2-(1,2,3,4-tetrahydro)naphthyl)-piperidin-4-ylium)-N-phenylpropanamide oxalate:oxalic acid dihydrate, bis(1-(3-((4-(2-isopropoxyphenyl)-1-piperazinyl)methyl)benzoyl)piperidine) succinate:succinic acid, bis(p-cyanophenyl)imidazolylmethane:succinic acid, *cis*-1-((4-(1-imidazolylmethyl)cyclohexyl)methyl)imidazole:succinic acid, (+)-2-(5,6-dimethoxy-1,2,3,4-tetrahydro-1-naphthyl)imidazoline:(+)-dibenzoyl-D-tartaric acid, raclopride:tartaric acid, 2,6-diamino-9-ethylpurine:5,5-diethylbarbituric acid, 5,5-diethylbarbituric acid:bis(2-aminopyridine), 5,5-diethylbarbituric acid:acetamide, 5,5-diethylbarbituric acid:KI_3, 5,5-diethylbarbituric acid:urea, bis(barbital):hexamethylphosphoramide, 5,5-diethylbarbituric acid:imidazole, barbital:1-methylimidazole, 5,5-diethylbarbituric acid:N-methyl-2-pyridone, 2,4-diamino-5-(3,4,5-trimethoxybenzyl)-pyrimidine:5,5-diethylbarbituric acid, bis(barbital):caffeine, bis(barbital):1-methylimidazole, bis(beta-cyclodextrin):bis(barbital) hydrate, tetrakis(beta-cyclodextrin):tetrakis(barbital), 9-ethyladenine:5,5-diethylbarbituric acid, barbital:N'-(*p*-cyanophenyl)-N-(*p*-iodophenyl)melamine, barbital:2-amino-4-(*m*-bromophenylamino)-6-chloro-1,3,5-triazine, 5,5-diethylbarbituric acid:N,N'-diphenylmelamine, 5,5-diethylbarbituric acid:N,N'-bis(*p*-chlorophenyl)melamine, N,N'-bis(*p*-bromophenyl)melamine:5,5-diethylbarbituric acid, 5,5-diethylbarbituric acid:N,N'-bis(*p*-iodophenyl)melamine, 5,5-diethylbarbituric acid:N,N'-bis(*p*-tolyl)melamine, 5,5-diethylbarbituric acid:N,N'-bis(*m*-tolyl)melamine, 5,5-diethylbarbituric acid:N,N'-bis(*m*-chlorophenyl)melamine, N,N'-Bis(*m*-methylphenyl)melamine:barbital, N,N'-bis(*m*-

chlorophenyl)melamine:barbital tetrahydrofuran solvate, 5,5-diethylbarbituric acid:N,N'-bis(*tert*-butyl)melamine, 5,5-diethylbarbituric acid:N,N'-di(*tert*-butyl)melamine, 6,6'-diquinolyl ether:5,5-diethylbarbituric acid, 5-*tert*-butyl-2,4,6-triaminopyrimidine:diethylbarbituric acid, N,N'-bis(4-carboxymethylphenyl)melamine:barbital ethanol solvate, N,N'-bis(4-*tert*-butylphenyl)melamine:barbital, tris(5,17-N,N'-bis(4-amino-6-(butylamino)-1,3,5-triazin-2-yl)diamino-11,23-dinitro-25,26,27,28-tetrapropoxycalix(4)arene):hexakis(diethylbarbituric acid) toluene solvate, N,N'-bis(*m*-fluorophenyl)melamine:barbital, N,N'-bis(*m*-bromophenyl)melamine:barbital acetone solvate, N,N'-bis(*m*-iodophenyl)melamine:barbital acetonitrile solvate, N,N'-bis(*m*-trifluoromethylphenyl)melamine:barbital acetonitrile solvate, aminopyrine:barbital, N,N'-bis(4-fluorophenyl)melamine:barbital, N,N'-bis(4-trifluoromethylphenyl)melamine:barbital, 2,4-diamino-5-(3,4,5-trimethoxybenzyl)pyrimidine:barbital, hydroxybutyrate:hydroxyvalerate, 2-aminopyrimidine:succinic acid, 1,3-bis(((6-methylpyrid-2-yl)amino)carbonyl)benzene:glutaric acid, 5-*tert*-butyl-2,4,6-triaminopyrimidine:diethylbarbituric acid, bis(dithiobiuret-S,S')nickel(II):diuracil, platinum 3,3'-dihydroxymethyl-2,2'-bipyridine dichloride:AgF_3CSO_3, 4,4'-bipyridyl:isophthalic acid, 4,4'-bipyridyl:1,4-naphthalenedicarboxylic acid, 4,4'-bipyridyl:1,3,5-cyclohexane-tricarboxylic acid, 4,4'-bipyridyl:tricaballylic acid, urotropin:azelaic acid, insulin:C8-HI (octanoyl-N^{ε}-LysB29-human insulin), isonicotinamide:cinnamic acid, isonicotinamide:3-hydroxybenzoic acid, isonicotinamide:3-N,N-dimethylaminobenzoic acid, isonicotinamide:3,5-bis(trifluoromethyl)-benzoic acid, isonicotinamide:d,l-mandelic acid, isonicotinamide:chloroacetic acid, isonicotinamide:fumaric acid monoethyl ester, isonicotinamide:12-bromododecanoic acid, isonicotinamide:fumaric acid, isonicotinamide:succinic acid, isonicotinamide:4-ketopimelic acid, isonicotinamide:thiodiglycolic acid, 1,3,5-cyclohexane-tricarboxylic acid:hexamethyltetramine, 1,3,5-cyclohexane-tricarboxylic acid:4,7-phenanthroline, 4,7-phenanthroline:oxalic acid, 4,7-phenanthroline:terephthalic acid, 4,7-phenanthroline: 1,3,5-cyclohexane-tricarboxylic acid, 4,7-phenanthroline:1,4-naphthalenedicarboxylic

acid, pyrazine:methanoic acid, pyrazine:ethanoic acid, pyrazine:propanoic acid, pyrazine:butanoic acid, pyrazine:pentanoic acid, pyrazine:hexanoic acid, pyrazine:heptanoic acid, pyrazine:octanoic acid, pyrazine:nonanoic acid, pyrazine:decanoic acid, diammine-(deoxy-quanyl-quanyl-N^7,N^7)-platinum:tris(glycine) hydrate, 2-aminopyrimidine:p-phenylenediacetic acid, bis(2-aminopyrimidin-1-ium)fumarate:fumaric acid, 2-aminopyrimidine:indole-3-acetic acid, 2-aminopyrimidine:N-methylpyrrole-2-carboxylic acid, 2-aminopyrimidine:thiophen-2-carboxylic acid, 2-aminopyrimidine:(+)-camphoric acid, 2,4,6-Trinitrobenzoic acid:2-aminopyrimidine, 2-aminopyrimidine:4-aminobenzoic acid, 2-aminopyrimidine:bis(phenoxyacetic acid), 2-aminopyrimidine:(2,4-dichlorophenoxy)acetic acid, 2-aminopyrimidine:(3,4-dichlorophenoxy)acetic acid, 2-aminopyrimidine:indole-2-carboxylic acid, 2-aminopyrimidine:terephthalic acid, 2-aminopyrimidine:bis(2-nitrobenzoic acid), 2-aminopyrimidine:bis(2-aminobenzoic acid), 2-aminopyrimidine:3-aminobenzoic acid, 2-hexeneoic acid:isonicotinamide, 4-nitrobenzoic acid:isonicotinamide, 3,5-dinitrobenzoic acid:isonicotinamide:4-methylbenzoic acid, 2-amino-5-nitropyrimidine:2-amino-3-nitropyridine, 3,5-dinitrobenzoic acid:4-chlorobenzamide, 3-dimethylaminobenzoic acid:4-chlorobenzamide, fumaric acid:4-chlorobenzamide, oxine:4-nitrobenzoic acid, oxine:3,5-dinitrobenzoic acid, oxine:3,5-dinitrosalicylic acid, 3-[2-(N',N'-dimethylhydrazino)-4-thiazolylmethylthio]-N^2-sulfamoylpropionamidine:maleic acid, 5-fluorouracil:9-ethylhypoxanthine, 5-fluorouracil:cytosine dihydrate, 5-fluorouracil:theophylline monohydrate, stearic acid:nicotinamide, *cis*-1-{[4-(1-imidazolylmethyl)cyclohexyl]methyl}imidazole:succinic acid, CGS18320B:succinic acid, sulfaproxyline:caffeine, 4-aminobenzoic acid:4-aminobenzonitrile, 3,5-dinitrobenzoic acid:isonicotinamide:3-methylbenzoic acid, 3,5-dinitrobenzoic acid:isonicotinamide:4-(dimethylamino)benzoic acid, 3,5-dinitrobenzoic acid:isonicotinamide:4-hydroxy-3-methoxycinnamic acid, isonicotinamide:oxalic acid, isonicotinamide:malonic acid, isonicotinamide:succinic acid, isonicotinamide:glutaric acid, isonicotinamide:adipic acid, benzoic acid:isonicotinamide, mazapertine:succinate, betaine:dichloronitrophenol, betainepyridine:dichloronitrophenol, betainepyridine:pentachlorophenol, 4-{2-[1-(2-hydroxyethyl)-4-pyridylidene]-

ethylidene}-cyclo-hexa-2,5-dien-1-one:methyl 2,4-dihydroxybenzoate, 4-{2-[1-(2-hydroxyethyl)-4-pyridylidene]-ethylidene}-cyclo-hexa-2,5-dien-1-one:2,4-dihydroxypropiophenone, 4-{2-[1-(2-hydroxyethyl)-4-pyridylidene]-ethylidene}-cyclo-hexa-2,5-dien-1-one:2,4-dihydroxyacetophenone, squaric acid:4,4'-dipyridylacetylene, squaric acid:1,2-bis(4-pyridyl)ethylene, chloranilic acid:1,4-bis[(4-pyridyl)ethynyl]benzene, 4,4'-bipyridine:phthalic acid, 4,4'-dipyridylacetylene:phthalic acid, bis(pentamethylcyclopentadienyl)iron:bromanilic acid, bis(pentamethylcyclopentadienyl)iron:chloranilic acid, bis(pentamethylcyclopentadienyl)iron:cyananilic acid, pyrazinotetrathiafulvalene:chloranilic acid, phenol:pentafluorophenol, co-crystals of *cis*-itraconazole, and co-crystals of topiramate are specifically excluded from the present invention.

In another embodiment, a pharmaceutical composition can be formulated to contain an API in co-crystal form as micronized or nano-sized particles. More specifically, another embodiment couples the processing of a pure API to a co-crystal form with the process of making a controlled particle size for manipulation into a pharmaceutical dosage form. This embodiment combines two processing steps into a single step via techniques such as, but not limited to, grinding, alloying, or sintering (i.e., heating a powder mix). The coupling of these processes overcomes a serious limitation of having to isolate and store the bulk drug that is required for a formulation, which in some cases can be difficult to isolate (e.g., amorphous, chemically or physically unstable).

Excipients employed in pharmaceutical compositions of the present invention can be solids, semi-solids, liquids or combinations thereof. Preferably, excipients are solids. Compositions of the invention containing excipients can be prepared by any known technique of pharmacy that comprises admixing an excipient with an API or therapeutic agent. A pharmaceutical composition of the invention contains a desired amount of API per dose unit and, if intended for oral administration, can be in the form, for example, of a tablet, a caplet, a pill, a hard or soft capsule, a lozenge, a cachet, a dispensable powder, granules, a suspension, an elixir, a dispersion, or any other form reasonably adapted for such administration. If intended for parenteral administration, it can be in the form, for

example, of a suspension or transdermal patch. If intended for rectal administration, it can be in the form, for example, of a suppository. Presently preferred are oral dosage forms that are discrete dose units each containing a predetermined amount of the API, such as tablets or capsules.

In another embodiment, APIs with an inappropriate pH for transdermal patches can be co-crystallized with an appropriate co-crystal former, thereby adjusting its pH to an appropriate level for use as a transdermal patch. In another embodiment, an APIs pH level can be optimized for use in a transdermal patch via co-crystallization with an appropriate co-crystal former.

Non-limiting examples follow of excipients that can be used to prepare pharmaceutical compositions of the invention.

Pharmaceutical compositions of the invention optionally comprise one or more pharmaceutically acceptable carriers or diluents as excipients. Suitable carriers or diluents illustratively include, but are not limited to, either individually or in combination, lactose, including anhydrous lactose and lactose monohydrate; starches, including directly compressible starch and hydrolyzed starches (e.g., Celutab™ and Emdex™); mannitol; sorbitol; xylitol; dextrose (e.g., Cerelose™ 2000) and dextrose monohydrate; dibasic calcium phosphate dihydrate; sucrose-based diluents; confectioner's sugar; monobasic calcium sulfate monohydrate; calcium sulfate dihydrate; granular calcium lactate trihydrate; dextrates; inositol; hydrolyzed cereal solids; amylose; celluloses including microcrystalline cellulose, food grade sources of alpha- and amorphous cellulose (e.g., RexcelJ), powdered cellulose, hydroxypropylcellulose (HPC) and hydroxypropylmethylcellulose (HPMC); calcium carbonate; glycine; bentonite; block co-polymers; polyvinylpyrrolidone; and the like. Such carriers or diluents, if present, constitute in total about 5% to about 99%, preferably about 10% to about 85%, and more preferably about 20% to about 80%, of the total weight of the composition. The carrier, carriers, diluent, or diluents selected preferably exhibit suitable flow properties and, where tablets are desired, compressibility.

Lactose, mannitol, dibasic sodium phosphate, and microcrystalline cellulose (particularly Avicel PH microcrystalline cellulose such as Avicel PH 101), either individually or in combination, are preferred diluents. These diluents are chemically

compatible with many co-crystals described herein. The use of extragranular microcrystalline cellulose (that is, microcrystalline cellulose added to a granulated composition) can be used to improve hardness (for tablets) and/or disintegration time. Lactose, especially lactose monohydrate, is particularly preferred. Lactose typically provides compositions having suitable release rates of co-crystals, stability, pre-compression flowability, and/or drying properties at a relatively low diluent cost. It provides a high density substrate that aids densification during granulation (where wet granulation is employed) and therefore improves blend flow properties and tablet properties.

Pharmaceutical compositions of the invention optionally comprise one or more pharmaceutically acceptable disintegrants as excipients, particularly for tablet formulations. Suitable disintegrants include, but are not limited to, either individually or in combination, starches, including sodium starch glycolate (e.g., Explotab™ of PenWest) and pregelatinized corn starches (e.g., National™ 1551 of National Starch and Chemical Company, National™ 1550, and Colorcon™ 1500), clays (e.g., Veegum™ HV of R.T. Vanderbilt), celluloses such as purified cellulose, microcrystalline cellulose, methylcellulose, carboxymethylcellulose and sodium carboxymethylcellulose, croscarmellose sodium (e.g., Ac-Di-Sol™ of FMC), alginates, crospovidone, and gums such as agar, guar, locust bean, karaya, pectin and tragacanth gums.

Disintegrants may be added at any suitable step during the preparation of the composition, particularly prior to granulation or during a lubrication step prior to compression. Such disintegrants, if present, constitute in total about 0.2% to about 30%, preferably about 0.2% to about 10%, and more preferably about 0.2% to about 5%, of the total weight of the composition.

Croscarmellose sodium is a preferred disintegrant for tablet or capsule disintegration, and, if present, preferably constitutes about 0.2% to about 10%, more preferably about 0.2% to about 7%, and still more preferably about 0.2% to about 5%, of the total weight of the composition. Croscarmellose sodium confers superior intragranular disintegration capabilities to granulated pharmaceutical compositions of the present invention.

Pharmaceutical compositions of the invention optionally comprise one or more pharmaceutically acceptable binding agents or adhesives as excipients, particularly for tablet formulations. Such binding agents and adhesives preferably impart sufficient cohesion to the powder being tableted to allow for normal processing operations such as sizing, lubrication, compression and packaging, but still allow the tablet to disintegrate and the composition to be absorbed upon ingestion. Such binding agents may also prevent or inhibit crystallization or recrystallization of a co-crsytal of the present invention once the salt has been dissolved in a solution. Suitable binding agents and adhesives include, but are not limited to, either individually or in combination, acacia; tragacanth; sucrose; gelatin; glucose; starches such as, but not limited to, pregelatinized starches (e.g., National™ 1511 and National™ 1500); celluloses such as, but not limited to, methylcellulose and carmellose sodium (e.g., Tylose™); alginic acid and salts of alginic acid; magnesium aluminum silicate; PEG; guar gum; polysaccharide acids; bentonites; povidone, for example povidone K-15, K-30 and K-29/32; polymethacrylates; HPMC; hydroxypropylcellulose (e.g., Klucel™ of Aqualon); and ethylcellulose (e.g., Ethocel™ of the Dow Chemical Company). Such binding agents and/or adhesives, if present, constitute in total about 0.5% to about 25%, preferably about 0.75% to about 15%, and more preferably about 1% to about 10%, of the total weight of the pharmaceutical composition.

Many of the binding agents are polymers comprising amide, ester, ether, alcohol or ketone groups and, as such, are preferably included in pharmaceutical compositions of the present invention. Polyvinylpyrrolidones such as povidone K-30 are especially preferred. Polymeric binding agents can have varying molecular weight, degrees of crosslinking, and grades of polymer. Polymeric binding agents can also be copolymers, such as block co-polymers that contain mixtures of ethylene oxide and propylene oxide units. Variation in these units' ratios in a given polymer affects properties and performance. Examples of block co-polymers with varying compositions of block units are Poloxamer 188 and Poloxamer 237 (BASF Corporation).

Pharmaceutical compositions of the invention optionally comprise one or more pharmaceutically acceptable wetting agents as excipients. Such wetting agents are preferably selected to maintain the co-crystal in close association with water, a condition

that is believed to improve bioavailability of the composition. Such wetting agents can also be useful in solubilizing or increasing the solubility of co-crystals.

Non-limiting examples of surfactants that can be used as wetting agents in pharmaceutical compositions of the invention include quaternary ammonium compounds, for example benzalkonium chloride, benzethonium chloride and cetylpyridinium chloride, dioctyl sodium sulfosuccinate, polyoxyethylene alkylphenyl ethers, for example nonoxynol 9, nonoxynol 10, and degrees Ctoxynol 9, poloxamers (polyoxyethylene and polyoxypropylene block copolymers), polyoxyethylene fatty acid glycerides and oils, for example polyoxyethylene (8) caprylic/capric mono- and diglycerides (e.g., Labrasol™ of Gattefosse), polyoxyethylene (35) castor oil and polyoxyethylene (40) hydrogenated castor oil; polyoxyethylene alkyl ethers, for example polyoxyethylene (20) cetostearyl ether, polyoxyethylene fatty acid esters, for example polyoxyethylene (40) stearate, polyoxyethylene sorbitan esters, for example polysorbate 20 and polysorbate 80 (e.g., Tween™ 80 of ICI), propylene glycol fatty acid esters, for example propylene glycol laurate (e.g., Lauroglycol™ of Gattefosse), sodium lauryl sulfate, fatty acids and salts thereof, for example oleic acid, sodium oleate and triethanolamine oleate, glyceryl fatty acid esters, for example glyceryl monostearate, sorbitan esters, for example sorbitan monolaurate, sorbitan monooleate, sorbitan monopalmitate and sorbitan monostearate, tyloxapol, and mixtures thereof. Such wetting agents, if present, constitute in total about 0.25% to about 15%, preferably about 0.4% to about 10%, and more preferably about 0.5% to about 5%, of the total weight of the pharmaceutical composition.

Wetting agents that are anionic surfactants are preferred. Sodium lauryl sulfate is a particularly preferred wetting agent. Sodium lauryl sulfate, if present, constitutes about 0.25% to about 7%, more preferably about 0.4% to about 4%, and still more preferably about 0.5% to about 2%, of the total weight of the pharmaceutical composition.

Pharmaceutical compositions of the invention optionally comprise one or more pharmaceutically acceptable lubricants (including anti-adherents and/or glidants) as excipients. Suitable lubricants include, but are not limited to, either individually or in combination, glyceryl behapate (e.g., Compritol™ 888 of Gattefosse); stearic acid and salts thereof, including magnesium, calcium and sodium stearates; hydrogenated vegetable oils (e.g., Sterotex™ of Abitec); colloidal silica; talc; waxes; boric acid;

sodium benzoate; sodium acetate; sodium fumarate; sodium chloride; DL-leucine; PEG (e.g., Carbowax™ 4000 and Carbowax™ 6000 of the Dow Chemical Company); sodium oleate; sodium lauryl sulfate; and magnesium lauryl sulfate. Such lubricants, if present, constitute in total about 0. 1% to about 10%, preferably about 0.2% to about 8%, and more preferably about 0.25% to about 5%, of the total weight of the pharmaceutical composition.

Magnesium stearate is a preferred lubricant used, for example, to reduce friction between the equipment and granulated mixture during compression of tablet formulations.

Suitable anti-adherents include, but are not limited to, talc, cornstarch, DL-leucine, sodium lauryl sulfate and metallic stearates. Talc is a preferred anti-adherent or glidant used, for example, to reduce formulation sticking to equipment surfaces and also to reduce static in the blend. Talc, if present, constitutes about 0.1% to about 10%, more preferably about 0.25% to about 5%, and still more preferably about 0.5% to about 2%, of the total weight of the pharmaceutical composition.

Glidants can be used to promote powder flow of a solid formulation. Suitable glidants include, but are not limited to, colloidal silicon dioxide, starch, talc, tribasic calcium phosphate, powdered cellulose and magnesium trisilicate. Colloidal silicon dioxide is particularly preferred.

Other excipients such as colorants, flavors and sweeteners are known in the pharmaceutical art and can be used in pharmaceutical compositions of the present invention. Tablets can be coated, for example with an enteric coating, or uncoated. Compositions of the invention can further comprise, for example, buffering agents. Optionally, one or more effervescent agents can be used as disintegrants and/or to enhance organoleptic properties of pharmaceutical compositions of the invention. When present in pharmaceutical compositions of the invention to promote dosage form disintegration, one or more effervescent agents are preferably present in a total amount of about 30% to about 75%, and preferably about 45% to about 70%, for example about 60%, by weight of the pharmaceutical composition.

According to a particularly preferred embodiment of the invention, an effervescent agent, present in a solid dosage form in an amount less than that effective to

promote disintegration of the dosage form, provides improved dispersion of the API in an aqueous medium. Without being bound by theory, it is believed that the effervescent agent is effective to accelerate dispersion of the API from the dosage form in the gastrointestinal tract, thereby further enhancing absorption and rapid onset of therapeutic effect. When present in a pharmaceutical composition of the invention to promote intragastrointestinal dispersion but not to enhance disintegration, an effervescent agent is preferably present in an amount of about 1% to about 20%, more preferably about 2.5% to about 15%, and still more preferably about 5% to about 10%, by weight of the pharmaceutical composition.

An "effervescent agent" herein is an agent comprising one or more compounds which, acting together or individually, evolve a gas on contact with water. The gas evolved is generally oxygen or, most commonly, carbon dioxide. Preferred effervescent agents comprise an acid and a base that react in the presence of water to generate carbon dioxide gas. Preferably, the base comprises an alkali metal or alkaline earth metal carbonate or bicarbonate and the acid comprises an aliphatic carboxylic acid.

Non-limiting examples of suitable bases as components of effervescent agents useful in the invention include carbonate salts (e.g., calcium carbonate), bicarbonate salts (e.g., sodium bicarbonate), sesquicarbonate salts, and mixtures thereof. Calcium carbonate is a preferred base.

Non-limiting examples of suitable acids as components of effervescent agents and/or solid organic acids useful in the invention include citric acid, tartaric acid (as D-, L-, or D/L-tartaric acid), malic acid (as D-, L-, or DL-malic acid), maleic acid, fumaric acid, adipic acid, succinic acid, acid anhydrides of such acids, acid salts of such acids, and mixtures thereof. Citric acid is a preferred acid.

In a preferred embodiment of the invention, where the effervescent agent comprises an acid and a base, the weight ratio of the acid to the base is about 1:100 to about 100:1, more preferably about 1:50 to about 50:1, and still more preferably about 1:10 to about 10:1. In a further preferred embodiment of the invention, where the effervescent agent comprises an acid and a base, the ratio of the acid to the base is approximately stoichiometric.

Excipients which solubilize APIs typically have both hydrophilic and hydrophobic regions, or are preferably amphiphilic or have amphiphilic regions. One type of amphiphilic or partially-amphiphilic excipient comprises an amphiphilic polymer or is an amphiphilic polymer. A specific amphiphilic polymer is a polyalkylene glycol, which is commonly comprised of ethylene glycol and/or propylene glycol subunits. Such polyalkylene glycols can be esterified at their termini by a carboxylic acid, ester, acid anhyride or other suitable moiety. Examples of such excipients include poloxamers (symmetric block copolymers of ethylene glycol and propylene glycol; e.g., poloxamer 237), polyalkyene glycolated esters of tocopherol (including esters formed from a di- or multi-functional carboxylic acid; e.g., d-alpha-tocopherol polyethylene glycol-1000 succinate), and macrogolglycerides (formed by alcoholysis of an oil and esterification of a polyalkylene glycol to produce a mixture of mono-, di- and tri-glycerides and mono- and di-esters; e.g., stearoyl macrogol-32 glycerides). Such pharmaceutical compositions are advantageously administered orally.

Pharmaceutical compositions of the present invention can comprise about 10 % to about 50 %, about 25 % to about 50 %, about 30 % to about 45 %, or about 30 % to about 35 % by weight of a co-crystal; about 10 % to about 50 %, about 25 % to about 50 %, about 30 % to about 45 %, or about 30 % to about 35 % by weight of an excipient which inhibits crystallization in aqueous solution, in simulated gastric fluid, or in simulated intestinal fluid; and about 5 % to about 50 %, about 10 % to about 40 %, about 15 % to about 35 %, or about 30 % to about 35 % by weight of a binding agent. In one example, the weight ratio of the co-crystal to the excipient which inhibits crystallization to binding agent is about 1 to 1 to 1.

Solid dosage forms of the invention can be prepared by any suitable process, not limited to processes described herein.

An illustrative process comprises (a) a step of blending an API of the invention with one or more excipients to form a blend, and (b) a step of tableting or encapsulating the blend to form tablets or capsules, respectively.

In a preferred process, solid dosage forms are prepared by a process comprising (a) a step of blending a co-crystal of the invention with one or more excipients to form a blend, (b) a step of granulating the blend to form a granulate, and (c) a step of tableting or

encapsulating the blend to form tablets or capsules respectively. Step (b) can be accomplished by any dry or wet granulation technique known in the art, but is preferably a dry granulation step. A salt of the present invention is advantageously granulated to form particles of about 1 micrometer to about 100 micrometer, about 5 micrometer to about 50 micrometer, or about 10 micrometer to about 25 micrometer. One or more diluents, one or more disintegrants and one or more binding agents are preferably added, for example in the blending step, a wetting agent can optionally be added, for example in the granulating step, and one or more disintegrants are preferably added after granulating but before tableting or encapsulating. A lubricant is preferably added before tableting. Blending and granulating can be performed independently under low or high shear. A process is preferably selected that forms a granulate that is uniform in API content, that readily disintegrates, that flows with sufficient ease so that weight variation can be reliably controlled during capsule filling or tableting, and that is dense enough in bulk so that a batch can be processed in the selected equipment and individual doses fit into the specified capsules or tablet dies.

In an alternative embodiment, solid dosage forms are prepared by a process that includes a spray drying step, wherein an API is suspended with one or more excipients in one or more sprayable liquids, preferably a non-protic (e.g., non-aqueous or non-alcoholic) sprayable liquid, and then is rapidly spray dried over a current of warm air. A granulate or spray dried powder resulting from any of the above illustrative processes can be compressed or molded to prepare tablets or encapsulated to prepare capsules. Conventional tableting and encapsulation techniques known in the art can be employed. Where coated tablets are desired, conventional coating techniques are suitable. Excipients for tablet compositions of the invention are preferably selected to provide a disintegration time of less than about 30 minutes, preferably about 25 minutes or less, more preferably about 20 minutes or less, and still more preferably about 15 minutes or less, in a standard disintegration assay.

Pharmaceutically acceptable co-crystals can be administered by controlled-, sustained-, or delayed-release means. Controlled-release pharmaceutical products have a common goal of improving drug therapy over that achieved by their non-controlled release counterparts. Ideally, the use of an optimally designed controlled-release

preparation in medical treatment is characterized by a minimum of drug substance being employed to cure or control the condition in a minimum amount of time. Advantages of controlled-release formulations include: 1) extended activity of the drug; 2) reduced dosage frequency; 3) increased patient compliance; 4) usage of less total drug; 5) reduction in local or systemic side effects; 6) minimization of drug accumulation; 7) reduction in blood level fluctuations; 8) improvement in efficacy of treatment; 9) reduction of potentiation or loss of drug activity; and 10) improvement in speed of control of diseases or conditions. (Kim, Cherng-ju, Controlled Release Dosage Form Design, 2 Technomic Publishing, Lancaster, Pa.: 2000).

Conventional dosage forms generally provide rapid or immediate drug release from the formulation. Depending on the pharmacology and pharmacokinetics of the drug, use of conventional dosage forms can lead to wide fluctuations in the concentrations of the drug in a patient's blood and other tissues. These fluctuations can impact a number of parameters, such as dose frequency, onset of action, duration of efficacy, maintenance of therapeutic blood levels, toxicity, side effects, and the like. Advantageously, controlled-release formulations can be used to control a drug's onset of action, duration of action, plasma levels within the therapeutic window, and peak blood levels. In particular, controlled- or extended-release dosage forms or formulations can be used to ensure that the maximum effectiveness of a drug is achieved while minimizing potential adverse effects and safety concerns, which can occur both from under dosing a drug (i.e., going below the minimum therapeutic levels) as well as exceeding the toxicity level for the drug.

Most controlled-release formulations are designed to initially release an amount of drug (active ingredient) that promptly produces the desired therapeutic effect, and gradually and continually release other amounts of drug to maintain this level of therapeutic or prophylactic effect over an extended period of time. In order to maintain this constant level of drug in the body, the drug must be released from the dosage form at a rate that will replace the amount of drug being metabolized and excreted from the body. Controlled-release of an active ingredient can be stimulated by various conditions including, but not limited to, pH, ionic strength, osmotic pressure, temperature, enzymes, water, and other physiological conditions or compounds.

A variety of known controlled- or extended-release dosage forms, formulations, and devices can be adapted for use with the co-crystals and compositions of the invention. Examples include, but are not limited to, those described in U.S. Pat. Nos.: 3,845,770; 3,916,899; 3,536,809; 3,598,123; 4,008,719; 5,674,533; 5,059,595; 5,591,767; 5,120,548; 5,073,543; 5,639,476; 5,354,556; 5,733,566; and 6,365,185 B1; each of which is incorporated herein by reference. These dosage forms can be used to provide slow or controlled-release of one or more active ingredients using, for example, hydroxypropylmethyl cellulose, other polymer matrices, gels, permeable membranes, osmotic systems (such as OROS® (Alza Corporation, Mountain View, Calif. USA)), multilayer coatings, microparticles, liposomes, or microspheres or a combination thereof to provide the desired release profile in varying proportions. Additionally, ion exchange materials can be used to prepare immobilized, adsorbed co-crystals and thus effect controlled delivery of the drug. Examples of specific anion exchangers include, but are not limited to, Duolite® A568 and Duolite® AP143 (Rohm & Haas, Spring House, PA. USA).

One embodiment of the invention encompasses a unit dosage form which comprises a pharmaceutically acceptable co-crystal, or a solvate, hydrate, dehydrate, anhydrous, or amorphous form thereof, and one or more pharmaceutically acceptable excipients or diluents, wherein the pharmaceutical composition or dosage form is formulated for controlled-release. Specific dosage forms utilize an osmotic drug delivery system.

A particular and well-known osmotic drug delivery system is referred to as OROS® (Alza Corporation, Mountain View, Calif. USA). This technology can readily be adapted for the delivery of compounds and compositions of the invention. Various aspects of the technology are disclosed in U.S. Pat. Nos. 6,375,978 B1; 6,368,626 B1; 6,342,249 B1; 6,333,050 B2; 6,287,295 B1; 6,283,953 B1; 6,270,787 B1; 6,245,357 B1; and 6,132,420; each of which is incorporated herein by reference. Specific adaptations of OROS® that can be used to administer compounds and compositions of the invention include, but are not limited to, the OROS® Push-Pull™, Delayed Push-Pull™, Multi-Layer Push-Pull™, and Push-Stick™ Systems, all of which are well known. See, e.g., http://www.alza.com. Additional OROS® systems that can be used for the controlled oral

delivery of compounds and compositions of the invention include OROS®-CT and L-OROS®. Id.; see also, Delivery Times, vol. II, issue II (Alza Corporation).

Conventional OROS® oral dosage forms are made by compressing a drug powder (e.g. co-crystal) into a hard tablet, coating the tablet with cellulose derivatives to form a semi-permeable membrane, and then drilling an orifice in the coating (e.g., with a laser). Kim, Cherng-ju, Controlled Release Dosage Form Design, 231-238 (Technomic Publishing, Lancaster, Pa.: 2000). The advantage of such dosage forms is that the delivery rate of the drug is not influenced by physiological or experimental conditions. Even a drug with a pH-dependent solubility can be delivered at a constant rate regardless of the pH of the delivery medium. But because these advantages are provided by a build-up of osmotic pressure within the dosage form after administration, conventional OROS® drug delivery systems cannot be used to effectively deliver drugs with low water solubility. Id. at 234. Because co-crystals of this invention can be far more soluble in water than the API itself, they are well suited for osmotic-based delivery to patients. This invention does, however, encompass the incorporation of conventional crystalline API (e.g. pure API without co-crystal former), and non-salt isomers and isomeric mixtures thereof, into OROS® dosage forms.

A specific dosage form of the invention comprises: a wall defining a cavity, the wall having an exit orifice formed or formable therein and at least a portion of the wall being semipermeable; an expandable layer located within the cavity remote from the exit orifice and in fluid communication with the semipermeable portion of the wall; a dry or substantially dry state drug layer located within the cavity adjacent to the exit orifice and in direct or indirect contacting relationship with the expandable layer; and a flow-promoting layer interposed between the inner surface of the wall and at least the external surface of the drug layer located within the cavity, wherein the drug layer comprises a co-crystal, or a solvate, hydrate, dehydrate, anhydrous, or amorphous form thereof. See U.S. Pat. No. 6,368,626, the entirety of which is incorporated herein by reference.

Another specific dosage form of the invention comprises: a wall defining a cavity, the wall having an exit orifice formed or formable therein and at least a portion of the wall being semipermeable; an expandable layer located within the cavity remote from the exit orifice and in fluid communication with the semipermeable portion of the wall; a

drug layer located within the cavity adjacent the exit orifice and in direct or indirect contacting relationship with the expandable layer; the drug layer comprising a liquid, active agent formulation absorbed in porous particles, the porous particles being adapted to resist compaction forces sufficient to form a compacted drug layer without significant exudation of the liquid, active agent formulation, the dosage form optionally having a placebo layer between the exit orifice and the drug layer, wherein the active agent formulation comprises a co-crystal, or a solvate, hydrate, dehydrate, anhydrous, or amorphous form thereof. See U.S. Pat. No. 6,342,249, the entirety of which is incorporated herein by reference.

The invention will now be described in further detail, by way of example, with reference to the accompanying drawings.

EXEMPLIFICATION

General Methods for the Preparation of Co-Crystals

a) High Throughput crystallization using the CrystalMax™ platform

CrystalMax™ comprises a sequence of automated, integrated high throughput robotic stations capable of rapid generation, identification and characterization of polymorphs, salts, and co-crystals of APIs and API candidates. Worksheet generation and combinatorial mixture design is carried out using proprietary design software Architect™. Typically, an API or an API candidate is dispensed from an organic solvent into tubes and dried under a stream of nitrogen. Salts and/or co-crystal formers may also be dispensed and dried in the same fashion. Water and organic solvents may be combinatorially dispensed into the tubes using a multi-channel dispenser. Each tube in a 96-tube array is then sealed within 15 seconds of combinatorial dispensing to avoid solvent evaporation. The mixtures are then rendered supersaturated by heating to 70 degrees C for 2 hours followed by a 1 degree C/minute cooling ramp to 5 degrees C. Optical checks are then conducted to detect crystals and/or solid material. Once a solid has been identified in a tube, it is isolated through aspiration and drying. Raman spectra

are then obtained on the solids and cluster classification of the spectral patterns is performed using proprietary software (Inquire™).

b) Crystallization from solution

Co-crystals may be obtained by dissolving the separate components in a solvent and adding one to the other. The co-crystal may then precipitate or crystallize as the solvent mixture is evaporated slowly. The co-crystal may also be obtained by dissolving the two components in the same solvent or a mixture of solvents.

c) Crystallization from the melt (Co-melting)

A co-crystal may be obtained by melting the two components together (i.e., co-melting) and allowing recrystallization to occur. In some cases, an anti-solvent may be added to facilitate crystallization.

d) Thermal microscopy

A co-crystal may be obtained by melting the higher melting component on a glass slide and allowing it to recrystallize. The second component is then melted and is also allowed to recrystallize. The co-crystal may form as a separated phase/band in between the eutectic bands of the two original components.

e) Mixing and/or grinding

A co-crystal may be obtained by mixing or grinding two components together in the solid state.

f) Co-sublimation

A co-crystal may be obtained by co-subliming a mixture of an API and a co-crystal former in the same sample cell as an intimate mixture either by heating, mixing or placing the mixture under vacuum. A co-crystal may also be obtained by co-sublimation using a Kneudsen apparatus where the API and the co-crystal former are contained in separate sample cells, connected to a single cold finger, each of the sample cells is

maintained at the same or different temperatures under a vaccum atmosphere in order to co-sublime the two components onto the cold-finger forming the desired co-crystal.

Analytical Methods

Procedure for DSC analysis

DSC analysis of the samples was performed using a Q1000 Differential Scanning Calorimeter (TA Instruments, New Castle, DE, U.S.A.), which uses Advantage for QW-Series, version 1.0.0.78, Thermal Advantage Release 2.0 (2001 TA Instruments-Water LLC). In addition, the analysis software used was Universal Analysis 2000 for Windows 95/95/2000/NT, version 3.1E;Build 3.1.0.40 (2001 TA Instruments-Water LLC).

For the DSC analysis, the purge gas used was dry nitrogen, the reference material was an empty aluminum pan that was crimped, and the sample purge was 50 mL/minute.

DSC analysis of the sample was performed by placing ≤ 2 mg of sample in an aluminum pan with a crimped pan closure. The starting temperature was typically 20 degrees C with a heating rate of 10 degrees C/minute, and the ending temperature was 300 degrees C. Unless otherwise indicated, all reported transitions are as stated +/- 1.0 degrees C.

Procedure for TGA analysis

TGA analysis of samples was performed using a Q500 Thermogravimetric Analyzer (TA Instruments, New Castle, DE, U.S.A.), which uses Advantage for QW-Series, version 1.0.0.78, Thermal Advantage Release 2.0 (2001 TA Instruments-Water LLC). In addition, the analysis software used was Universal Analysis 2000 for Windows 95/95/2000/NT, version 3.1E;Build 3.1.0.40 (2001 TA Instruments-Water LLC).

For all of the TGA experiments, the purge gas used was dry nitrogen, the balance purge was 40 mL/minute N_2, and the sample purge was 60 mL/minute N_2.

TGA of the sample was performed by placing ≤ 2 mg of sample in a platinum pan. The starting temperature was typically 20 degrees C with a heating rate of 10 degrees C/minute, and the ending temperature was 300 degrees C.

Procedure for PXRD analysis

A powder X-ray diffraction pattern for the samples was obtained using a D/Max Rapid, Contact (Rigaku/MSC, The Woodlands, TX, U.S.A.), which uses as its control software RINT Rapid Control software, Rigaku Rapid/XRD, version 1.0.0 (1999 Rigaku Co.). In addition, the analysis software used were RINT Rapid display software, version 1.18 (Rigaku/MSC), and JADE XRD Pattern Processing, versions 5.0 and 6.0 ((1995-2002, Materials Data, Inc.).

For the PXRD analysis, the acquisition parameters were as follows: source was Cu with a K line at 1.5406Å; x-y stage was manual; collimator size was 0.3 or 0.8 mm; capillary tube (Charles Supper Company, Natick, MA, U.S.A.) was 0.3 mm ID; reflection mode was used; the power to the X-ray tube was 46 kV; the current to the X-ray tube was 40 mA; the omega-axis was oscillating in a range of 0-5 degrees at a speed of 1 degree/minute; the phi-axis was spinning at an angle of 360 degrees at a speed of 2 degrees/second; 0.3 or 0.8 mm collimator; the collection time was 60 minutes; the temperature was room temperature; and the heater was not used. The sample was presented to the X-ray source in a boron rich glass capillary.

In addition, the analysis parameters were as follows: the integration 2-theta range was 2-40 or 60 degrees; the integration chi range was 0-360 degrees; the number of chi segments was 1; the step size used was 0.02; the integration utility was cylint; normalization was used; dark counts were 8; omega offset was 180; and chi and phi offsets were 0.

The relative intensity of peaks in a diffractogram is not necessarily a limitation of the PXRD pattern because peak intensity can vary from sample to sample, e.g., due to crystalline impurities. Further, the angles of each peak can vary by about +/- 0.1 degrees, preferably +/-0.05. The entire pattern or most of the pattern peaks may also shift by about +/- 0.1 degree due to differences in calibration, settings, and other variations from instrument to instrument and from operator to operator.

Procedure for Raman Acquisition, Filtering and Binning

Acquisition

The sample was either left in the glass vial in which it was processed or an aliquot of the sample was transferred to a glass slide. The glass vial or slide was positioned in the sample chamber. The measurement was made using an Almega™ Dispersive Raman (Almega™ Dispersive Raman, Thermo-Nicolet, 5225 Verona Road, Madison, WI 53711-4495) system fitted with a 785nm laser source. The sample was manually brought into focus using the microscope portion of the apparatus with a 10x power objective (unless otherwise noted), thus directing the laser onto the surface of the sample. The spectrum was acquired using the parameters outlined in Table XXII. (Exposure times and number of exposures may vary; changes to parameters will be indicated for each acquisition.)

Filtering and Binning

Each spectrum in a set was filtered using a matched filter of feature size 25 to remove background signals, including glass contributions and sample fluorescence. This is particularly important as large background signal or fluorescence limit the ability to accurately pick and assign peak positions in the subsequent steps of the binning process. Filtered spectra were binned using the peak pick and bin algorithm with the parameters given in Table XXIII. The sorted cluster diagrams for each sample set and the corresponding cluster assignments for each spectral file were used to identify groups of samples with similar spectra, which was used to identify samples for secondary analyses.

Table XXII. Raman Spectral acquisition parameters

Parameter	Setting Used
Exposure time (s)	2.0
Number of exposures	10
Laser source wavelength (nm)	785
Laser power (%)	100
Aperture shape	pin hole
Aperture size (um)	100
Spectral range	104-3428
Grating position	Single
Temperature at acquisition (degrees C)	24.0

Table XXIII. Raman Filtering and Binning Parameters

Parameter	Setting Used
Filtering Parameters	
Filter type	Matched
Filter size	25
QC Parameters	
Peak Height Threshold	1000
Region for noise test (cm^{-1})	0-10000
RMS noise threshold	10000
Automatically eliminate failed spectra	Yes
Region of Interest	
Include (cm^{-1})	104-3428
Exclude region I (cm^{-1})	
Exclude region II (cm^{-1})	
Exclude region III (cm^{-1})	
Exclude region IV (cm^{-1})	
Peak Pick Parameters	
Peak Pick Sensitivity	Variable
Peak Pick Threshold	100
Peak Comparison Parameters	
Peak Window (cm^{-1})	2
Analysis Parameters	
Number of clusters	Variable

Procedure for Single Crystal X-Ray Diffraction

Single crystal x-ray data were collected on a Bruker SMART-APEX CCD diffractometer (M. J. Zaworotko, Department of Chemistry, University of South Florida). Lattice parameters were determined from least squares analysis. Reflection data was

integrated using the program SAINT. The structure was solved by direct methods and refined by full matrix least squares using the program SHELXTL (Sheldrick, G. M. SHELXTL, Release 5.03; Siemans Analytical X-ray Instruments Inc.: Madison, WI).

The co-crystals of the present invention can be characterized, e.g., by the TGA or DSC data or by any one, any two, any three, any four, any five, any six, any seven, any eight, any nine, any ten, or any single integer number of PXRD 2-theta angle peaks or Raman shift peaks listed herein or disclosed in a figure, or by single crystal x-ray diffraction data.

Example 1

1:1 celecoxib:nicotinamide co-crystals were prepared. Celecoxib (100 mg, 0.26 mmol) and nicotinamide (32.0 mg, 0.26 mmol) were each dissolved in acetone (2 mL). The two solutions were mixed and the resulting mixture was allowed to evaporate slowly overnight. The precipitated solid was redissolved in acetone a second time and left to evaporate to dryness. The powder was collected and characterized. Detailed characterization of the celecoxib:nicotinamide co-crystal is listed in Table XXIV. Fig. 1A shows the PXRD diffractogram after subtraction of background noise. Fig. 1B shows the raw PXRD data. Fig. 2 shows a DSC thermogram of the celecoxib:nicotinamide co-crystal. Fig. 3 shows a TGA thermogram of the celecoxib:nicotinamide co-crystal. Fig. 4 shows a Raman spectrum of the celecoxib:nicotinamide co-crystal.

Example 2

Co-crystals of celecoxib and 18-crown-6 were prepared. A solution of celecoxib (157.8 mg, 0.4138 mmol) in Et_2O (10.0 mL) was added to 18-crown-6 (118.1 mg, 0.447 mmol). The opaque solid dissolves immediately and a white solid subsequently began to crystallize very rapidly. The solid was collected via filtration and was washed with additional diethyl ether (5 mL). Detailed characterization of the celecoxib:18-crown-6 co-crystal is listed in Table XXIV. Fig. 5A shows the PXRD diffractogram after subtraction of background noise. Fig. 5B shows the raw PXRD data. Fig. 6 shows a

DSC thermogram of the celecoxib:18-crown-6 co-crystal. Fig. 7 shows a TGA thermogram of the celecoxib:18-crown-6 co-crystal.

Example 3

Co-crystals of topiramate and 18-crown-6 were prepared. To topiramate (100 mg, 0.29 mmol) dissolved in diethyl ether (5 mL) was added 18-crown-6 (78 mg, 0.29 mmol) in diethyl ether (5 mL). Upon addition of 18-crown-6, the solution became cloudy and was sonicated for 30 seconds. The solution was left standing for 1 hour and a colorless precipitate was observed. The precipitate was collected, washed with diethyl ether and dried to give a 1:1 co-crystal of topiramate:18-crown-6 as a colorless solid. Detailed characterization of the co-crystal is listed in Table XXIV. Fig. 8A shows the PXRD diffractogram after subtraction of background noise. Fig. 8B shows the raw PXRD data. Fig. 9 shows a DSC thermogram of the topiramate:18-crown-6 co-crystal.

Example 4

Co-crystals of olanzapine and nicotinamide (Forms I, II and III) were prepared. A 9-block experiment was designed with 12 solvents. (A block is a receiving plate, which can be, for example, an industry standard 24 well, 96 well, 384 well, or 1536 well format, or a custom format.) 864 crystallization experiments with 10 co-crystal formers and 3 concentrations were carried out using the CrystalMax™ platform. Form I was obtained from mixtures containing 1:1 and 1:2 molar ratios of olanzapine:nicotinamide in 1,2-dichloroethane. Form II was obtained from mixtures containing a 1:2 molar ratio of olanzapine and nicotinamide in isopropyl acetate. PXRD and DSC characterization of the olanzapine:nicotinamide co-crystals are listed in Table XXIV. Fig. 10A shows the PXRD diffractogram of form I after subtraction of background noise. Fig. 10B shows the raw PXRD data of form I. Fig. 11 shows a DSC thermogram of the olanzapine:nicotinamide form I co-crystal. Fig. 12 shows the PXRD diffractogram of olanzapine:nicotinamide form II after subtraction of background noise.

Co-crystals of olanzapine and nicotinamide (Form III) were prepared. Olanzapine (40 microliters of 25 mg/mL stock solution in tetrahydrofuran) and nicotinamide (37.6 microliters of 20 mg/mL stock solution in methanol) were added to a glass vial and dried under a flow of nitrogen. To the solid mixture was added isopropyl acetate (100 microliters) and the vial was sealed with an aluminum cap. The suspension was then heated at 70 degrees C for two hours in order to dissolve all of the solid material. The solution was then cooled to 5 degrees C and maintained at that temperature for 24 hours. After 24 hours the vial was uncapped and the mixture was concentrated to 50 microliters of total volume. The vial was then resealed with an aluminum cap and was maintained at 5 degrees C for an additional 24 hours. Large, yellow plates were observed and were collected (Form III). The solid was characterized with single crystal x-ray diffraction and powder x-ray diffraction. PXRD characterization of the co-crystal is listed in Table XXIV. Fig. 13A shows the PXRD diffractogram of form III after subtraction of background noise. Fig. 13B shows the raw PXRD data of form III. Figs. 14A-D show packing diagrams of the olanzapine:nicotinamide form III co-crystal.

Single crystal x-ray analysis reveals that the olanzapine:nicotinamide (Form III) co-crystal is made up of a ternary system containing olanzapine, nicotinamide, water and isopropyl acetate in the unit cell. The co-crystal crystallizes in the monoclinic space group $P2_1/c$ and contains two olanzapine molecules, one nicotinamide molecule, 4 water molecules and one isopropyl acetate molecule in the asymmetric unit. The packing diagram is made up of a two-dimensional hydrogen-bonded network with the water molecules connecting the olanzapine and nicotinamide moieties. The packing diagram is also comprised of alternating olanzapine and nicotinamide layers connected through hydrogen bonding via the water and isopropyl acetate molecules, as shown in Figure 14B. The olanzapine layer propagates along the b axis at c/4 and 3c/4. The nicotinamide layer propagates along the b axis at c/2. The top of Figure 14C illustrates the nicotinamide superstructure. The nicotinamide molecules form dimers which hydrogen bond to chains of 4 water molecules. The water chains terminate with isopropyl acetate molecules on each side.

Crystal data: $C_{45}H_{64}N_{10}O_7S_2$, M = 921.18, monoclinic P21/c; a = 14.0961(12) Å, b = 12.5984(10) Å, c = 27.219(2) Å, $\alpha = 90°$, $\beta = 97.396(2)°$, $\gamma = 90°$, T = 100(2) K, Z =

4, D_c = 1.276 Mg/m^3,U = 4793.6(7) Å^3, λ = 0.71073 Å; 24952 reflections measured, 8457 unique (R_{int} = 0.0882). Final residuals were R_1 = 0.0676, wR_2 = 0.1461 for I>2σ(I), and R_1 = 0.1187, wR_2 = 0.1687 for all 8457 data.

Example 5

A co-crystal of *cis*-itraconazole and succinic acid was prepared. To a solution of succinic acid (16.8 mg, 0.142 mmol) in tetrahydrofuran (THF) (0.50 mL) was added *cis*-itraconazole (100 mg, 0.142 mmol). A clear solution formed with heating (60 degrees C) and stirring. Upon cooling to room temperature (25 degrees C), crystals began to form. The solid was collected by filtration and washed with cold THF (2 mL). The white solid was air-dried and placed in a glass vial. The crystalline substance was found to be a succinic acid co-crystal of *cis*-itraconazole. The solid was characterized by PXRD and DSC. Fig. 15 shows the PXRD diffractogram after subtraction of background noise. Fig. 16 shows a DSC thermogram of the co-crystal.

Example 6

A co-crystal of *cis*-itraconazole and fumaric acid was prepared. To a blend of fumaric acid (8.40 mg, 0.072 mmol) and *cis*-itraconazole (51.8 mg, 0.073 mmol) was added tetrahydrofuran (THF) (1.0 mL). A clear solution formed with heating (60 degrees C) and stirring. Upon cooling to room temperature (25 degrees C), no crystals formed. To the clear solution was added t-butyl methyl ether (1.0 mL). A white solid formed immediately and was collected by filtration and washed with cold t-butyl methyl ether (2 mL). The white solid was air-dried and placed in a glass vial. The crystalline substance was found to be a fumaric acid co-crystal of *cis*-itraconazole. The solid was characterized by PXRD and DSC. Fig. 17 shows the PXRD diffractogram after subtraction of background noise. Fig. 18 shows a DSC thermogram of the co-crystal.

Example 7

A co-crystal of *cis*-itraconazole and L-tartaric acid was prepared. To a solution of L-tartaric acid (21.3 mg, 0.142 mmol) in tetrahydrofuran (THF) (0.50 mL) was added *cis*-itraconazole (100 mg, 0.142 mmol). A clear solution formed with heating (60 degrees C) and stirring. Upon cooling to room temperature (25 degrees C), crystals began to form. The solid was collected by filtration and washed with cold THF (2 mL). The white solid was air-dried and placed in a glass vial. The crystalline substance was found to be an L-tartaric acid co-crystal of *cis*-itraconazole. The solid was characterized by PXRD and DSC. Fig. 19 shows the PXRD diffractogram after subtraction of background noise. Fig. 20 shows a DSC thermogram of the co-crystal.

Example 8

A co-crystal of *cis*-itraconazole and L-malic acid was prepared. To a solution of L-malic acid (19.1 mg, 0.143 mmol) in tetrahydrofuran (THF) (0.50 mL) was added *cis*-itraconazole (100 mg, 0.142 mmol). A clear solution formed with heating (60 degrees C) and stirring. Upon cooling to room temperature (25 degrees C), crystals began to form. The solid was collected by filtration and washed with cold THF (2 mL). The white solid was air-dried and placed in a glass vial. The crystalline substance was found to be an L-malic acid co-crystal of *cis*-itraconazole. The solid was characterized by PXRD and DSC. Fig. 21 shows the PXRD diffractogram after subtraction of background noise. Fig. 22 shows a DSC thermogram of the co-crystal.

Example 9

A co-crystal of *cis*-itraconazole hydrochloride and DL-tartaric acid was prepared. To a suspension of *cis*-itraconazole freebase (20.1 g, 0.0285 mol) in absolute ethanol (100 mL) was added a solution of hydrochloric acid (1.56 g, 0.0428 mol) and DL-tartaric acid (2.99 g, 0.0171mol) in absolute ethanol (100 mL). A clear solution formed with stirring and heating to reflux. The hot solution was gravity filtered and allowed to cool to room temperature (25 degrees C). Upon cooling white crystals formed. The solid was

collected by filtration and washed with cold absolute ethanol (15 mL). The white solid was dried in a vacuum oven overnight at 80 degrees C. The crystalline substance was found to be a DL-tartaric acid co-crystal of *cis*-itraconazole hydrochloride. The solid was characterized by PXRD and DSC. Fig. 23 shows the PXRD diffractogram after subtraction of background noise. Fig. 24 shows a DSC thermogram of the co-crystal.

Example 10

Co-crystals of modafinil and malonic acid were prepared. Using a 250 mg/ml modafinil-acetic acid solution, malonic acid was dissolved on a hotplate (about 67 degrees C) at a 1:2 modafinil to malonic acid ratio. The mixture was dried under flowing nitrogen overnight. A powdery white solid was produced. After further drying for 1 day, acetic acid was removed (as determined by TGA) and the crystal structure of the modafinil:malonic acid (Form I) co-crystal, as determined by PXRD, remained the same. The modafinil:malonic acid (Form I) co-crystal was also prepared by grinding the API and co-crystal former together. 2.50 g of modafinil was mixed with 1.01 g of malonic acid in a large mortar and pestle (malonic acid added in increments over 7 days with about a 1:1.05 ratio made on the first day and increments added over the next seven days which resulted in a 1:2 modafinil:malonic acid ratio). The mixture was ground for 45 minutes initially and 20 minutes each time more malonic acid was added. On the seventh day the mixture of co-crystal and starting components was heated in a sealed 20 mL vial at 80 degrees C for about 35 minutes to facilitate completion of the co-crystal formation. PXRD analysis of the resultant material was completed and the diffractogram is shown in Fig. 25, after subtraction of background noise. Fig. 26 shows a DSC thermogram of the modafinil:malonic acid Form I co-crystal. Fig. 27 shows the Raman spectrum of the modafinil:malonic acid Form I co-crystal. Fig. 27 comprises peaks, in order of decreasing intensity, of 1004, 222, 633, 265, 1032, 1183, 814, 1601, 490, 718, 767, 361, 917, 1104, 889, 412, 1225, 1251, 1398, 1442, 1731, 1298, 3065, and 2949 cm^{-1}. Single crystal data of the modafinil:malonic acid Form I co-crystal were acquired and are reported below.

Crystal data: $C_{18}H_{19}NO_6S$, M = 377.40, monoclinic C2/c; a = 18.728(8) angstroms, b = 5.480(2) angstroms, c = 33.894(13) angstroms, alpha = 90 degrees, beta = 91.864(9) degrees, gamma = 90 degrees, T = 100(2) K, Z = 8, D_c = 1.442 Mg/m^3, U = 3477(2) cubic angstroms, λ = 0.71073 angstroms, 6475 reflections measured, 3307 unique (R_{int} = 0.1567). Final residuals were R_1 = 0.1598, wR_2 = 0.3301 for I>2sigma(I), and R_1 = 0.2544, wR_2 = 0.3740 for all 3307 data.

A polymorph of the modafinil:malonic acid Form I co-crystal was prepared in a vial. 11.4 mg of modafinil and 8.9 mg of malonic acid were dissolved in 2 mL of acetone. The solids dissolved at room temperature, and the vial was left open to evaporate the solvent in air. Large parallelogram shaped crystals formed on the walls and bottom of the vial. The PXRD diffractogram of the large crystals showed modafinil:malonic acid co-crystals Form II, a polymorphic form of modafinil:malonic acid Form I. Fig. 28 shows the PXRD diffractogram of the modafinil:malonic acid Form II co-crystal after subtraction of background noise.

Example 11

Co-crystals of modafinil and glycolic acid were prepared. Modafinil (1 mg, 0.0037mmol) and glycolic acid (0.30 mg, 0.0037 mmol) were dissolved in acetone (400 microliters). The solution was allowed to evaporate to dryness and the resulting solid was characterized using PXRD. PXRD data for the modafinil:glycolic acid co-crystal is listed in Table XXIV. Fig. 29A shows the PXRD diffractogram after subtraction of background noise. Fig. 29B shows the raw PXRD data.

Example 12

Co-crystals of modafinil and maleic acid were prepared. Using a 250 mg/ml modafinil-acetic acid solution, maleic acid was dissolved on a hotplate (about 67 degrees C) at a 2:1 modafinil to maleic ratio. The mixture was dried under flowing nitrogen overnight. A clear amorphous material remained. Solids began to grow after 2 days stored in a sealed vial at room temperature. The solid was collected and characterized as

the modafinil:maleic acid co-crystal using PXRD. Fig. 30A shows the PXRD diffractogram after subtraction of background noise. Fig. 30B shows the raw PXRD data.

Example 13

Co-crystals of 5-fluorouracil and urea were prepared. To 5-fluorouracil (1g, 7.69 mmol) and urea (0.46g, 7.69 mmol) was added methanol (100 mL). The solution was heated at 65 degrees C and sonicated until all the material dissolved. The solution was then cooled to 5 degrees C and maintained at that temperature overnight. After about 3 days a white precipitate was observed and collected. The solid was characterized by DSC, PXRD, Raman spectroscopy, and TGA as the 5-fluorouracil:urea co-crystal. Characterization data are listed in Table XXIV. Fig. 31A shows the PXRD diffractogram after subtraction of background noise. Fig. 31B shows the raw PXRD data. Fig. 32 shows a DSC thermogram of the 5-fluorouracil:urea co-crystal. Fig. 33 shows a TGA thermogram of the 5-fluorouracil:urea co-crystal. Fig. 34 shows a Raman spectrum of the 5-fluorouracil:urea co-crystal. Single crystal data of the 5-fluorouracil:urea co-crystal were acquired and are reported below.

Crystal data: $C_5H_7FN_4O_3$, M = 190.15, monoclinic C2/C, a = 9.461(3) angstroms, b = 10.487(3) angstroms, c = 15.808(4) angstroms, alpha = 90 degrees, beta = 99.891(5), gamma = 90 degrees, T = 100(2) K, Z = 8, D_c = 1.635 Mg/m^3, U = 1545.2(7) cubic angstroms, λ = 0.71073 angstroms, 3419 reflections measured, 1633 unique (R_{int} = 0.0330). Final residuals were R_1 = 0.0667, wR_2 = 0.1505 for I>2sigma(I), and R_1 = 0.0872, wR_2 = 0.1598 for all 1633 data.

Example 14

Co-crystals of hydrochlorothiazide and nicotinic acid were prepared. Hydrochlorothiazide (12.2 mg, 0.041 mmol) and nicotinic acid (5 mg, 0.041 mmol) were dissolved in methanol (1 mL). The solution was then cooled to 5 degrees C and maintained at that temperature for 12 hours. A white solid precipitated and was collected and characterized as the hydrochlorothiazide:nicotinic acid co-crystal using PXRD. Fig.

35A shows the PXRD diffractogram after subtraction of background noise. Fig. 35B shows the raw PXRD data.

Example 15

Co-crystals of hydrochlorothiazide and 18-crown-6 were prepared. Hydrochlorothiazide (100 mg, 0.33 mmol) was dissolved in diethyl ether (15 mL) and was added to a solution of 18-crown-6 (87.2 mg, 0.33 mmol) in diethyl ether (15 mL). A white precipitate immediately began to form and was collected and characterized as the hydrochlorothiazide:18-crown-6 co-crystal using PXRD. Fig. 36A shows the PXRD diffractogram after subtraction of background noise. Fig. 36B shows the raw PXRD data.

Example 16

Co-crystals of hydrochlorothiazide and piperazine were prepared. Hydrochlorothiazide (17.3 mg, 0.058 mmol) and piperazine (5 mg, 0.058 mmol) were dissolved in a 1:1 mixture of ethyl acetate and acetonitrile (1 mL). The solution was then cooled to 5 degrees C and maintained at that temperature for 12 hours. A white solid precipitated and was collected and characterized as the hydrochlorothiazide:piperazine co-crystal using PXRD. Fig. 37A shows the PXRD diffractogram after subtraction of background noise. Fig. 37B shows the raw PXRD data.

Example 17

Acetaminophen:4,4'-bipyridine:water (1:1:1 stoichiometry)

50 mg (0.3307 mmol) acetaminophen and 52 mg (0.3329 mmol) 4,4'-bipyridine were dissolved in hot water and allowed to stand. Slow evaporation yielded colorless needles of a 1:1:1 acetaminophen:4,4'-bipyridine:water co-crystal, as shown in Figs. 38A-B.

Crystal data: (Bruker SMART-APEX CCD Diffractometer). triclinic, space group $P\bar{1}$; a = 7.0534(8), b = 9.5955(12), c = 19.3649(2) Å, α = 86.326(2), β = 80.291(2),

$\gamma = 88.880(2)°$, $U = 1308.1(3)$ Å^3, T = 200(2) K, Z = 2, μ(Mo-Kα) = 0.090 mm^{-1}, $D_c = 1.294$ Mg/m^3, $\lambda = 0.71073$ Å, F(000) = 537, $2\theta_{max} = 25.02°$; 6289 reflections measured, 4481 unique ($R_{int} = 0.0261$). Final residuals for 344 parameters were $R_1 = 0.0751$, $wR_2 = 0.2082$ for $I>2\sigma(I)$, and $R_1 = 0.1119$, $wR_2 = 0.2377$ for all 4481data.

Crystal packing: The co-crystals contain bilayered sheets in which water molecules act as a hydrogen bonded bridge between the network bipyridine moieties and the acetaminophen. Bipyridine guests are sustained by π-π stacking interactions between two network bipyridines. The layers stack via π-π interactions between the phenyl groups of the acetaminophen moieties.

Differential Scanning Calorimetry: (TA Instruments 2920 DSC), 57.77 degrees C (endotherm); m.p. = 58-60 degrees C (MEL-TEMP); (acetaminophen m.p. = 169 degrees C, 4,4'-bipyridine m.p. = 111-114 degrees C).

Example 18

Phenytoin:Pyridone (1:1 stoichiometry)

28 mg (0.1109 mmol) phenytoin and 11 mg (0.1156 mmol) 4-hydroxypyridone were dissolved in 2 mL acetone and 1 mL ethanol with heating and stirring. Slow evaporation yielded colorless needles of a 1:1 phenytoin:pyridone co-crystal, as shown in Figs. 39A-B.

Crystal data: (Bruker SMART-APEX CCD Diffractometer), $C_{20}H_{17}N_3O_3$, M = 347.37, monoclinic *P2$_1$/c*; a = 16.6583(19), b = 8.8478(10), c = 11.9546(14) Å, $\beta = 96.618(2)°$, $U = 1750.2(3)$ Å^3, T = 200(2) K, Z = 4, μ(Mo-Kα) = 0.091 mm^{-1}, $D_c = 1.318$ Mg/m^3, $\lambda = 0.71073$ Å, F(000) = 728, $2\theta_{max} = 56.60°$; 10605 reflections measured, 4154 unique ($R_{int} = 0.0313$). Final residuals for 247 parameters were $R_1 = 0.0560$, $wR_2 = 0.1356$ for $I>2\sigma(I)$, and $R_1 = 0.0816$, $wR_2 = 0.1559$ for all 4154 data.

Crystal packing: The co-crystal is sustained by hydrogen bonding of adjacent phentoin molecules between the carbonyl and the amine closest to the tetrahedral carbon, and by hydrogen bonding between pyridone carbonyl functionalities and the amine not involved in phenytoin-phenytoin interactions. The pyridone carbonyl also hydrogen bonds with adjacent pyridone molecules forming a one-dimensional network.

Infrared Spectroscopy: (Nicolet Avatar 320 FTIR), characteristic peaks for the co-crystal were identified as: 2° amine found at 3311cm^{-1}, carbonyl (ketone) found at 1711cm^{-1}, olephin peak found at 1390cm^{-1}.

Differential Scanning Calorimetry: (TA Instruments 2920 DSC), 233.39 degrees C (endotherm) and 271.33 degrees C (endotherm); m.p. = 231-233 degrees C (MEL-TEMP); (phenytoin m.p. = 295 degrees C, pyridone m.p. = 148 degrees C).

Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA), a 29.09% weight loss starting at 192.80 degrees C, 48.72% weight loss starting at 238.27 degrees C, and 18.38% loss starting at 260.17 degrees C followed by complete decomposition.

Powder x-ray diffraction: (Rigaku Miniflex Diffractometer using Cu Kα (λ = 1.540562), 30kV, 15mA). The powder data were collected over an angular range of 3° to 40° 2θ in continuous scan mode using a step size of 0.02° 2θ and a scan speed of 2.0°/minute. PXRD: Showed analogous peaks to the simulated PXRD derived from the single crystal data. experimental (calculated): 5.2 (5.3); 11.1 (11.3); 15.1 (15.2); 16.2 (16.4); 16.7 (17.0); 17.8 (17.9); 19.4 (19.4); 19.8 (19.7); 20.3 (20.1); 21.2 (21.4); 23.3 (23.7); 26.1 (26.4); 26.4 (26.6); 27.3 (27.6); 29.5 (29.9).

Example 19

Aspirin (acetylsalicylic acid):4,4'-bipyridine (2:1 stoichiometry)

50 mg (0.2775 mmol) aspirin and 22 mg (0.1388 mmol) 4,4'-bipyridine were dissolved in 4 mL hexane. 8 mL ether was added to the solution and allowed to stand for one hour, yielding colorless needles of a 2:1 aspirin:4,4'-bipyridine co-crystal, as shown in Figs. 40A-D. Alternatively, aspirin:4,4'-bipyridine (2:1 stoichiometry) can be made by grinding the solid ingredients in a pestle and mortar.

Crystal data: (Bruker SMART-APEX CCD Diffractometer), $C_{28}H_{24}N_2O_8$, M = 516.49, orthorhombic *Pbcn*; a = 28.831(3), b = 11.3861(12), c = 8.4144(9) Å, U = 2762.2(5) Å^3, T = 173(2) K, Z = 4, μ(Mo-Kα) = 0.092 mm^{-1}, D_c = 1.242 Mg/m^3, λ = 0.71073 Å, F(000) = 1080, $2\theta_{max}$ = 25.02°; 12431 reflections measured, 2433 unique

(R_{int} = 0.0419). Final residuals for 202 parameters were R_1 = 0.0419, wR_2 = 0.1358 for I>2σ(I), and R_1 = 0.0541, wR_2 = 0.1482 for all 2433 data.

Crystal packing: The co-crystal contains the carboxylic acid-pyridine heterodimer that crystallizes in the *Pbcn* space group. The structure is an inclusion compound containing disordered solvent in the channels. In addition to the dominant hydrogen bonding interaction of the heterodimer, π-π stacking of the bipyridine and phenyl groups of the aspirin and hydrophobic interactions contribute to the overall packing interactions.

Infrared Spectroscopy: (Nicolet Avatar 320 FTIR), characteristic (-COOH) peak at 1679 cm^{-1} was shifted up and less intense at 1694cm^{-1}, where as the lactone peak is shifted down slightly from 1750cm^{-1} to 1744cm^{-1}.

Differential Scanning Calorimetry: (TA Instruments 2920 DSC), 95.14 degrees C (endotherm); m.p. = 91-96 degrees C (MEL-TEMP); (aspirin m.p. = 1345 degrees C, 4,4'-bipyridine m.p. = 111-114 degrees C).

Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA), weight loss of 9% starting at 22.62 degrees C, 49.06% weight loss starting at 102.97 degrees C followed by complete decomposition starting at 209.37 degrees C.

Example 20

Ibuprofen:4,4'-Bipyridine (2:1 stoichiometry)

50 mg (0.242 mmol) racemic ibuprofen and 18mg (0.0960 mmol) 4,4'-bipyridine were dissolved in 5 mL acetone. Slow evaporation of the solvent yielded colorless needles of a 2:1 ibuprofen:4,4'-bipyridine co-crystal, as shown in Figs. 41A-D.

Crystal data: (Bruker SMART-APEX CCD Diffractometer), $C_{36}H_{44}N_2O_4$, M = 568.73, triclinic, space group *P-1*; a = 5.759(3), b = 11.683(6), c = 24.705(11) Å, α = 93.674(11), β = 90.880(10), γ = 104.045(7)°, *U* = 1608.3(13) $Å^3$, T= 200(2) K, Z = 2, μ(Mo-Kα) = 0.076 mm^{-1}, D_c = 1.174 Mg/m^3, λ = 0.71073 Å, F(000) = 612, $2\theta_{max}$ = 23.29°; 5208 reflections measured, 3362 unique (R_{int} = 0.0826). Final residuals for 399 parameters were R_1 = 0.0964, wR_2 = 0.2510 for I>2σ(I), and R_1 = 0.1775, wR_2 = 0.2987 for all 3362 data.

Crystal packing: The co-crystal contains ibuprofen:bipyridine heterodimers, sustained by two hydrogen bonded carboxylic acidpyridine supramolecular synthons, arranged in a herringbone motif that packs in the space group *P-1*. The heterodimer is an extended version of the homodimer and packs to form a two-dimensional network sustained by π-π stacking of the bipyridine and phenyl groups of the ibuprofen and hydrophobic interactions from the ibuprofen tails.

Infrared Spectroscopy: (Nicolet Avatar 320 FTIR). Analysis observed stretching of aromatic C-H at 2899 cm^{-1}; N--H bending and scissoring at 1886 $cm._1$; C=O stretching at 1679 cm^{-1}; C-H out-of-plane bending for both 4,4'-bipyridine and ibuprofen at 808 cm^{-1} and 628 cm^{-1}.

Differential Scanning Calorimetry: (TA Instruments 2920 DSC), 64.85 degrees C (endotherm) and 118.79 degrees C (endotherm); m.p. = 113-120 degrees C (MEL-TEMP); (ibuprofen m.p. = 75-77 degrees C, 4,4'-bipyridine m.p. = 111-114 degrees C).

Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA), 13.28% weight loss between room temperature and 100.02 degrees C immediately followed by complete decomposition.

Powder x-ray diffraction: (Rigaku Miniflex Diffractometer using Cu Kα (λ = 1.540562), 30kV, 15mA). The powder data were collected over an angular range of 3° to 40° 2θ in continuous scan mode using a step size of 0.02° 2θ and a scan speed of 2.0°/minute. PXRD derived from the single crystal data, experimental (calculated): 3.4 (3.6); 6.9 (7.2); 10.4 (10.8); 17.3 (17.5); 19.1 (19.7).

Example 21

Flurbiprofen:4,4'-bipyridine (2:1 stoichiometry)

50 mg (0.2046 mmol) flurbiprofen and 15 mg (0.0960 mmol) 4,4'-bipyridine were dissolved in 3 mL acetone. Slow evaporation of the solvent yielded colorless needles of a 2:1 flurbiprofen:4,4'-bipyridine co-crystal, as shown in Figs. 42A-D.

Crystal data: (Bruker SMART-APEX CCD Diffractometer), $C_{40}H_{34}F_2N_2O_4$, M = 644.69, monoclinic *P2₁/n*; a = 5.860(4), b = 47.49(3), c = 5.928(4) Å, β = 107.382 (8)°, *U* = 1574.3(19) $Å^3$, T = 200(2) K, $\mathbb{Z}$ = 2, μ(Mo-Kα) = 0.096 mm^{-1}, D_c = 1.360

Mg/m^3, $\lambda = 0.71073$ Å, F(000) = 676, $2\theta_{max} = 21.69°$; 4246 reflections measured, 1634 unique ($R_{int} = 0.0677$). Final residuals for 226 parameters were $R_1 = 0.0908$, $wR_2 = 0.2065$ for $I>2\sigma(I)$, and $R_1 = 0.1084$, $wR_2 = 0.2209$ for all 1634 data.

Crystal packing: The co-crystal contains flurbiprofen:bipyridine heterodimers, sustained by two hydrogen bonded carboxylic acidpyridine supramolecular synthon, arranged in a herringbone motif that packs in the space group *P2₁/n*. The heterodimer is an extended version of the homodimer and packs to form a two-dimensional network sustained by π-π stacking and hydrophobic interactions of the bipyridine and phenyl groups of the flurbiprofen.

Infrared Spectroscopy: (Nicolet Avatar 320 FTIR), aromatic C-H stretching at 3057 cm^{-1} and 2981 cm^{-1}; N--H bending and scissoring at 1886 cm^{-1}; C=O stretching at 1690 cm^{-1}; C=C and C=N ring stretching at 1418 cm^{-1}.

Differential Scanning Calorimetry: (TA Instruments 2920 DSC), 162.47 degrees C (endotherm); m.p. = 155-160 degrees C (MEL-TEMP); (flurbiprofen m.p. = 110-111 degrees C, 4,4'-bipyridine m.p. = 111-114 degrees C).

Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA), 30.93% weight loss starting at 31.13 degrees C and a 46.26% weight loss starting at 168.74 degrees C followed by complete decomposition.

Powder x-ray diffraction: (Rigaku Miniflex Diffractometer using Cu Kα ($\lambda = 1.540562$), 30kV, 15mA), the powder data were collected over an angular range of 3° to 40° 2θ in continuous scan mode using a step size of 0.02° 2θ and a scan speed of 2.0°/minute. PXRD derived from the single crystal data: experimental (calculated): 16.8 (16.8); 17.1 (17.5); 18.1 (18.4); 19.0 (19.0); 20.0 (20.4); 21.3 (21.7); 22.7 (23.0); 25.0 (25.6); 26.0 (26.1); 26.0 (26.6); 26.1 (27.5); 28.2 (28.7); 29.1 (29.7).

Example 22

Flurbiprofen:trans-1,2-bis (4-pyridyl) ethylene (2:1 stoichiometry)

25 mg (0.1023 mmol) flurbiprofen and 10 mg (0.0548 mmol) trans-1, 2-bis (4-pyridyl) ethylene were dissolved in 3 mL acetone. Slow evaporation of the solvent

yielded colorless needles of a 2:1 flurbiprofen:1,2-bis (4-pyridyl) ethylene co-crystal, as shown in Figs. 43A-B.

Crystal data: (Bruker SMART-APEX CCD Diffractometer), $C_{42}H_{36}F_2N_2O_4$, M = 670.73, monoclinic *P2₁/n*; a = 5.8697(9), b = 47.357(7), c = 6.3587(10) Å, β = 109.492(3)°, *U* = 1666.2(4) Å^3, T = 200(2) K, Z = 2, μ(Mo-Kα) = 0.093 mm^{-1}, D_c = 1.337 Mg/m^3, λ = 0.71073 Å, F(000) = 704, $2\theta_{max}$ = 21.69°, 6977 reflections measured, 2383 unique (R_{int} = 0.0383). Final residuals for 238 parameters were R_1 = 0.0686, wR_2 = 0.1395 for I>2σ(I), and R_1 = 0.1403, wR_2 = 0.1709 for all 2383 data.

Crystal packing: The co-crystal contains flurbiprofen:1,2-bis (4-pyridyl) ethylene heterodimers, sustained by two hydrogen bonded carboxylic acid-pyridine supramolecular synthons, arranged in a herringbone motif that packs in the space group *P2₁/n*. The heterodimer from 1,2-bis (4-pyridyl) ethylene further extends the homodimer relative to example 21 and packs to form a two-dimensional network sustained by π-π stacking and hydrophobic interactions of the bipyridine and phenyl groups of the flurbiprofen.

Infrared Spectroscopy: (Nicolet Avatar 320 FTIR), aromatic C-H stretching at 2927 cm^{-1} and 2850 cm^{-1}; N--H bending and scissoring at 1875 cm^{-1}; C=O stretching at 1707 cm^{-1}; C=C and C=N ring stretching at 1483 cm^{-1}.

Differential Scanning Calorimetry: (TA Instruments 2920 DSC), 100.01 degrees C, 125.59 degrees C and 163.54 degrees C (endotherms); m.p. = 153-158 degrees C (MEL-TEMP); (flurbiprofen m.p. = 110-111 degrees C, trans-1, 2-bis (4-pyridyl) ethylene m.p. = 150-153 degrees C).

Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA), 91.79% weight loss starting at 133.18 degrees C followed by complete decomposition.

Powder x-ray diffraction: (Rigaku Miniflex Diffractometer using Cu Kα (λ = 1.540562), 30kV, 15mA), the powder data were collected over an angular range of 3° to 40° 2θ in continuous scan mode using a step size of 0.02° 2θ and a scan speed of 2.0°/minute. PXRD derived from the single crystal data, experimental (calculated): 3.6 (3.7); 17.3 (17.7); 18.1 (18.6); 18.4 (18.6); 19.1 (19.3); 22.3 (22.5); 23.8 (23.9); 25.9 (26.4); 28.1 (28.5).

Example 23

Carbamazepine:*p*-Phthalaldehyde (2:1 stoichiometry)

25 mg (0.1058 mmol) carbamazepine and 7 mg (0.0521 mmol) *p*-phthalaldehyde were dissolved in approximately 3 mL methanol. Slow evaporation of the solvent yielded colorless needles of a 2:1 carbamazepine:*p*-phthalaldehyde co-crystal, as shown in Figs. 44A-B.

Crystal data: (Bruker SMART-APEX CCD Diffractometer), $C_{38}H_{30}N_4O_4$, M = 606.66, monoclinic *C2/c*; a = 29.191(16), b = 4.962(3), c = 20.316(11) Å, β = 92.105(8)°, U = 2941(3) Å^3, T= 200(2) K, Z = 4, μ(Mo-Kα) = 0.090 mm^{-1}, D_c = 1.370 Mg/m^3, λ = 0.71073 Å, F(000) = 1272, $2\theta_{max}$ = 43.66°, 3831 reflections measured, 1559 unique (R_{int} = 0.0510). Final residuals for 268 parameters were R_1 = 0.0332, wR_2 = 0.0801 for I>2σ(I), and R_1 = 0.0403, wR_2 = 0.0831 for all 1559 data.

Crystal packing: The co-crystals contain hydrogen bonded carboxamide homodimers that crystallize in the space group *C2/c*. The 1° amines of the homodimer are bifurcated to the carbonyl of the *p*-phthalaldehyde forming a chain with an adjacent homodimer. The chains pack in a crinkled tape motif sustained by π-π interactions between phenyl rings of the carbamazepine.

Infrared Spectroscopy: (Nicolet Avatar 320 FTIR). The 1° amine unsymmetrical and symmetrical stretching was shifted down to 3418 cm^{-1}; aliphatic aldehyde and 1° amide C=O stretching was shifted up to 1690 cm^{-1}; N-H in-plane bending at 1669 cm^{-1}; C-H aldehyde stretching at 2861 cm^{-1} and H-C=O bending at 1391 cm^{-1}.

Differential Scanning Calorimetry: (TA Instruments 2920 DSC), 128.46 degrees C (endotherm), m.p. = 121-124 degrees C (MEL-TEMP), (carbamazepine m.p. = 190.2 degrees C, *p*-phthalaldehyde m.p. = 116 degrees C).

Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA), 17.66% weight loss starting at 30.33 degrees C then a 17.57% weight loss starting at 100.14 degrees C followed by complete decomposition.

Powder x-ray diffraction: (Rigaku Miniflex Diffractometer using Cu Kα (λ = 1.540562), 30kV, 15mA). The powder data were collected over an angular range of 3° to 40° 2θ in continuous scan mode using a step size of 0.02° 2θ and a scan speed of

2.0°/minute. PXRD derived from the single crystal data, experimental (calculated): 8.5 (8.7); 10.6 (10.8); 11.9 (12.1); 14.4 (14.7) 15.1 (15.2); 18.0 (18.1); 18.5 (18.2); 19.8 (18.7); 23.7 (24.0); 24.2 (24.2); 26.4 (26.7); 27.6 (27.9); 27.8 (28.2); 28.7 (29.1); 29.3 (29.6); 29.4 (29.8).

Example 24

Carbamazepine:nicotinamide (1:1 stoichiometry)

25 mg (0.1058 mmol) carbamazepine and 12 mg (0.0982 mmol) nicotinamide were dissolved in 4 mL of DMSO, methanol or ethanol. Slow evaporation of the solvent yielded colorless needles of a 1:1 carbamazepine:nicotinamide co-crystal, as shown in Fig. 45.

Using a separate method, 25 mg (0.1058 mmol) carbamazepine and 12 mg (0.0982mmol) nicotinamide were ground together with mortar and pestle. The solid was determined to be 1:1 carbamazepine:nicotinamide microcrystals (PXRD).

1:1 carbamazepine:nicotinamide co-crystals were also prepared via another method. A 12-block experiment was designed with 12 solvents. (A block is a receiving plate, which can be an industry standard 96 well, 384 well, or 1536 well format, or a custom format.) 1152 crystallization experiments were carried out using the CrystalMax™ platform. The co-crystal was obtained from samples containing toluene, acetone, or isopropyl acetate. The resulting co-crystal was characterized by PXRD and DSC and these data are shown in Figs. 46 and 47, respectively. The co-crystals prepared from toluene, aceone, or isopropyl acetate may contain impurities such as carbamazepine in free form due to incomplete purification.

Crystal data: (Bruker SMART-APEX CCD Diffractometer), $C_{21}H_{18}N_4O_2$, M = 358.39, monoclinic *P2₁/n*; a = 5.0961(8), b = 17.595(3), c = 19.647(3) Å, β = 90.917(3)°, *U* = 1761.5(5) Å^3, T = 200(2) K, Z = 4, μ(Mo-Kα) = 0.090 mm^{-1}, D_c = 1.351 Mg/m^3, λ = 0.71073 Å, F(000) = 752, $2\theta_{max}$ = 56.60°, 10919 reflections measured, 4041 unique (R_{int} = 0.0514). Final residuals for 248 parameters were R_1 = 0.0732, wR_2 = 0.1268 for I>2σ(I), and R_1 = 0.1161, wR_2 = 0.1430 for all 4041 data.

Crystal packing: The co-crystals contain hydrogen bonded carboxamide homodimers. The 1° amines are bifurcated to the carbonyl of the nicotinamide on each side of the dimer. The 1° amines of each nicotinamide are hydrogen bonded to the carbonyl of the adjoining dimer. The dimers form chains with π-π interactions from the phenyl groups of the carbamazepine.

Infrared Spectroscopy: (Nicolet Avatar 320 FTIR), unsymmetrical and symmetrical stretching shifts down to 3443 cm^{-1} and 3388 cm^{-1} accounting for 1° amines; 1° amide C=O stretching at 1690 cm^{-1}; N-H in-plane bending at 1614 cm^{-1}; C=C stretching shifted down to 1579 cm^{-1}; aromatic H's from 800 cm^{-1} to 500 cm^{-1} are present.

Differential Scanning Calorimetry: (TA Instruments 2920 DSC), 74.49 degrees C (endotherm) and 159.05 degrees C (endotherm), m.p. = 153-158 degrees C (MEL-TEMP), (carbamazepine m.p. = 190.2 degrees C, nicotinamide m.p. = 150-160 degrees C).

Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA), 57.94% weight loss starting at 205.43 degrees C followed by complete decomposition.

Powder x-ray diffraction: (Rigaku Miniflex Diffractometer using Cu Kα (λ = 1.540562), 30kV, 15mA). The powder data were collected over an angular range of 3° to 40° 2θ in continuous scan mode using a step size of 0.02° 2θ and a scan speed of 2.0°/minute. PXRD: Showed analogous peaks to the simulated PXRD derived from the single crystal data. PXRD analysis experimental (calculated): 6.5 (6.7); 8.8 (9.0); 10.1 (10.3); 13.2 (13.5); 15.6 (15.8); 17.7 (17.9); 17.8 (18.1); 18.3 (18.6); 19.8 (20.1); 20.4 (20.7); 21.6 (N/A); 22.6 (22.8); 22.9 (23.2); 26.4 (26.7); 26.7 (27.0); 28.0 (28.4).

Example 25

Carbamazepine:saccharin (1:1 stoichiometry)

25 mg (0.1058mmol) carbamazepine and 19 mg (0.1037 mmol) saccharin were dissolved in approximately 4 mL ethanol. Slow evaporation of the solvent yielded colorless needles of a 1:1 carbamazepine:saccharin co-crystal, as shown in Fig. 48. Solubility measurements indicate that this co-crystal of carbamazepine has improved

solubility over previously known forms of carbamazepine (*e.g.*, increased molar solubility and longer solubility in aqueous solutions).

1:1 carbamazepine:saccharin co-crystals were also prepared via another method. A 12-block experiment was designed with 12 solvents. (A block is a receiving plate, which can be an industry standard 96 well, 384 well, or 1536 well format, or a custom format.) 1152 crystallization experiments were carried out using the CrystalMax™ platform. The carbamazepine:saccharin co-crystal was obtained from a mixture of isopropyl acetate and heptane. The resulting co-crystal was characterized by PXRD and DSC and these data are shown in Figures 49 and 50, respectively. The co-crystal prepared from a mixture of isopropyl acetate and heptane may contain impurities such as carbamazepine in free form due to incomplete purification.

Crystal data: (Bruker SMART-APEX CCD Diffractometer), $C_{22}H_{17}N_3O_4S$, M = 419.45, triclinic *P-1*; a = 7.5140(11), b = 10.4538(15), c = 12.6826(18) Å, $\alpha = 83.642(2)°$, $\beta = 85.697(2)°$, $\gamma = 75.411(2)°$, $U = 957.0(2)$ Å^3, T = 200(2) K, Z = 2, μ(Mo-Kα) = 0.206 mm^{-1}, D_c = 1.456 Mg/m^3, λ = 0.71073 Å, F(000) = 436, $2\theta_{max} = 56.20°$; 8426 reflections measured, 4372 unique (R_{int} = 0.0305). Final residuals for 283 parameters were R_1 = 0.0458, wR_2 = 0.1142 for $I>2\sigma(I)$, and R_1 = 0.0562, wR_2 = 0.1204 for all 4372 data.

Crystal packing: The co-crystals contain hydrogen bonded carboxamide homodimers. The 2° amines of the saccharin are hydrogen bonded to the carbonyl of the carbamazepine on each side forming a tetramer. The crystal has a space group of *P-1* with π-π interactions between the phenyl groups of the carbamazepine and the saccharin phenyl groups.

Infrared Spectroscopy: (Nicolet Avatar 320 FTIR), unsymmetrical and symmetrical stretching shifts up to 3495 cm^{-1} accounting for 1° amines; C=O aliphatic stretching was shifted up to 1726 cm^{-1}; N-H in-plane bending at 1649 cm^{-1}; C=C stretching shifted down to 1561 cm^{-1}; (O=S=O) sulfonyl peak at 1330 cm^{-1} C-N aliphatic stretching 1175 cm^{-1}.

Differential Scanning Calorimetry: (TA Instruments 2920 DSC), 75.31 degrees C (endotherm) and 177.32 degrees C (endotherm), m.p. = 148-155 degrees C (MEL-TEMP); (carbamazepine m.p. = 190.2 degrees C, saccharin m.p. = 228.8 degrees C).

Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA), 3.342% weight loss starting at 67.03 degrees C and a 55.09% weight loss starting at 118.71 degrees C followed by complete decomposition.

Powder x-ray diffraction: (Rigaku Miniflex Diffractometer using Cu Kα (λ = 1.540562), 30kV, 15mA). The powder data were collected over an angular range of 3° to 40° 2θ in continuous scan mode using a step size of 0.02° 2θ and a scan speed of 2.0 °/minute. PXRD derived from the single crystal data, experimental (calculated): 6.9 (7.0); 12.2 (12.2); 13.6 (13.8); 14.0 (14.1); 14.1 (14.4); 15.3 (15.6); 15.9 (15.9); 18.1 (18.2); 18.7 (18.8); 20.2 (20.3); 21.3 (21.5); 23.7 (23.9); 26.3 (26.4); 28.3 (28.3).

Example 26

Carbamazepine:2,6-pyridinedicarboxylic acid (1:1 stoichiometry)

36 mg (0.1524 mmol) carbamazepine and 26 mg (0.1556 mmol) 2,6-pyridinedicarboxylic acid were dissolved in approximately 2 mL ethanol. Slow evaporation of the solvent yielded clear needles of a 1:1 carbamazepine:2,6-pyridinedicarboxylic acid co-crystal, as shown in Figs. 51A-B.

Crystal data: (Bruker SMART-APEX CCD Diffractometer). $C_{22}H_{17}N_3O_5$, M=403.39, orthorhombic P2(1)2(1)2(1); a=7.2122, b=14.6491, c=17.5864 Å,α=90°, β=90°, γ=90°, U=1858.0(2) $Å^3$, T=100 K, Z=4, μ(MO-Kα)=0.104 mm^{-1}, D_c=1.442 Mg/m^3, λ=0.71073Å , F(000)840, $2\theta_{max}$=28.3. 16641 reflections measured, 4466 unique (R_{int}=0.093). Final residuals for 271 parameters were R_1=0.0425 and wR_2=0.0944 for I>2σ(I).

Crystal packing: Each hydrogen on the carbamazepine 1° amine is hydrogen bonded to a carbonyl group of a different 2,6-pyridinedicarboxylic acid moiety. The carbonyl of the carbamazepine carboxamide is hydrogen bonded to two hydroxide groups of one 2,6-pyridinedicarboxylic acid moiety.

Infrared Spectroscopy: (Nicolet Avatar 320 FTIR). 3439 cm^{-1}, (N-H stretch, 1° amine, carbamazepine); 1734 cm^{-1}, (C=O); 1649 cm^{-1}, (C=C).

Melting Point: 214-216 degrees C (MEL-TEMP). (carbamazepine m.p. = 191-192 degrees C, 2,6-pyridinedicarboxylic acid m.p. = 248-250 degrees C).

Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA). 69% weight loss starting at 215 degrees C and a 17% weight loss starting at 392 degrees C followed by complete decomposition.

Example 27

Carbamazepine:5-nitroisophthalic acid (1:1 stoichiometry)

40 mg (0.1693 mmol) carbamazepine and 30 mg (0.1421 mmol) 5-nitroisophthalic acid were dissolved in approximately 3 mL methanol or ethanol. Slow evaporation of the solvent yielded yellow needles of a 1:1 carbamazepine:5-nitroisophthalic acid co-crystal, as shown in Figs. 52A-B.

Crystal data: (Bruker SMART-APEX CCD Diffractometer). monoclinic C2/c; a=34.355(8), b=5.3795(13), c=23.654(6) Å,α=90°, β=93.952(6)°, γ=90°, U=4361.2(18)Å^3, T=200(2) K, Z=4, μ(MO-Kα)=0.110 mm^{-1}, D_c=1.439 Mg/m^3, λ=0.71073Å , F(000)1968, $2\theta_{max}$=26.43°. 11581 reflections measured, 4459 unique (R_{int}=0.0611). Final residuals for 311 parameters were R_1=0.0725, wR_2=0.1801 for I>2σ(I), and R_1=0.1441, wR_2=0.1204 for all 4459 data.

Crystal packing: The co-crystals are sustained by hydrogen bonded carboxylic acid homodimers between the two 5-nitroisophthalic acid moieties and hydrogen bonded carboxy-amide heterodimers between the carbamazepine and 5-nitroisophthalic acid moiety. There is solvent hydrogen bonded to an additional N-H donor from the carbamazepine moiety.

Infrared Spectroscopy: (Nicolet Avatar 320 FTIR). 3470 cm^{-1}, (N-H stretch, 1° amine, carbamazepine); 3178 cm^{-1}, (C-H stretch, alkene); 1688 cm^{-1}, (C=O); 1602 cm^{-1}, (C=C).

Differential Scanning Calorimetry: (TA Instruments 2920 DSC). 190.51 degrees C (endotherm). m.p. = NA (decomposes at 197-200 degrees C) (MEL-TEMP). (carbamazepine m.p. = 191-192 degrees C, 5-nitroisophthalic acid m.p. = 260-261 degrees C).

Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA). 32.02% weight loss starting at 202 degrees C, a 12.12% weight loss starting at 224

degrees C and a 17.94% weight loss starting at 285 degrees C followed by complete decomposition.

Powder x-ray diffraction: (Rigaku Miniflex Diffractometer using CuKα (λ=1.540562), 30kV, 15mA). The powder data were collected over an angular range of 3 to 40 2 in continuous scan mode using a step size of 0.02 2 and a scan speed of 2.0 /min. PXRD: Showed analogous peaks to the simulated PXRD derived from the single crystal data. PXRD analysis experimental (calculated): 10.138 (10.283), 15.291 (15.607), 17.438 (17.791), 21.166 (21.685), 31.407 (31.738), 32.650 (32.729).

Example 28

Carbamazepine:1,3,5,7-adamantane tetracarboxylic acid (2:1 stoichiometry)

15 mg (0.1524 mmol) carbamazepine and 20 mg (0.1556 mmol) 1,3,5,7-adamantanetetracarboxylic acid were dissolved in approximately 1 mL methanol or 1 mL ethanol. Slow evaporation of the solvent yields clear plates of a 2:1 carbamazepine:1,3,5,7-adamantanetetracarboxylic acid co-crystal, as shown in Figs. 53A-B.

Crystal data: (Bruker SMART-APEX CCD Diffractometer). $C_{44}H_{40}N_4O_{10}$, M=784.80, monoclinicC2/c; a=18.388(4), b=12.682(3), c=16.429(3) Å, β=100.491(6)°, U=3767.1(14) $Å^3$, T=100(2) K, Z=4, μ(MO-Kα)=0.099 mm^{-1}, D_c=1.384 Mg/m^3, λ=0.71073Å , F(000)1648, $2\theta_{max}$=28.20°. 16499 reflections measured, 4481 unique (R_{int}=0.052). Final residuals for 263 parameters were R_1=0.0433 and wR_2=0.0913 for I>2σ(I).

Crystal packing: The co-crystals form a single 3D network of four tetrahedron, linked by square planes similar to the *PtS* topology. The crystals are sustained by hydrogen bonding.

Infrared Spectroscopy: (Nicolet Avatar 320 FTIR). 3431 cm^{-1}, (N-H stretch, 1° amine, carbamazepine); 3123 cm^{-1}, (C-H stretch, alkene); 1723 cm^{-1}, (C=O); 1649 cm^{-1}, (C=C).

Melting Point: (MEL-TEMP). 258-260 degrees C (carbamazepine m.p. = 191-192 degrees C, adamantanetetracarboxylic acid m.p. = >390 degrees C).

Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA). 9% weight loss starting at 189 degrees C, a 52% weight loss starting at 251 degrees C and a 31% weight loss starting at 374 degrees C followed by complete decomposition.

Example 29

Carbamazepine:benzoquinone (1:1 stoichiometry)

25 mg (0.1058 mmol) carbamazepine and 11 mg (0.1018 mmol) benzoquinone was dissolved in 2 mL methanol or THF. Slow evaporation of the solvent produced an average yield of yellow crystals of a 1:1 carbamazepine:benzoquinone co-crystal, as shown in Figs. 54A-B.

Crystal data: (Bruker SMART-APEX CCD Diffractometer). $C_{21}H_{16}N_2O_3$, M=344.36, monoclinic P2(1)/c; a=10.3335(18), b=27.611(5), c=4.9960(9) Å, β=102.275(3)°, U=1392.9(4) Å^3, T=100(2) K, Z=3, D_c=1.232 Mg/m^3, μ(MO-Kα)=0.084 mm^{-1}, λ=0.71073Å, F(000)540, $2\theta_{max}$=28.24°. 8392 reflections measured, 3223 unique (R_{int}=0.1136). Final residuals for 199 parameters were R_1=0.0545 and wR_2=0.1358 for I>2σ(I), and R_1=0.0659 and wR_2=0.1427 for all 3223 data.

Crystal packing: The co-crystals contain hydrogen bonded carboxamide homodimers. Each 1° amine on the carbamazepine is bifurcated to a carbonyl group of a benzoquinone moiety. The dimers form infinite chains.

Infrared Spectroscopy: (Nicolet Avatar 320 FTIR). 3420 cm^{-1}, (N-H stretch, 1° amine, carbamazepine); 2750 cm^{-1}, (aldehyde stretch); 1672 cm^{-1}, (C=O); 1637 cm^{-1}, (C=C, carbamazepine).

Melting Point: 170 degrees C (MEL-TEMP). (carbamazepine m.p. = 191-192 degrees C, benzoquinone m.p. = 115.7 degrees C).

Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA). 20.62% weight loss starting at 168 degrees C and a 78% weight loss starting at 223 degrees C followed by complete decomposition.

Example 30

Carbamazepine:trimesic acid (1:1 stoichiometry)

36 mg (0.1524 mmol) carbamazepine and 31 mg (0.1475 mmol) trimesic acid were dissolved in a solvent mixture of approximately 2 mL methanol and 2 mL dichloromethane. Slow evaporation of the solvent mixture yielded white starbursts of a 1:1 carbamazepine:trimesic acid co-crystal, as shown in Figs. 55A-B.

1:1 carbamazepine:trimesic acid co-crystals were also prepared via another method. A 9-block experiment was designed with 10 solvents. 864 crystallization experiments with 8 co-crystal formers and 3 concentrations were carried out using the CrystalMax™ platform. The co-crystal was obtained from samples containing methanol. The resulting co-crystal was characterized by PXRD and the diffractogram is shown in Fig. 56.

Crystal data: (Bruker SMART-APEX CCD Diffractometer). $C_{24}H_{18}N_2O_7$, M=446.26, monoclinic C2/c; a=32.5312(50), b=5.2697(8), c=24.1594(37) Å,α=90°, β=98.191(3)°, γ=90°, U=4099.39(37) Å^3, T=-173 K, Z=8, μ(MO-Kα)=0.110 mm^{-1}, D_c=1.439 Mg/m^3, λ=0.71073Å, F(000)1968, $2\theta_{max}$=26.43°. 11581 reflections measured, 4459 unique (R_{int}=0.0611). Final residuals for 2777 parameters were R_1=0.1563, wR_2=0.1887 for I>2σ(I), and R_1=0.1441, wR_2=0.1204 for all 3601 data.

Crystal packing: The co-crystals are sustained by hydrogen bonded carboxylic acid homodimers between carbamazepine and trimesic acid moieties and hydrogen bonded carboxylic acid-amine heterodimers between two trimesic acid moieties arranged in a stacked ladder formation.

Infrared Spectroscopy: (Nicolet Avatar 320 FTIR). 3486 cm^{-1}(N-H stretch, 1° amine, carbamazepine); 1688 cm^{-1} (C=O, 1° amide stretch, carbamazepine); 1602 cm^{-1} (C=C, carbamazepine).

Differential Scanning Calorimetry: (TA Instruments 2920 DSC). 273 degrees C (endotherm). m.p. = NA, decomposes at 278 degrees C (MEL-TEMP). (carbamazepine m.p. = 191-192 degrees C, trimesic acid m.p. = 380 degrees C)

Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA). 62.83% weight loss starting at 253 degrees C and a 30.20% weight loss starting at 278 degrees C followed by complete decomposition.

Powder x-ray diffraction: (Rigaku Miniflex Diffractometer using CuKα (λ=1.540562), 30kV, 15mA). The powder data were collected over an angular range of 3 to 40 degrees 2-theta in continuous scan mode using a step size of 0.02 degrees 2-theta and a scan speed of 2.0/min. PXRD analysis experimental: 10.736, 12.087, 16.857, 24.857, 27.857.

Table XXIV. Detailed Characterization of Co-Crystals All PXRD peaks are in units of degrees 2-theta All Raman shifts are in units of cm^{-1}
Celecoxib:Nicotinamide (Example 1) PXRD: 3.77, 7.56, 9.63, 14.76, 15.21, 16.01, 17.78, 18.68, 19.31, 20.44, 21.19, 22.10 DSC: Two endothermic transitions at about 117 and 119 degrees C and a sharp endotherm at about 130 degrees C TGA: Decomposition beginning at about 150 degrees C Raman: 1618, 1599, 1452, 1370, 1163, 1044, 973, 796, 632, 393, 206
Celecoxib:18-Crown-6 (Example 2) PXRD: 8.73, 11.89, 12.57, 13.13, 15.01, 16.37, 17.03, 17.75, 18.45, 20.75, 22.37, 23.11, 24.33, 24.97, 26.61, 28.15 DSC: Sharp endotherm at about 190 degrees C TGA: Decomposition above 200 degrees C with a 25% weight loss between about 190-210 degrees C
Topiramate:18-Crown-6 (Example 3) PXRD: 10.79, 11.07, 12.17, 13.83, 16.13, 18.03, 18.51, 18.79, 19.21, 21.43, 22.25, 24.11 DSC: Sharp endotherm at about 135 degrees C TGA: Rapid decomposition beginning at about 135 degrees C and leveling off slightly after 200 degrees C Raman: 2995, 2943, 1472, 1427, 1262, 849, 805, 745, 629, 280, 226
Olanzapine:Nicotinamide (Example 4) PXRD (Form I): 4.89, 8.65, 12.51, 14.19, 15.59, 17.15, 19.71, 21.05, 23.95, 24.59, 25.53, 26.71 PXRD (Form II): 5.13, 8.65, 11.87, 14.53, 17.53, 18.09, 19.69, 24.19, 26.01 (data as received) PXRD (Form III): 6.41, 12.85, 14.91, 18.67, 21.85, 24.37 DSC (Form I): Slightly broad endotherm at about 126 degrees C
cis-Itraconazole:Succinic Acid (Example 5) PXRD: 3.01, 6.01, 8.13, 9.05, 15.87, 16.17, 17.29, 24.47 DSC: Single endothermic transition at about 160 degrees C ± 1.0 degrees C TGA: Less than 0.1 % volatile components by weight

cis-Itraconazole:Fumaric Acid (Example 6) PXRD: 4.61, 5.89, 9.23, 10.57, 15.51, 16.23, 16.93, 19.05, 20.79 DSC: The material had a weak endothermic transition at about 142 degrees C and a strong endothermic transition at about 180 degrees C TGA: The sample loses 0.5 % of its weight on the TGA between room temperature and 100 degrees C
cis-Itraconazole:L-Tartaric Acid (Example 7) PXRD: 4.13, 6.19, 8.49, 16.13, 17.23, 18.07, 19.13, 20.79, 22.85, 26.17 DSC: An endothermic transition at about 181 degrees C TGA: Less than 0.1 % volatile components by weight by TGA
cis-Itraconazole:L-Malic acid (Example 8) PXRD: 4.43, 6.07, 8.85, 15.93, 17.05, 20.49, 21.27, 22.85, 23.17, 26.17 DSC: The sample has a strong endothermic transition at about 154 degrees C TGA: The sample contained less than 0.1% volatile components by weight
cis-ItraconazoleHCl:DL-Tartaric acid (Example 9) PXRD: 3.73, 10.95, 13.83, 16.53, 17.75, 19.65, 21.11, 23.95 DSC: The sample has a peak endothermic transition at about 162 degrees C TGA: The sample contained less than 0.1 % volatile components by weight
Modafinil:Malonic acid (Example 10) PXRD (Form I): 5.11, 9.35, 16.87, 18.33, 19.53, 21.38, 22.05, 22.89, 24.73, 25.19, 25.81, 28.59 PXRD (Form II): 5.90, 9.54, 15.79, 18.02, 20.01, 21.66, 22.47, 25.30 DSC (Form I): Endothermic transition at about 106 degrees C Raman (Form I): 1601, 1183, 1032, 1004, 814, 633, 265, 222
Modafinil:Glycolic acid (Example 11) PXRD: 6.09, 9.51, 14.91, 15.97, 19.01, 20.03, 21.59, 22.43, 22.75, 23.75, 25.03, 25.71
Modafinil:Maleic acid (Example 12) PXRD: 4.69, 6.15, 9.61, 10.23, 15.65, 16.53, 17.19, 18.01, 19.27, 19.53, 19.97, 21.83, 22.45, 25.65
5-fluorouracil:Urea (Example 13) PXRD: 11.23, 12.69, 13.27, 15.93, 16.93, 20.37, 23.65, 25.55, 26.87, 32.49 DSC: Sharp endotherm at about 208 degrees C TGA: Approximately 32 percent weight loss between 150 and 220 degrees C Raman: 1347, 1024, 757, 644, 545
Hydrochlorothiazide:Nicotinic acid (Example 14) PXRD: 8.57, 13.23, 14.31, 16.27, 17.89, 18.75, 21.13, 21.45, 24.41, 25.73, 26.57, 27.43
Hydrochlorothiazide:18-crown-6 (Example 15) PXRD: 9.97, 10.43, 11.57, 11.81, 12.83, 14.53, 15.67, 16.61, 19.05, 20.31, 20.65, 21.09, 21.85, 22.45, 23.63, 24.21, 25.33, 26.73
Hydrochlorothiazide:Piperazine (Example 16) PXRD: 6.85, 13.75, 15.93, 18.71, 20.67, 20.93, 23.27, 24.17, 28.33, 28.87, 30.89
Acetaminophen:4,4'-Bipyridine:water (Example 17) DSC: Endothermic transition at about 58 degrees C

Phenytoin:Pyridone (Example 18) PXRD: 5.2, 11.1, 15.1, 16.2, 16.7, 17.8, 19.4, 19.8, 20.3, 21.2, 23.3, 26.1, 26.4, 27.3, 29.5 DSC: Endothermic transitions at about 233 and 271 degrees C TGA: 29.09 percent weight loss starting at about 193 degrees C, 48.72 percent weight loss starting at about 238 degrees C, 18.38 percent weight loss starting at about 260 degrees C
Aspirin:4,4'-Bipyridine (Example 19) DSC: Endothermic transition at about 95 degrees C TGA: 9 percent weight loss starting at about 23 degrees C, 49.06 percent weight loss starting at about 103 degrees C, decomposition starting at about 209 degrees C
Ibuprofen:4,4'-Bipyridine (Example 20) PXRD: 3.4, 6.9, 10.4, 17.3, 19.1 DSC: Endothermic transitions at about 65 and 119 degrees C TGA: 13.28 percent weight loss between room temperature and about 100 degrees C
Flurbiprofen:4,4'-Bipyridine (Example 21) PXRD: 16.8, 17.1, 18.1, 19.0, 20.0, 21.3, 22.7, 25.0, 26.0, 26.1, 28.2, 29.1 DSC: Endothermic transition at about 162 degrees C TGA: 30.93 percent weight loss starting at about 31 degrees C, 46.26 percent weight loss starting at about 169 degrees C
Flurbiprofen:trans-1,2-bis (4-pyridyl) ethylene (Example 22) PXRD: 3.6, 17.3, 18.1, 18.4, 19.1, 22.3, 23.8, 25.9, 28.1 DSC: Endothermic transitions at about 100, 126, and 164 degrees C TGA: 91.79 percent weight loss starting at about 133 degrees C
Carbamazepine:p-phthalaldehyde (Example 23) PXRD: 8.5, 10.6, 11.9, 14.4, 15.1, 18.0, 18.5, 19.8, 23.7, 24.2, 26.4, 27.6, 27.8, 28.7, 29.3, 29.4 DSC: Endothermic transition at about 128 degrees C TGA: 17.66 percent weight loss starting at about 30 degrees C, 17.57 percent weight loss starting at about 100 degrees C
Carbamazepine:Nicotinamide (Example 24) PXRD: 6.5, 8.8, 10.1, 13.2, 15.6, 17.7, 17.8, 18.3, 19.8, 20.4, 21.6, 22.6, 22.9, 26.4, 26.7, 28.0 DSC: Sharp endotherm at about 157 degrees C TGA: Decomposition beginning at about 150 degrees C
Carbamazepine:Saccharin (Example 25) PXRD: 6.9, 12.2, 13.6, 14.0, 14.1, 15.3, 15.9, 18.1, 18.7, 20.2, 21.3, 23.7, 26.3, 28.3 DSC: Endotherms were present at about 75 and 177 degrees C TGA: 3.342 percent weight loss starting at about 67 degrees C, 55.09 percent weight loss starting at about 119 degrees C
Carbamazepine:2,6-pyridinecarboxylic acid (Example 26) TGA: 69 percent weight loss starting at about 215 degrees C, 17 percent weight loss starting at about 392 degrees C

Carbamazepine:5-nitroisophthalic acid (Example 27) PXRD: 10.14, 15.29, 17.44, 21.17, 31.41, 32.65 DSC: Endotherm at about 191 degrees C TGA: 32.02 percent weight loss starting at about 202 degrees C, 12.12 percent weight loss starting at about 224 degrees C, 17.94 percent weight loss starting at about 285 degrees C
Carbamazepine:1,3,5,7-adamantane tetracarboxylic acid (Example 28) TGA: 9 percent weight loss starting at about 189 degrees C, 52 percent weight loss starting at about 251 degrees C, 31 percent weight loss starting at about 374 degrees C
Carbamazepine:Benzoquinone (Example 29) TGA: 20.62 percent weight loss starting at about 168 degrees C, 78 percent weight loss starting at about 223 degrees C
Carbamazepine:Trimesic acid (Example 30) PXRD: 10.89, 12.23, 14.83, 16.25, 17.05, 18.13, 18.47, 21.47, 21.95, 24.57, 25.11, 27.99 DSC: Endothermic transition at about 273 degrees C TGA: 62.83 percent weight loss starting at about 253 degrees C, 30.20 percent weight loss starting at about 278 degrees C

Example 31

A co-crystal with a modulated dissolution profile has been prepared. Celecoxib: nicotinamide co-crystals were prepared via methods shown in Example 1. (See Fig. 57)

Example 32

A co-crystal with a modulated dissolution profile has been prepared. *cis*-Itraconazole: succinic acid, *cis*-itraconazole:L-tartaric acid and *cis*-itraconazole:L-malic acid co-crystals were prepared via methods shown in Examples 5, 7 and 8. (See Fig. 58)

Example 33

A co-crystal of an unsaltable or difficult to salt API has been prepared. Celecoxib: nicotinamide co-crystals were prepared via methods shown in Example 1.

Example 34

A co-crystal with an improved hygroscopicity profile has been prepared. Celecoxib: nicotinamide co-crystals were prepared via methods shown in Example 1. (See Fig. 59)

Example 35

A co-crystal with reduced form diversity as compared to the API has been prepared. Co-crystals of carbamazepine and saccharin have been prepared via method shown in Example 25.

Example 36

The formulation of a modafinil:malonic acid form I co-crystal was completed using lactose. Two mixtures, one of modafinil and lactose, and the second of modafinil:malonic acid co-crystal and lactose, were ground together in a mortar an pestle. The mixtures targeted a 1:1 weight ratio of modafinil to lactose. In the modafinil and lactose mixture, 901.2 mg of modafinil and 901.6 mg of lactose were ground together. In the modafinil:malonic acid co-crystal and lactose mixture, 1221.6 mg of co-crystal and 871.4 mg of lactose were ground together. The resulting powders were analyzed by PXRD and DSC. The PXRD patterns and DSC thermograms of the mixtures showed virtually no change upon comparison with both individual components. The DSC of the co-crystal mixture showed only the co-crystal melting peak at 113.6 degrees C with a heat of fusion of 75.9 J/g. This heat of fusion is 59.5 % of that found for the co-crystal alone (127.5 J/g). This result is consistent with a 58.4 % weight ratio of co-crystal in the mixture. The DSC of the modafinil and lactose mixture had a melting point of 165.7 degrees C. This is slightly lower then the measured melting point of modafinil (168.7 degrees C). The heat of fusion of the mixture (59.3 J/g) is 46.9 % that of the modafinil alone (126.6 J/g), which is consistent with the estimated value of 50 %.

The *in vitro* dissolution of both the modafinil:malonic acid form I co-crystal and pure modafinil were tested in capsules. Both gelatin and hydroxypropylmethyl cellulose

(HPMC) capsules were used in the dissolution study. The capsules were formulated with and without lactose. All formulations were ground in a mortar and pestle prior to transfer into a capsule. The dissolution of the capsules was tested in 0.01 M HCl (See Figure 61).

In 0.01M HCl, using sieved and ground materials in gelatin capsules:

Modafinil and the modafinil:malonic acid form I co-crystal were passed through a 38 micrometer sieve. Gelatin capsules (Size 0, B&B Pharmaceuticals, Lot # 15-01202) were filled with 200.0 mg sieved modafinil, 280.4 mg sieved modafinil:malonic acid co-crystal, 200.2 mg ground modafinil, or 280.3 mg ground modafinil:malonic acid co-crystal. Dissolution studies were performed in a Vankel VK 7000 Benchsaver Dissolution Testing Apparatus with the VK750D heater/circulator set at 37 degrees C. At 0 minutes, the capsules were dropped into vessels containing 900 mL 0.01 M HCl and stirred by paddles.

Absorbance readings were taken using a Cary 50 Spectrophotometer (wavelength set at 260nm) at the following time points: 0, 5, 10, 15, 20, 25, 30, 40, 50, and 60 minutes. The absorbance values were compared to those of standards and the modafinil concentrations of the solutions were calculated.

In 0.01M HCl, using ground materials in gelatin or HPMC capsules, with and without lactose:

Modafinil and the modafinil:malonic acid form I co-crystal were mixed with equivalent amounts of lactose (Spectrum, Lot QV0460) for approximately 5 minutes. Gelatin capsules (Size 0, B&B Pharmaceuticals, Lot # 15-01202) were filled with 400.2 mg modafinil and lactose (approximately 200 mg modafinil), or 561.0 mg modafinil:malonic acid form I co-crystal and lactose (approximately 200 mg modafinil). HPMC capsules (Size 0, Shionogi, Lot # A312A6) were filled with 399.9 mg modafinil and lactose, 560.9 mg modafinil:malonic acid co-crystal and lactose, 199.9 mg modafinil, or 280.5 mg modafinil:malonic acid form I co-crystal. The dissolution study was carried out as described above.

Example 37

The modafinil:malonic acid form I co-crystal (from Example 10) was administered to dogs in a pharmacokinetic study. Particles of modafinil:malonic acid co-crystal with a median particle size of about 16 micrometers were administered in the study. As a reference, micronized modafinil with a median particle size of about 2 micrometers was also administered in the study. The AUC of the modafinil:malonic acid co-crystal was determined to be 40 to 60 percent higher than that of the pure modafinil. Such a higher bioavailability illustrates the modulation of an important pharmacokinetic parameter due to an embodiment of the present invention. A compilation of important pharmacokinetic parameters measured during the animal study are included in Table XXV.

Table XXV- Pharmacokinetic parameters of modafinil:malonic acid co-crystal and pure modafinil in dogs

Parameter	Pure Modafinil	Modafinil:malonic acid co-crystal
Median particle size	2 micrometers	16 micrometers
C_{max} (ng/mL)	11.0 ± 5.9	10.3 ± 3.4
T_{max} (hours)	1.3 ± 0.6	1.7 ± 0.6
AUC (relative)	1.0	1.4-1.6
Half-life (hours)	2.1 ± 0.7	5.1 ± 2.4

The increased half-life and bioavailability of modafinil in the malonic acid form I co-crystal may be due to the presence of malonic acid. It is believed that the malonic acid may be inhibiting one or more pathways responsible for the metabolism or elimination of modafinil. It is noted that modafinil and malonic acid share a similar structure: each including two carbonyl or sulfonyl groups separated by a $-CH_2-$ and each molecule is terminated with a group that is capable of participation in a hydrogen bond with an enzyme. Such a mechanism may take place with other APIs or co-crystal formers of similar structure.

Example 38

The stability of the modafinil:malonic acid form I co-crystal was measured at various temperatures and relative humidities over a four week period. No degradation was found to occur at 20 or 40 degrees C. At 60 degrees C, about 0.14 percent degradation per day was determined based on a simple exponential model. At 80 degrees C, about 8 percent degradation per day was determined.

TABLE I

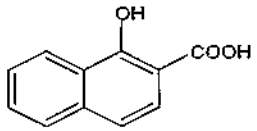
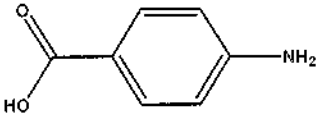
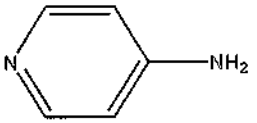
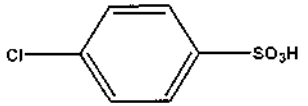
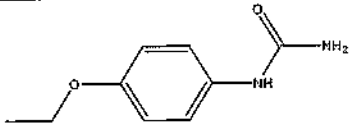
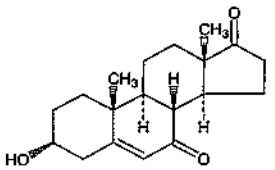
Co-Crystal Former	MW (g/mol)	MP (°C)	Class	Functionality	# acceptors	# donors	Molecular Strucutre	pKa Values
1-Hydroxy-2-naphthoic acid	188.18	191-192	2	Carboxylic acid, alcohol	1	2		2.7, 13.5
4-aminobenzoic acid	137.14	187-188	2	Amine, carboxylic acid	1	3		4.7, 4.8
4-aminopyridine	94.11	158-159	3	Amine, pyridine	1	2		10
4-Chlorobenzene-sulfonic acid	192.63	67	1	SO_3H	3	1		0-1
4-ethoxyphenyl urea	180.2	173-174	3	Amide, NH	2	3		~7-9
7-oxo-DHEA	303	190-192	1	Alcohol, Ketone	3	1		

TABLE I

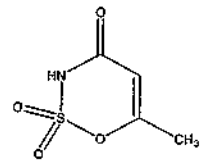
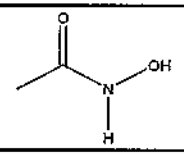
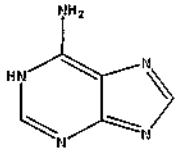
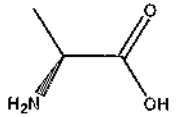
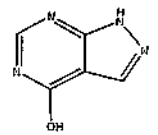
Co-Crystal Former	MW (g/mol)	MP (°C)	Class	Functionality	# acceptors	# donors	Molecular Strucutre	pKa Values
Acesulfame	163.15	123-124	3	SO_2, Amide	4	1		~5-7
Acetohydroxamic acid	75.07	89-92	3	Amide, NH, OH	2	2		8.7
Adenine	135.13	220 (sub.)	1	Amine, NH	3	3		3.8
Adipic Acid	146.14	152	1	Carboxylic acid	2	2	$HOOC(CH_2)_4COOH$	4.44, 5.44
Alanine	89.09	289-291	1	Amine, carboxillic acid	1	3		2.35, 9.87
Allopurinaol	136.11	> 350	3	OH, NH	4	2		10.2

TABLE I

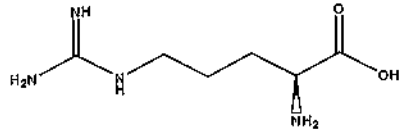
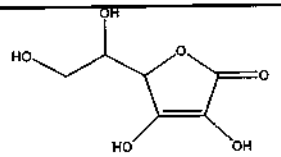
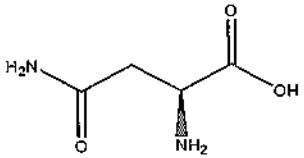
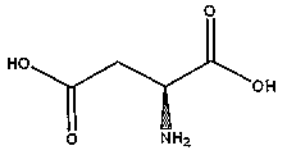
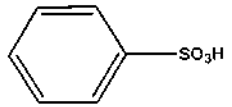
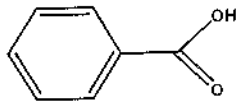
Co-Crystal Former	MW (g/mol)	MP (°C)	Class	Functionality	# acceptors	# donors	Molecular Strucutre	pKa Values
Arginine	174.2	244 (dec.)	1	Amine, COOH	2	7		2.18, 9.09, 13.2
Ascorbic acid	176.12	190-192	1	C=O, OH	6	4		4.17, 11.57
Asparagine	132.12	234-235	1	Amine, amide, COOH	3	5		2.02, 8.5
Aspartic acid	133.1	270-271	1	Amine, COOH	2	4		1.88, 3.65, 9.60
Benzenesulfonic Acid	158.18	43-44	1	SO_3H	2	1		0.70, 1.58
Benzoic acid*	122.12	122-123	2	COOH	1	1		4.19

TABLE I

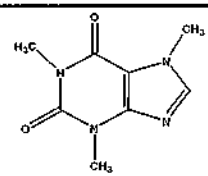
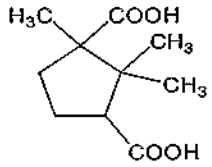
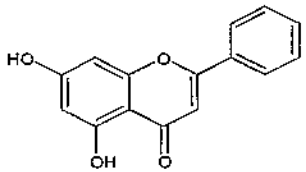
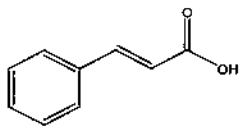
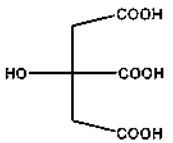
Co-Crystal Former	MW (g/mol)	MP (°C)	Class	Functionality	# acceptors	# donors	Molecular Strucutre	pKa Values
Caffeine	194.19	238	3	C=O	3	0		
Camphoric acid	200.23	186-189	2	Carboxylic acid	2	2		4.72, 5.83
Capric acid	172.27	31.4	1	Carboxylic acid	1	1	$CH_3(CH_2)_8COOH$	4.9
Chrysin	254.24	285	1	Phenol, ether, ketone	2	2		
Cinnamic acid	144.2	133	3	Carboxylic acid	1	1		4.4
Citric Acid	192.12	153	1	OH, COOH	4	4		3.13, 4.76, 6.40

TABLE I

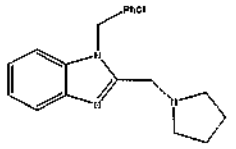
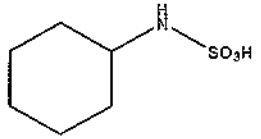
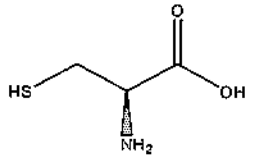
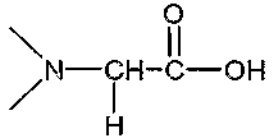
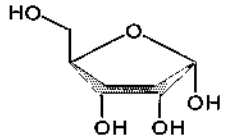
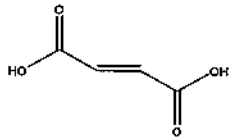
Co-Crystal Former	MW (g/mol)	MP (°C)	Class	Functionality	# acceptors	# donors	Molecular Strucutre	pKa Values
Clemizole	325.84	167	1	Pyrrolidine	3	0		
Cyclamic acid	179.24	169-170	3	NH, SO_3H	2	2		-2
Cysteine	121.15	---	1	Amine, COOH, SH	2	4		1.71, 8.33, 10.78
Dimethylglycine	103.1	178-192	1	Amine, Carboxylic acid	2	1		2.5
D-Ribose	150.13	87	1	Alcohol, ether	1	4		
Fumaric acid	116.07	287	1	COOH	2	2		3.03, 4.38

TABLE I

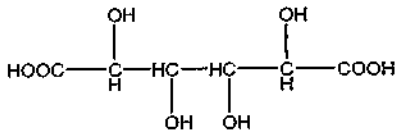
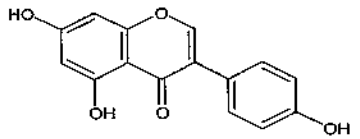
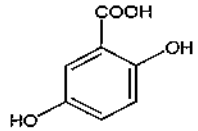
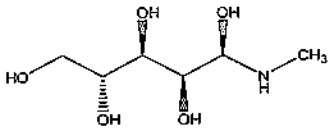
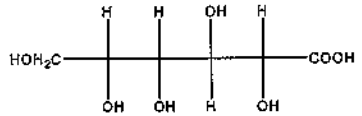
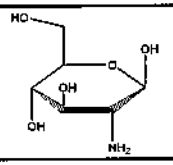
Co-Crystal Former	MW (g/mol)	MP (°C)	Class	Functionality	# acceptors	# donors	Molecular Strucutre	pKa Values
Galactaric acid	210.14	255 (dec)	1	Carboxylic acid, alcohol	2	6		3.08, 3.63
Genistein	270.24	297-298	1	Alcohol, Phenol, ether, ketone	2	3		
Gentisic acid	154.12	199-200 form I, 205 form II	2	Carboxylic acid, alcohol, phenol	1	3		2.93
Glucamine, N-Methyl	195.22	128-129	1	Alcohol, Amine	5	6		8.03(B)
Gluconic acid	196.15	131	1	OH, COOH	6	6		3.76
Glucosamine	179.17	88	1	OH	5	6		6.91

TABLE I

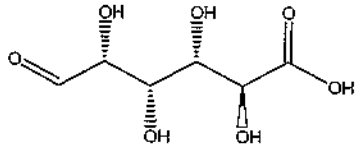
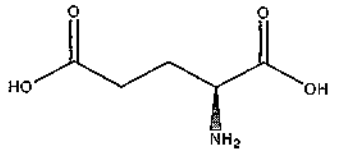
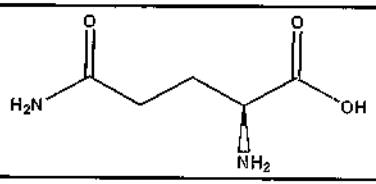
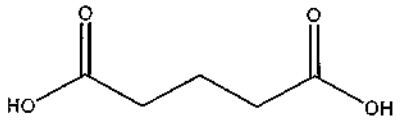
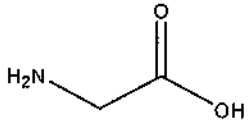
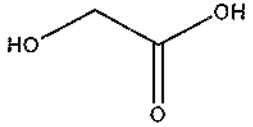
Co-Crystal Former	MW (g/mol)	MP (°C)	Class	Functionality	# acceptors	# donors	Molecular Strucutre	pKa Values
Glucuronic acid	194.14	165	1	Carboxylic acid, alcohol, aldehyde	2	5		3.18
Glutamic acid	147.13	160	1	Amine, COOH	2	4		2.19, 4.25, 9.67
Glutamine	146.15	185-186	1	Amine, Amide, COOH	2	5		2.17, 9.13
Glutaric acid	132.11	98-98	1	COOH	2	2		2.7, 4.5
Glycine	75.07	182	1	Amine, COOH	2	3		2.34, 9.6
Glycolic acid	76.05	80	1	OH, COOH	2	2		3.82

TABLE I

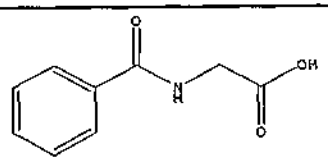
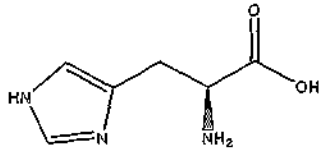
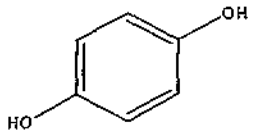
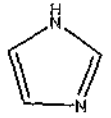
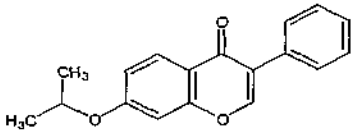
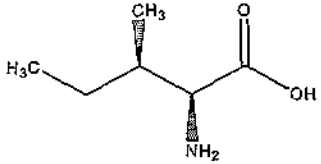
Co-Crystal Former	MW (g/mol)	MP (°C)	Class	Functionality	# acceptors	# donors	Molecular Strucutre	pKa Values
Hippuric acid	179.17	187-188	1	Amide, NH, COOH	2	2		3.55
Histidine	155.16	287 (dec.)	1	Amine, COOH, Imidazole	2	4		1.78, 5.97, 8.97
Hydroquinone*	110.11	170-171	2	OH, Phenol	2	2		~10
Imidazole	68.08	90-91	1	NH	1	1		6.92
Ipriflavone	280.32	115-117	1	Ketone, ether	3	0		
Isoleucine	131.17	168-170 (sub.)	1	Amine, COOH	1	3		2.32, 9.76

TABLE I

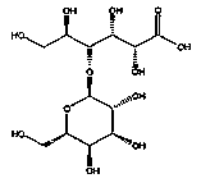
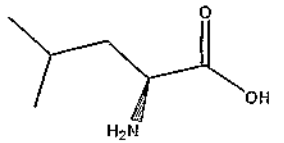
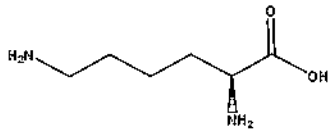
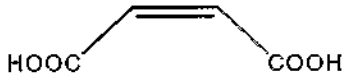
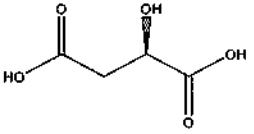
Co-Crystal Former	MW (g/mol)	MP (°C)	Class	Functionality	# acceptors	# donors	Molecular Strucutre	pKa Values
Lactobionic acid	358.3	128-130	2	Alcohol, carboxylic acid, ether	1	9		3.2
Lauric acid	200.32	44-48	1	Carboxylic acid	1	1	$CH_3(CH_2)_{10}COOH$	~4.5
Leucine	131.17	145-148 (sub.)	1	Carboxylic acid, amine	1	3		2.36, 9.6
Lysine	146.19	225 (dec.)	1	Amine, COOH	1	5		2.2, 8.9, 10.28
Maleic	116.07	138-139	1	COOH	2	2		1.92, 6.23
Malic acid	134.09	131-132	1	OH, COOH	3	3		3.46, 5.1

TABLE I

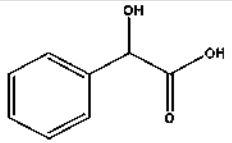
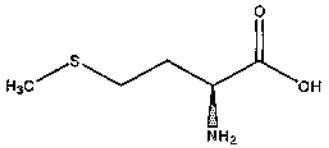
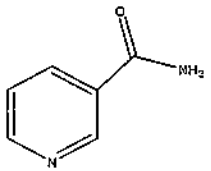
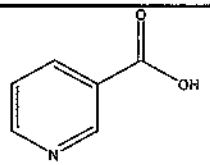
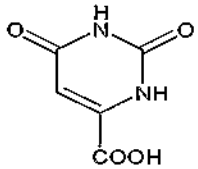
Co-Crystal Former	MW (g/mol)	MP (°C)	Class	Functionality	# acceptors	# donors	Molecular Strucutre	pKa Values
Malonic	104.06	135	1	COOH	2	2		2.83, 5.70
Mandelic acid	152.15	119	1	OH, COOH	2	2		3.37
Methionine	149.21	280-282 (dec.)	1	Amine, COOH, S-Me	2	3		2-3, 9
Nicotinamide	122.12	128-131	1	Pyridine, amide	2	2		3.3
Nicotinic acid	123.11	236-237	2	Carboxylic acid, pyridine	2	1		2.07(B), 4.85
Orotic acid	156.1	345-346	2	Carboxilic acid, lactam	3	3		5.85, 8.95

TABLE I

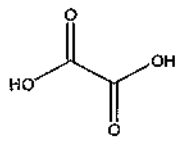
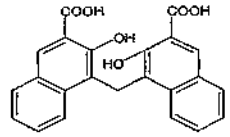
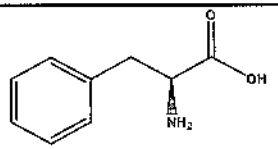
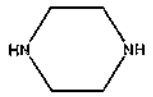
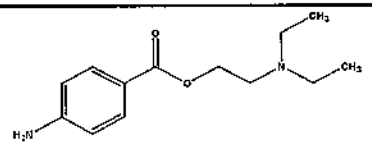
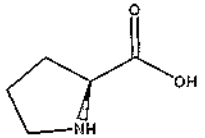
Co-Crystal Former	MW (g/mol)	MP (°C)	Class	Functionality	# acceptors	# donors	Molecular Strucutre	pKa Values
Oxalic acid	90.04	189 (dec)	2	Carboxilic acid	2	2		1.27, 4.27
Palmitic acid	256.43	63-64	1	Carboxylic acid	1	1	$CH_3(CH_2)_{14}COOH$	4.9
Pamoic	388.38	280 (dec)	2	Carboxylic acid, phenol	2	4		2.51, 3.1
Phenylalanine	165.19	283 (dec.)	1	Amine, COOH	1	3		~2, ~9
Piperazine	86.14	106	1	NH	0	2		9.82(B)
Procaine	236.31	61	1	Amine, C=O	2	2		8.9(B)
Proline	115.13	220-222 (dec.)	1	COOH, NH	1	2		1.99, 10.6

TABLE I

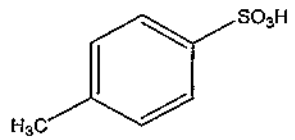
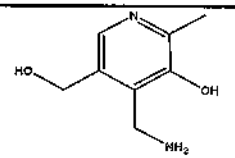
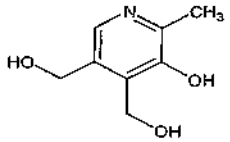
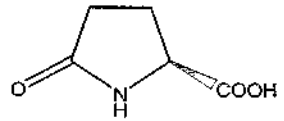
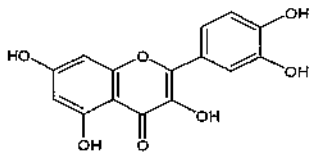
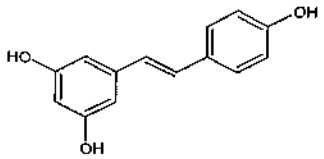
Co-Crystal Former	MW (g/mol)	MP (°C)	Class	Functionality	# acceptors	# donors	Molecular Strucutre	pKa Values
p-Toluenesulfonic acid	172.2	106-107	2	Sulfonic acid	2	1		-1.34
Pyridoxamine	168	193-194	2	OH, Amine, Pyridine	3	4		~9
Pyridoxine	170	160	2	Alcohol, Pyridine	3	3		~9
Pyroglutamic acid	129.12	162	2	Carboxylic acid, Lactam	2	2		3.32
Quercetin	302.24	314 dec.	1	Phenol, ether, ketone	2	5		
Resveratrol	228.24	253-255	1	Phenol	0	3		

TABLE I

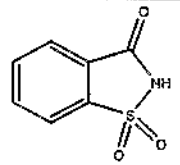
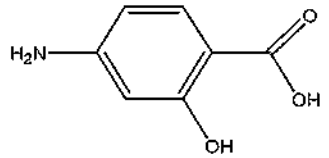
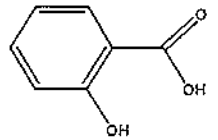
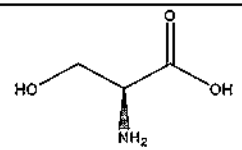
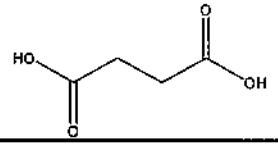
Co-Crystal Former	MW (g/mol)	MP (°C)	Class	Functionality	# acceptors	# donors	Molecular Strucutre	pKa Values
Saccharin	183.19	228-230	1	Amide, C=O, S=O, N-H	3	1		2
Salicylic acid, 4-amino	153.14	150-151	3	COOH, OH, Analine	1	4		3.25, 10, 3.5(B)
Salicylic acid	138.12	159	3	COOH, OH	2	2		2.98, 13.82
Sebacic acid	202.25	134.5	1	Carboxylic acid	2	2	$HOOC(CH_2)_8COOH$	4.59, 5.59
Serine	105.09	228 (dec.)	1	Carboxylic acid, amine, OH	2	3		2.21, 9.15
Stearic acid	284.47	70-71	1	Carboxylic acid	1	1	$CH_3(CH_2)_{16}COOH$	4.9
Succinic acid	118.09	185-187	1	Carboxylic acid	2	2		4.21, 5.64

TABLE I

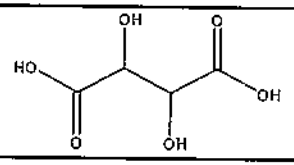
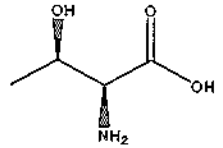
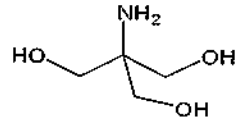
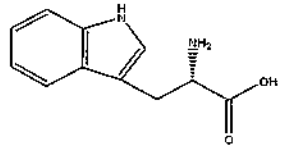
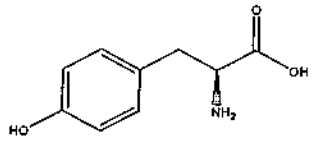
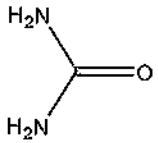
Co-Crystal Former	MW (g/mol)	MP (°C)	Class	Functionality	# acceptors	# donors	Molecular Strucutre	pKa Values
Tartaric acid	150.09	205-206	1	Carboxylic acid	4	4		3.02, 4.36
Threonine	119.12	255-257 (dec.)	1	Amine, COOH, OH	2	4		2.15, 9.12
TRIS	121.13	171-172	2	Amine, OH	3	5		5.91, 8.3
Tryptophan	204.23	289 (dec.)	1	Amine, COOH, Indole	1	4		2.38, 9.39
Tyrosine	181.19	342-344	1	Amine, COOH, OH	2	3		2.2, 9.11, 10.07
Urea	60.06	Dec.	1	C=O, NH2	1	4		~8

TABLE I

Co-Crystal Former	MW (g/mol)	MP (°C)	Class	Functionality	# acceptors	# donors	Molecular Structure	pKa Values
Valine	117.15	315	1	Amine, COOH	1	3		~4.5, ~9
Vitamin K5	209.68	280-282 (dec.)	3	Amine, OH	1	3		~9
Xylitol	152.15	93-95 (I)	2	OH	5	5		~9

TABLE II

Co-crystal Former	Co-crystal Former Functional Group	Interacting Group						
1,5-Napthalene-disulfonic Acid	Sulfonic Acid	pyridine	ketone	aldehyde	ether	ester	amide	Carboxylic Acid
1-Hydroxy-2-naphthoic acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
1-Hydroxy-2-naphthoic acid	alcohol	alcohol	ketone	thiol	amide	amine	analine	phenol
4-Aminobenzoic Acid	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol
4-Aminobenzoic Acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
4-aminopyridine	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol
4-aminopyridine	Pyridine	*alcohol	pyridinium	*	*amide	nitro	*amine	*Carboxylic Acid
4-Chlorobenzene-Sulfonic Acid	Sulfonic Acid	pyridine	ketone	aldehyde	ether	ester	amide	Carboxylic Acid
4-ethoxyphenyl Urea	Amide	alcohol	ketone	thiol	amide	amine	analine	phenol
4-ethoxyphenyl Urea	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol
7-oxo-DHEA	alcohol	alcohol	ketone	thiol	amide	amine	analine	phenol
7-oxo-DHEA	Ketone	alcohol		thiol	amide	amine	analine	phenol
Acesulfame	Sulfone	pyridine	ketone	aldehyde	ether	ester	amide	carboxilic acid
Acesulfame	Amide	alcohol	ketone	thiol	amide	amine	analine	phenol
Acetohydroxamic Acid	Amide	alcohol	ketone	thiol	amide	amine	analine	phenol
Acetohydroxamic Acid	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol
Acetohydroxamic Acid	Alcohol	alcohol	ketone	thiol	amide	amine	analine	phenol
Adenine	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol
Adenine	N	*alcohol	pyridinium	*	*amide	nitro	*amine	*carboxilic acid
Adipic acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Alanine	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol
Alanine	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Allopurinaol	Alcohol	alcohol	ketone	thiol	amide	amine	analine	phenol
Allopurinaol	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol
Arginine	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol
Arginine	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Ascorbic Acid	Ketone	alcohol		thiol	amide	amine	analine	phenol
Ascorbic Acid	Alcohol	alcohol	ketone	thiol	amide	amine	analine	phenol
Ascorbic Acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol

TABLE II

Co-crystal Former								
1,5-Napthalene-disulfonic Acid	amine	metals	thioether		sulfate	alcohol		
1-Hydroxy-2-naphthoic acid	phosphate	sulfate	sulfone	nitrate	pyridine	carboxilic acid	metals	aldehyde
1-Hydroxy-2-naphthoic acid	phosphate	sulfate	sulfone	nitrate	pyridine	carboxilic acid	metals	aldehyde
4-Aminobenzoic Acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
4-Aminobenzoic Acid	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
4-aminopyridine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
4-aminopyridine	*sulfonamide	*ketone	ether	triazole		ammonium	oxime	*chlorine
4-Chlorobenzene-Sulfonic Acid	amine	metals	thioether		sulfate	alcohol		
4-ethoxyphenyl Urea	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
4-ethoxyphenyl Urea	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
7-oxo-DHEA	phosphate	sulfate	sulfone	nitrate	pyridine	carboxilic acid	metals	aldehyde
7-oxo-DHEA	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Acesulfame	amine	metals	thioether		sulfate	alcohol		
Acesulfame	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Acetohydroxamic Acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Acetohydroxamic Acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Acetohydroxamic Acid	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Adenine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Adenine	*sulfonamide	*ketone	ether	triazole		ammonium	oxime	*chlorine
Adipic acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Alanine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Alanine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Allopurinaol	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Allopurinaol	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Arginine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Arginine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Ascorbic Acid	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Ascorbic Acid	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Ascorbic Acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals

TABLE II

Co-crystal Former								
1,5-Napthalene-disulfonic Acid								
1-Hydroxy-2-naphthoic acid	ester	ether	cyano		furan	bromine	chlorine	s-heterocyclic
1-Hydroxy-2-naphthoic acid	ester	ether	cyano		furan	bromine	chlorine	s-heterocyclic
4-Aminobenzoic Acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
4-Aminobenzoic Acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
4-aminopyridine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
4-aminopyridine		thiol	n-heterocyclic ring	thionedisulfide	pyrrolidindione	iodine	hydrazone	thiocyanate
4-Chlorobenzene-Sulfonic Acid								
4-ethoxyphenyl Urea	aldehyde	ester	ether	cyano		furan	bromine	chlorine
4-ethoxyphenyl Urea	aldehyde	ester	ether	cyano		furan	bromine	chlorine
7-oxo-DHEA	ester	ether	cyano		furan	bromine	chlorine	s-heterocyclic
7-oxo-DHEA	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Acesulfame								
Acesulfame	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Acetohydroxamic Acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Acetohydroxamic Acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Acetohydroxamic Acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Adenine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Adenine		thiol	n-heterocyclic ring	thionedisulfide	pyrrolidindione	iodine	hydrazone	thiocyanate
Adipic acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Alanine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Alanine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Allopurinaol	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Allopurinaol	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Arginine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Arginine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Ascorbic Acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Ascorbic Acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Ascorbic Acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine

TABLE II

Co-crystal Former							
1,5-Napthalene-disulfonic Acid							
1-Hydroxy-2-naphthoic acid	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		fluorine
1-Hydroxy-2-naphthoic acid	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		fluorine
4-Aminobenzoic Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
4-Aminobenzoic Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
4-aminopyridine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
4-aminopyridine	*bromine		hydroxamic acid	cyano	carboxamide	*sulfonic acid	*phosphoric acid
4-Chlorobenzene-Sulfonic Acid							
4-ethoxyphenyl Urea	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
4-ethoxyphenyl Urea	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
7-oxo-DHEA	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		fluorine
7-oxo-DHEA	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Acesulfame							
Acesulfame	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Acetohydroxamic Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Acetohydroxamic Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Acetohydroxamic Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Adenine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Adenine	*bromine		hydroxamic acid	cyano	carboxamide	*sulfonic acid	*phosphoric acid
Adipic acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Alanine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Alanine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Allopurinaol	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Allopurinaol	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Arginine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Arginine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Ascorbic Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Ascorbic Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Ascorbic Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	

TABLE II

Co-crystal Former								
1,5-Napthalene-disulfonic Acid								
1-Hydroxy-2-naphthoic acid	carbamate	imidazole	BF4					
1-Hydroxy-2-naphthoic acid	carbamate	imidazole	BF4					
4-Aminobenzoic Acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
4-Aminobenzoic Acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
4-aminopyridine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
4-aminopyridine	N-oxide	ester	ether	fluorine	acetate	thione	dithiadiazocyclopentadienyl	
4-Chlorobenzene-Sulfonic Acid								
4-ethoxyphenyl Urea	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
4-ethoxyphenyl Urea	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
7-oxo-DHEA	carbamate	imidazole	BF4					
7-oxo-DHEA	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Acesulfame								
Acesulfame	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Acetohydroxamic Acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Acetohydroxamic Acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Acetohydroxamic Acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Adenine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Adenine	N-oxide	ester	ether	fluorine	acetate	thione	dithiadiazocyclopentadienyl	
Adipic acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Alanine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Alanine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Allopurinaol	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Allopurinaol	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Arginine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Arginine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Ascorbic Acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Ascorbic Acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Ascorbic Acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea

TABLE II

Co-crystal Former				
1,5-Napthalene-disulfonic Acid				
1-Hydroxy-2-naphthoic acid				
1-Hydroxy-2-naphthoic acid				
4-Aminobenzoic Acid	iodine			
4-Aminobenzoic Acid	iodine			
4-aminopyridine	iodine			
4-aminopyridine				
4-Chlorobenzene-Sulfonic Acid				
4-ethoxyphenyl Urea	iodine	epoxide	peroxide	
4-ethoxyphenyl Urea	iodine			
7-oxo-DHEA				
7-oxo-DHEA	iodine			
Acesulfame				
Acesulfame	iodine	epoxide	peroxide	
Acetohydroxamic Acid	iodine	epoxide	peroxide	
Acetohydroxamic Acid	iodine			
Acetohydroxamic Acid	iodine	epoxide		
Adenine	iodine			
Adenine				
Adipic acid	iodine			
Alanine	iodine			
Alanine	iodine			
Allopurinaol	iodine	epoxide		
Allopurinaol	iodine			
Arginine	iodine			
Arginine	iodine			
Ascorbic Acid	iodine			
Ascorbic Acid	iodine	epoxide		
Ascorbic Acid	iodine			

TABLE II

Co-crystal Former	Co-crystal Former Functional Group	Interacting Group						
Asparagine	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol
Asparagine	Amide	alcohol	ketone	thiol	amide	amine	analine	phenol
Asparagine	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Aspartic Acid	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol
Aspartic Acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Benzenesulfonic Acid	Sulfonic Acid	pyridine	ketone	aldehyde	ether	ester	amide	Carboxylic Acid
Benzoic Acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Caffeine	Ketone	alcohol		thiol	amide	amine	analine	phenol
Camphoric acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Capric acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Genistein	Ketone	alcohol		thiol	amide	amine	analine	phenol
Genistein	Phenol	amine	amide	sulfoxide	n	pyridine	cyano	aldehyde
Genistein	Ether	aromatic-N	amide	amine	aromatic_s	Sp2 amine	sulfoxide	chlorate
Cinnamic acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Citric Acid	Alcohol	alcohol	ketone	thiol	amide	amine	analine	phenol
Citric Acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Clemizole	Pyrrolidine	*alcohol	pyridinium	*	*amide	nitro	*amine	*carboxilic acid
Cyclamic Acid	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol
Cyclamic Acid	Sulfonic Acid	pyridine	ketone	aldehyde	ether	ester	amide	Carboxylic Acid
Cysteine	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol
Cysteine	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Cysteine	Thiol	carboxylic acid	sodium	aldehyde	ketone	-N	cadmium	
Dimethylglycine	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Dimethylglycine	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol
D-ribose	Ether	aromatic-N	amide	amine	aromatic_s	Sp2 amine	sulfoxide	chlorate
D-ribose	Alcohol	alcohol	ketone	thiol	amide	amine	analine	phenol
Fumaric Acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Galactaric acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Galactaric acid	alcohol	alcohol	ketone	thiol	amide	amine	analine	phenol
Chrysin	Ketone	alcohol		thiol	amide	amine	analine	phenol

TABLE II

Co-crystal Former								
Asparagine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Asparagine	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Asparagine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Aspartic Acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Aspartic Acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Benzenesulfonic Acid	amine	metals	thioether		sulfate	alcohol		
Benzoic Acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Caffeine	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Camphoric acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Capric acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Genistein	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Genistein		alchohol		ester	ether	n-oxide	chlorine	fluorine
Genistein	chlorine		cyano	ester	amine	nitro	nitrate	bromine
Cinnamic acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Citric Acid	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Citric Acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Clemizole	*sulfonamide	*ketone	ether	triazole		ammonium	oxime	*chlorine
Cyclamic Acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Cyclamic Acid	amine	metals	thioether		sulfate	alcohol		
Cysteine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Cysteine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Cysteine	arsenic	chlorine	alcohol	potassium	Ru		Rb	Sb
Dimethylglycine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Dimethylglycine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
D-ribose	chlorine		cyano	ester	amine	nitro	nitrate	bromine
D-ribose	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Fumaric Acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Galactaric acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Galactaric acid	phosphate	sulfate	sulfone	nitrate	pyridine	carboxilic acid	metals	aldehyde
Chrysin	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals

TABLE II

Co-crystal Former								
Asparagine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Asparagine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Asparagine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Aspartic Acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Aspartic Acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Benzenesulfonic Acid								
Benzoic Acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Caffeine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Camphoric acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Capric acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Genistein	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Genistein	bromine	iodine	ketone	sulfonic acid	sulfate	phosphate	phosphonic acid	carboxylic acid
Genistein	aldehyde	ketone	peroxide	epoxide			heterocyclic-S	iodine
Cinnamic acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Citric Acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Citric Acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Clemizole		thiol	n-heterocyclic ring	thionedisulfide	pyrrolidindione	iodine	hydrazone	thiocyanate
Cyclamic Acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Cyclamic Acid								
Cysteine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Cysteine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Cysteine								
Dimethylglycine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Dimethylglycine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
D-ribose	aldehyde	ketone	peroxide	epoxide			heterocyclic-S	iodine
D-ribose	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Fumaric Acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Galactaric acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Galactaric acid	ester	ether	cyano		furan	bromine	chlorine	s-heterocyclic
Chrysin	aldehyde	ester	ether	cyano		furan	bromine	chlorine

TABLE II

Co-crystal Former							
Asparagine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Asparagine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Asparagine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Aspartic Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Aspartic Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Benzenesulfonic Acid							
Benzoic Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Caffeine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Camphoric acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Capric acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Genistein	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Genistein	nitro	sulfone	analine				
Genistein	ester	ether	carboxylic acid	sulfate	sulfone		alcohol
Cinnamic acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Citric Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Citric Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Clemizole	*bromine		hydroxamic acid	cyano	carboxamide	*sulfonic acid	*phosphoric acid
Cyclamic Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Cyclamic Acid							
Cysteine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Cysteine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Cysteine							
Dimethylglycine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Dimethylglycine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
D-ribose	ester	ether	carboxylic acid	sulfate	sulfone		alcohol
D-ribose	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Fumaric Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Galactaric acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Galactaric acid	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		fluorine
Chrysin	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	

TABLE II

Co-crystal Former								
Asparagine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Asparagine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Asparagine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Aspartic Acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Aspartic Acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Benzenesulfonic Acid								
Benzoic Acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Caffeine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Camphoric acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Capric acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Genistein	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Genistein								
Genistein		phospphate	cyanamide					
Cinnamic acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Citric Acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Citric Acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Clemizole	N-oxide	ester	ether	fluorine	acetate	thione	dithiadiazocyclopentadienyl	
Cyclamic Acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Cyclamic Acid								
Cysteine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Cysteine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Cysteine								
Dimethylglycine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Dimethylglycine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
D-ribose		phospphate	cyanamide					
D-ribose	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Fumaric Acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Galactaric acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Galactaric acid	carbamate	imidazole	BF4					
Chrysin	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea

TABLE II

Co-crystal Former			
Asparagine	iodine		
Asparagine	iodine	epoxide	peroxide
Asparagine	iodine		
Aspartic Acid	iodine		
Aspartic Acid	iodine		
Benzenesulfonic Acid			
Benzoic Acid	iodine		
Caffeine	iodine		
Camphoric acid	iodine		
Capric acid	iodine		
Genistein	iodine		
Genistein			
Genistein			
Cinnamic acid	iodine		
Citric Acid	iodine	epoxide	
Citric Acid	iodine		
Clemizole			
Cyclamic Acid	iodine		
Cyclamic Acid			
Cysteine	iodine		
Cysteine	iodine		
Cysteine			
Dimethylglycine	iodine		
Dimethylglycine	iodine		
D-ribose			
D-ribose	iodine	epoxide	
Fumaric Acid	iodine		
Galactaric acid	iodine		
Galactaric acid			
Chrysin	iodine		

TABLE II

Co-crystal Former	Co-crystal Former Functional Group	Interacting Group						
Chrysin	Phenol	amine	amide	sulfoxide	n	pyridine	cyano	aldehyde
Chrysin	Ether	aromatic-N	amide	amine	aromatic_s	Sp2 amine	sulfoxide	chlorate
Gentisic acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Gentisic acid	Phenol	amine	amide	sulfoxide	n	pyridine	cyano	aldehyde
Glucamine, N-methyl	alcohol	alcohol	ketone	thiol	amide	amine	analine	phenol
Glucamine, N-methyl	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol
Gluconic Acid	Alcohol	alcohol	ketone	thiol	amide	amine	analine	phenol
Gluconic Acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Glucosamine	alcohol	alcohol	ketone	thiol	amide	amine	analine	phenol
Glucuronic acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Glucuronic acid	alcohol	alcohol	ketone	thiol	amide	amine	analine	phenol
Glucuronic acid	Aldehyde	alcohol	ketone	thiol	amide	amine	analine	phenol
Glutamic Acid	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol
Glutamic Acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Glutamine	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol
Glutamine	Amide	alcohol	ketone	thiol	amide	amine	analine	phenol
Glutamine	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Glutaric Acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Glycine	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol
Glycine	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Glycolic Acid	Alcohol	alcohol	ketone	thiol	amide	amine	analine	phenol
Glycolic Acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Hippuric Acid	Amide	alcohol	ketone	thiol	amide	amine	analine	phenol
Hippuric Acid	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol
Hippuric Acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Histidine	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol
Histidine	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Histidine	Imidazole	imidazole	chlorine	acetamide	carboxylate		thione	nitro
Hydroquinone	Alcohol	alcohol	ketone	thiol	amide	amine	analine	phenol
Hydroquinone	Phenol	amine	amide	sulfoxide	n	pyridine	cyano	aldehyde
Imidazole	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol

TABLE II

Co-crystal Former								
Chrysin		alchohol		ester	ether	n-oxide	chlorine	fluorine
Chrysin	chlorine		cyano	ester	amine	nitro	nitrate	bromine
Gentisic acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Gentisic acid		alchohol		ester	ether	n-oxide	chlorine	fluorine
Glucamine, N-methyl	phosphate	sulfate	sulfone	nitrate	pyridine	carboxilic acid	metals	aldehyde
Glucamine, N-methyl	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Gluconic Acid	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Gluconic Acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Glucosamine	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Glucuronic acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Glucuronic acid	phosphate	sulfate	sulfone	nitrate	pyridine	carboxilic acid	metals	aldehyde
Glucuronic acid	phosphate	sulfate	sulfone	nitrate	pyridine	aromatic	carboxilic acid	metals
Glutamic Acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Glutamic Acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Glutamine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Glutamine	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Glutamine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Glutaric Acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Glycine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Glycine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Glycolic Acid	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Glycolic Acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Hippuric Acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Hippuric Acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Hippuric Acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Histidine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Histidine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Histidine	cyanamide	ketone	cyano	Carboxylic Acid	alcohol		thiol	amine
Hydroquinone	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Hydroquinone		alchohol		ester	ether	n-oxide	chlorine	fluorine
Imidazole	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals

TABLE II

Co-crystal Former								
Chrysin	bromine	iodine	ketone	sulfonic acid	sulfate	phosphate	phosphonic acid	carboxylic acid
Chrysin	aldehyde	ketone	peroxide	epoxide			heterocyclic-S	iodine
Gentisic acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Gentisic acid	bromine	iodine	ketone	sulfonic acid	sulfate	phosphate	phosphonic acid	carboxylic acid
Glucamine, N-methyl	ester	ether	cyano		furan	bromine	chlorine	s-heterocyclic
Glucamine, N-methyl	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Gluconic Acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Gluconic Acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Glucosamine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Glucuronic acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Glucuronic acid	ester	ether	cyano		furan	bromine	chlorine	s-heterocyclic
Glucuronic acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Glutamic Acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Glutamic Acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Glutamine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Glutamine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Glutamine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Glutaric Acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Glycine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Glycine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Glycolic Acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Glycolic Acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Hippuric Acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Hippuric Acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Hippuric Acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Histidine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Histidine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Histidine	phosphinic acid hemihydrate	chlorine	sulfonyl	sulfoxide	amide	fluorine	sulfonate ester	
Hydroquinone	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Hydroquinone	bromine	iodine	ketone	sulfonic acid	sulfate	phosphate	phosphonic acid	carboxylic acid
Imidazole	aldehyde	ester	ether	cyano		furan	bromine	chlorine

TABLE II

Co-crystal Former							
Chrysin	nitro	sulfone	analine				
Chrysin	ester	ether	carboxylic acid	sulfate	sulfone		alcohol
Gentisic acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Gentisic acid	nitro	sulfone	analine				
Glucamine, N-methyl	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		fluorine
Glucamine, N-methyl	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Gluconic Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Gluconic Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Glucosamine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Glucuronic acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Glucuronic acid	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		fluorine
Glucuronic acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Glutamic Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Glutamic Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Glutamine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Glutamine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Glutamine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Glutaric Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Glycine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Glycine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Glycolic Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Glycolic Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Hippuric Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Hippuric Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Hippuric Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Histidine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Histidine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Histidine							
Hydroquinone	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Hydroquinone	nitro	sulfone	analine				
Imidazole	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	

TABLE II

Co-crystal Former								
Chrysin								
Chrysin		phospphate	cyanamide					
Gentisic acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Gentisic acid								
Glucamine, N-methyl	carbamate	imidazole	BF4					
Glucamine, N-methyl	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Gluconic Acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Gluconic Acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Glucosamine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Glucuronic acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Glucuronic acid	carbamate	imidazole	BF4					
Glucuronic acid	fluorine	carbamate	imidazole	BF4	alkane	aromatic	N-SO2	thiourea
Glutamic Acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Glutamic Acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Glutamine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Glutamine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Glutamine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Glutaric Acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Glycine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Glycine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Glycolic Acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Glycolic Acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Hippuric Acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Hippuric Acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Hippuric Acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Histidine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Histidine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Histidine								
Hydroquinone	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Hydroquinone								
Imidazole	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea

TABLE II

Co-crystal Former				
Chrysin				
Chrysin				
Gentisic acid	iodine			
Gentisic acid				
Glucamine, N-methyl				
Glucamine, N-methyl	iodine			
Gluconic Acid	iodine	epoxide		
Gluconic Acid	iodine			
Glucosamine	iodine	epoxide		
Glucuronic acid	iodine			
Glucuronic acid				
Glucuronic acid	iodine	epoxide		
Glutamic Acid	iodine			
Glutamic Acid	iodine			
Glutamine	iodine			
Glutamine	iodine	epoxide	peroxide	
Glutamine	iodine			
Glutaric Acid	iodine			
Glycine	iodine			
Glycine	iodine			
Glycolic Acid	iodine	epoxide		
Glycolic Acid	iodine			
Hippuric Acid	iodine	epoxide	peroxide	
Hippuric Acid	iodine			
Hippuric Acid	iodine			
Histidine	iodine			
Histidine	iodine			
Histidine				
Hydroquinone	iodine	epoxide		
Hydroquinone				
Imidazole	iodine			

TABLE II

Co-crystal Former	Co-crystal Former Functional Group	Interacting Group						
Ipriflavone	Ether	aromatic-N	amide	amine	aromatic_s	Sp2 amine	sulfoxide	chlorate
Ipriflavone	Ketone	alcohol		thiol	amide	amine	analine	phenol
Isoleucine	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol
Isoleucine	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
lactobionic acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Lactobionic acid	alcohol	alcohol	ketone	thiol	amide	amine	analine	phenol
Lactobionic acid	Ether	aromatic-N	amide	amine	aromatic_s	Sp2 amine	sulfoxide	chlorate
Lauric acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Leucine	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Leucine	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol
Lysine	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol
Lysine	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Maleic	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Malic Acid	Alcohol	alcohol	ketone	thiol	amide	amine	analine	phenol
Malic Acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Malonic	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Mandelic Acid	Alcohol	alcohol	ketone	thiol	amide	amine	analine	phenol
Mandelic Acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Methionine	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol
Methionine	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Methionine	Thioether	-N	amide	amine	_s	Sp2 amine	sulfoxide	chlorate
Nicotinamide	Pyridine	*alcohol		*	*amide	nitro	*amine	*Carboxylic Acid
Nicotinamide	Amide	alcohol	ketone	thiol	amide	amine	analine	phenol
Nicotinic Acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Nicotinic Acid	Pyridine	*alcohol		*	*amide	nitro	*amine	*Carboxylic Acid
Orotic acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Orotic acid	Lactam	alcohol	ketone	thiol	amide	amine	analine	phenol
Oxalic acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Palmitic acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Pamoic acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Pamoic acid	alcohol	alcohol	ketone	thiol	amide	amine	analine	phenol
Pamoic acid	Phenol	amine	amide	sulfoxide	n	pyridine	cyano	aldehyde

TABLE II

Co-crystal Former								
Ipriflavone	chlorine		cyano	ester	amine	nitro	nitrate	bromine
Ipriflavone	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Isoleucine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Isoleucine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
lactobionic acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Lactobionic acid	phosphate	sulfate	sulfone	nitrate	pyridine	carboxilic acid	metals	aldehyde
Lactobionic acid	chlorine		cyano	ester	amine	nitro	nitrate	bromine
Lauric acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	
Leucine	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Leucine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Lysine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Lysine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Maleic	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Malic Acid	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Malic Acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Malonic	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Mandelic Acid	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Mandelic Acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Methionine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Methionine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Methionine	chlorine		cyano	ester	amine	nitro	nitrate	bromine
Nicotinamide	*sulfonamide	*ketone	ether	triazole		ammonium	oxime	*chlorine
Nicotinamide	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Nicotinic Acid	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Nicotinic Acid	*sulfonamide	*ketone	ether	triazole		ammonium	oxime	*chlorine
Orotic acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	
Orotic acid	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Oxalic acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	
Palmitic acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	
Pamoic acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	
Pamoic acid	phosphate	sulfate	sulfone	nitrate	pyridine	carboxilic acid	metals	aldehyde
Pamoic acid		alchohol		ester	ether	n-oxide	chlorine	fluorine

TABLE II

Co-crystal Former								
Ipriflavone	aldehyde	ketone	peroxide	epoxide			heterocyclic-S	iodine
Ipriflavone	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Isoleucine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Isoleucine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
lactobionic acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Lactobionic acid	ester	ether	cyano		furan	bromine	chlorine	s-heterocyclic
Lactobionic acid	aldehyde	ketone	peroxide	epoxide			heterocyclic-S	iodine
Lauric acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Leucine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Leucine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Lysine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Lysine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Maleic	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Malic Acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Malic Acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Malonic	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Mandelic Acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Mandelic Acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Methionine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Methionine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Methionine	aldehyde	ketone	peroxide	epoxide	Ag	Se	heterocyclic-S	iodine
Nicotinamide		thiol	n-heterocyclic ring	thionedisulfide	pyrrolidindione	iodine	hydrazone	thiocyanate
Nicotinamide	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Nicotinic Acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Nicotinic Acid		thiol	n-heterocyclic ring	thionedisulfide	pyrrolidindione	iodine	hydrazone	thiocyanate
Orotic acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Orotic acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Oxalic acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Palmitic acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Pamoic acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Pamoic acid	ester	ether	cyano		furan	bromine	chlorine	s-heterocyclic
Pamoic acid	bromine	iodine	ketone	sulfonic acid	sulfate	phosphate	phosphonic acid	carboxylic acid

TABLE II

Co-crystal Former							
Ipriflavone	ester	ether	carboxylic acid	sulfate	sulfone		alcohol
Ipriflavone	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Isoleucine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Isoleucine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
lactobionic acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Lactobionic acid	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		fluorine
Lactobionic acid	ester	ether	carboxylic acid	sulfate	sulfone		alcohol
Lauric acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Leucine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Leucine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Lysine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Lysine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Maleic	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Malic Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Malic Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Malonic	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Mandelic Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Mandelic Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Methionine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Methionine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Methionine	ester	ether	carboxylic acid	sulfate	sulfone		alcohol
Nicotinamide	*bromine		hydroxamic acid	cyano	carboxamide	*sulfonic acid	*phosphoric acid
Nicotinamide	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Nicotinic Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Nicotinic Acid	*bromine		hydroxamic acid	cyano	carboxamide	*sulfonic acid	*phosphoric acid
Orotic acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Orotic acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Oxalic acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Palmitic acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Pamoic acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Pamoic acid	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		fluorine
Pamoic acid	nitro	sulfone	analine				

TABLE II

Co-crystal Former								
Ipriflavone		phospphate	cyanamide					
Ipriflavone	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Isoleucine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Isoleucine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
lactobionic acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Lactobionic acid	carbamate	imidazole	BF4					
Lactobionic acid		phospphate	cyanamide					
Lauric acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Leucine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Leucine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Lysine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Lysine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Maleic	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Malic Acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Malic Acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Malonic	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Mandelic Acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Mandelic Acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Methionine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Methionine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Methionine		phospphate						
Nicotinamide	N-oxide	ester	ether	fluorine	acetate	thione	dithiadiazocyclopentadienyl	
Nicotinamide	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Nicotinic Acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Nicotinic Acid	N-oxide	ester	ether	fluorine	acetate	thione	dithiadiazocyclopentadienyl	
Orotic acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Orotic acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Oxalic acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Palmitic acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Pamoic acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Pamoic acid	carbamate	imidazole	BF4					
Pamoic acid								

TABLE II

Co-crystal Former			
Ipriflavone			
Ipriflavone	iodine		
Isoleucine	iodine		
Isoleucine	iodine		
lactobionic acid	iodine		
Lactobionic acid			
Lactobionic acid			
Lauric acid	iodine		
Leucine	iodine		
Leucine	iodine		
Lysine	iodine		
Lysine	iodine		
Maleic	iodine		
Malic Acid	iodine	epoxide	
Malic Acid	iodine		
Malonic	iodine		
Mandelic Acid	iodine	epoxide	
Mandelic Acid	iodine		
Methionine	iodine		
Methionine	iodine		
Methionine			
Nicotinamide			
Nicotinamide	iodine	epoxide	peroxide
Nicotinic Acid	iodine		
Nicotinic Acid			
Orotic acid	iodine		
Orotic acid	iodine	epoxide	peroxide
Oxalic acid	iodine		
Palmitic acid	iodine		
Pamoic acid	iodine		
Pamoic acid			
Pamoic acid			

TABLE II

Co-crystal Former	Co-crystal Former Functional Group	Interacting Group						
Phenylalanine	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol
Phenylalanine	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Piperazine	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol
Procaine	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol
Procaine	Ketone	alcohol		thiol	amide	amine	analine	phenol
Proline	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Proline	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol
p-Toluenesulfonic acid	Sulfonic Acid	pyridine	ketone	aldehyde	ether	ester	amide	Carboxylic Acid
Pyridoxamine	Alcohol	alcohol	ketone	thiol	amide	amine	analine	phenol
Pyridoxamine	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol
Pyridoxamine	Pyridine	*alcohol		*	*amide	nitro	*amine	*Carboxylic Acid
Pyridoxine (4-Pyridoxic Acid)	Pyridine	*alcohol	pyridinium	*	*amide	nitro	*amine	*Carboxylic Acid
Pyridoxine (4-Pyridoxic Acid)	Alcohol	alcohol	ketone	thiol	amide	amine	analine	phenol
Pyroglutamic acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Pyroglutamic acid	Lactam	alcohol	ketone	thiol	amide	amine	analine	phenol
Quercetin	Ketone	alcohol		thiol	amide	amine	analine	phenol
Quercetin	Phenol	amine	amide	sulfoxide	n	pyridine	cyano	aldehyde
Quercetin	Ether	aromatic-N	amide	amine	aromatic_s	Sp2 amine	sulfoxide	chlorate
Resveratrol	Ketone	alcohol		thiol	amide	amine	analine	phenol
Resveratrol	Phenol	amine	amide	sulfoxide	n	pyridine	cyano	aldehyde
Saccharin	Amide	alcohol	ketone	thiol	amide	amine	analine	phenol
Saccharin	Ketone	alcohol		thiol	amide	amine	analine	phenol
Saccharin	Sulfoxide	pyridine	ketone	aldehyde	ether	ester	amide	Carboxylic Acid
Saccharin	Amine	alcohol	ketone	thiol	amide		analine	phenol
Salicylic Acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Salicylic Acid	Alcohol	alcohol	ketone	thiol	amide	amine	analine	phenol
Salicylic Acid, 4-amino	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Salicylic Acid, 4-amino	alcohol	alcohol	ketone	thiol	amide	amine	analine	phenol
Salicylic Acid, 4-amino	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol

TABLE II

Co-crystal Former								
Phenylalanine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Phenylalanine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Piperazine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Procaine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Procaine	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Proline	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Proline	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
p-Toluenesulfonic acid	amine	metals	thioether		sulfate	alcohol		
Pyridoxamine	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Pyridoxamine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Pyridoxamine	*sulfonamide	*ketone	ether	triazole		ammonium	oxime	*chlorine
Pyridoxine (4-Pyridoxic Acid)	*sulfonamide	*ketone	ether	triazole		ammonium	oxime	*chlorine
Pyridoxine (4-Pyridoxic Acid)	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Pyroglutamic acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Pyroglutamic acid	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Quercetin	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Quercetin		alchohol		ester	ether	n-oxide	chlorine	fluorine
Quercetin	chlorine		cyano	ester	amine	nitro	nitrate	bromine
Resveratrol	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Resveratrol		alchohol		ester	ether	n-oxide	chlorine	fluorine
Saccharin	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Saccharin	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Saccharin	amine	metals	thioether		sulfate	alcohol		
Saccharin	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Salicylic Acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Salicylic Acid	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Salicylic Acid, 4-amino	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Salicylic Acid, 4-amino	phosphate	sulfate	sulfone	nitrate	pyridine	carboxilic acid	metals	aldehyde
Salicylic Acid, 4-amino	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals

TABLE II

Co-crystal Former								
Phenylalanine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Phenylalanine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Piperazine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Procaine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Procaine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Proline	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Proline	aldehyde	ester	ether	cyano		furan	bromine	chlorine
p-Toluenesulfonic acid								
Pyridoxamine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Pyridoxamine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Pyridoxamine		thiol	n-heterocyclic ring	thionedisulfide		iodine	hydrazone	thiocyanate
Pyridoxine (4-Pyridoxic Acid)		thiol	n-heterocyclic ring	thionedisulfide	pyrrolidindione	iodine	hydrazone	thiocyanate
Pyridoxine (4-Pyridoxic Acid)	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Pyroglutamic acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Pyroglutamic acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Quercetin	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Quercetin	bromine	iodine	ketone	sulfonic acid	sulfate	phosphate	phosphonic acid	carboxylic acid
Quercetin	aldehyde	ketone	peroxide	epoxide			heterocyclic-S	iodine
Resveratrol	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Resveratrol	bromine	iodine	ketone	sulfonic acid	sulfate	phosphate	phosphonic acid	carboxylic acid
Saccharin	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Saccharin	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Saccharin								
Saccharin	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Salicylic Acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Salicylic Acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Salicylic Acid, 4-amino	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Salicylic Acid, 4-amino	ester	ether	cyano		furan	bromine	chlorine	s-heterocyclic
Salicylic Acid, 4-amino	aldehyde	ester	ether	cyano		furan	bromine	chlorine

TABLE II

Co-crystal Former							
Phenylalanine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Phenylalanine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Piperazine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Procaine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Procaine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Proline	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Proline	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
p-Toluenesulfonic acid							
Pyridoxamine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Pyridoxamine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Pyridoxamine	*bromine		hydroxamic acid	cyano	carboxamide	*sulfonic acid	*phosphoric acid
Pyridoxine (4-Pyridoxic Acid)	*bromine		hydroxamic acid	cyano	carboxamide	*sulfonic acid	*phosphoric acid
Pyridoxine (4-Pyridoxic Acid)	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Pyroglutamic acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Pyroglutamic acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Quercetin	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Quercetin	nitro	sulfone	analine				
Quercetin	ester	ether	carboxylic acid	sulfate	sulfone		alcohol
Resveratrol	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Resveratrol	nitro	sulfone	analine				
Saccharin	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Saccharin	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Saccharin							
Saccharin	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Salicylic Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Salicylic Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Salicylic Acid, 4-amino	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Salicylic Acid, 4-amino	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		fluorine
Salicylic Acid, 4-amino	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	

TABLE II

Co-crystal Former								
Phenylalanine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Phenylalanine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Piperazine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Procaine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Procaine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Proline	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Proline	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
p-Toluenesulfonic acid								
Pyridoxamine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Pyridoxamine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Pyridoxamine	N-oxide	ester	ether	fluorine	acetate	thione	dithiadiazocyclopentadienyl	
Pyridoxine (4-Pyridoxic Acid)	N-oxide	ester	ether	fluorine	acetate	thione	dithiadiazocyclopentadienyl	
Pyridoxine (4-Pyridoxic Acid)	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Pyroglutamic acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Pyroglutamic acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Quercetin	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Quercetin								
Quercetin		phospphate	cyanamide					
Resveratrol	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Resveratrol								
Saccharin	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Saccharin	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Saccharin								
Saccharin	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Salicylic Acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Salicylic Acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Salicylic Acid, 4-amino	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Salicylic Acid, 4-amino	carbamate	imidazole	BF4					
Salicylic Acid, 4-amino	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea

TABLE II

Co-crystal Former			
Phenylalanine	iodine		
Phenylalanine	iodine		
Piperazine	iodine		
Procaine	iodine		
Procaine	iodine		
Proline	iodine		
Proline	iodine		
p-Toluenesulfonic acid			
Pyridoxamine	iodine	epoxide	
Pyridoxamine	iodine		
Pyridoxamine			
Pyridoxine (4-Pyridoxic Acid)			
Pyridoxine (4-Pyridoxic Acid)	iodine	epoxide	
Pyroglutamic acid	iodine		
Pyroglutamic acid	iodine	epoxide	peroxide
Quercetin	iodine		
Quercetin			
Quercetin			
Resveratrol	iodine		
Resveratrol			
Saccharin	iodine	epoxide	peroxide
Saccharin	iodine		
Saccharin			
Saccharin	iodine		
Salicylic Acid	iodine		
Salicylic Acid	iodine	epoxide	
Salicylic Acid, 4-amino	iodine		
Salicylic Acid, 4-amino			
Salicylic Acid, 4-amino	iodine		

TABLE II

Co-crystal Former	Co-crystal Former Functional Group	Interacting Group						
Sebacic acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Serine	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Serine	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol
Serine	Alcohol	alcohol	ketone	thiol	amide	amine	analine	phenol
Stearic acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Succinic Acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Tartaric Acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Threonine	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol
Threonine	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Threonine	alcohol	alcohol	ketone	thiol	amide	amine	analine	phenol
Tris	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol
Tris	Alcohol	alcohol	ketone	thiol	amide	amine	analine	phenol
Tryptophan	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol
Tryptophan	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Tryptophan	Indole	*alcohol	pyridinium	*	*amide	nitro	*amine	*carboxilic acid
Tyrosine	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol
Tyrosine	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Tyrosine	Alcohol	alcohol	ketone	thiol	amide	amine	analine	phenol
Urea	Ketone	alcohol		thiol	amide	amine	analine	phenol
Urea	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol
Urea	Amide	alcohol	ketone	thiol	amide	amine	analine	phenol
Valine	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol
Valine	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Vitamin K5	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol
Vitamin K5	Alcohol	alcohol	ketone	thiol	amide	amine	analine	phenol
Xylitol	Alcohol	alcohol	ketone	thiol	amide	amine	analine	phenol

TABLE II

Co-crystal Former								
Sebacic acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Serine	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Serine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Serine	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Stearic acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Succinic Acid	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Tartaric Acid	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Threonine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Threonine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Threonine	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Tris	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Tris	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Tryptophan	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Tryptophan	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Tryptophan	*sulfonamide	*ketone	ether	triazole		ammonium	oxime	*chlorine
Tyrosine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Tyrosine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Tyrosine	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Urea	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Urea	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Urea	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Valine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Valine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Vitamin K5	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Vitamin K5	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Xylitol	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals

TABLE II

Co-crystal Former								
Sebacic acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Serine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Serine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Serine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Stearic acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Succinic Acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Tartaric Acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Threonine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Threonine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Threonine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Tris	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Tris	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Tryptophan	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Tryptophan	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Tryptophan		thiol	n-heterocyclic ring	thionedisulfide	pyrrolidindione	iodine	hydrazone	thiocyanate
Tyrosine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Tyrosine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Tyrosine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Urea	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Urea	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Urea	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Valine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Valine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Vitamin K5	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Vitamin K5	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Xylitol	aldehyde	ester	ether	cyano		furan	bromine	chlorine

TABLE II

Co-crystal Former							
Sebacic acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Serine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Serine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Serine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Stearic acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Succinic Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Tartaric Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Threonine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Threonine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Threonine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Tris	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Tris	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Tryptophan	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Tryptophan	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Tryptophan	*bromine		hydroxamic acid	cyano	carboxamide	*sulfonic acid	*phosphoric acid
Tyrosine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Tyrosine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Tyrosine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Urea	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Urea	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Urea	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Valine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Valine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Vitamin K5	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Vitamin K5	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Xylitol	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	

TABLE II

Co-crystal Former								
Sebacic acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Serine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Serine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Serine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Stearic acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Succinic Acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Tartaric Acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Threonine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Threonine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Threonine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Tris	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Tris	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Tryptophan	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Tryptophan	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Tryptophan	N-oxide	ester	ether	fluorine	acetate	thione	dithiadiazocyclopentadienyl	
Tyrosine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Tyrosine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Tyrosine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Urea	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Urea	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Urea	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Valine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Valine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Vitamin K5	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Vitamin K5	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Xylitol	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea

TABLE II

Co-crystal Former			
Sebacic acid	iodine		
Serine	iodine		
Serine	iodine		
Serine	iodine	epoxide	
Stearic acid	iodine		
Succinic Acid	iodine		
Tartaric Acid	iodine		
Threonine	iodine		
Threonine	iodine		
Threonine	iodine	epoxide	
Tris	iodine		
Tris	iodine	epoxide	
Tryptophan	iodine		
Tryptophan	iodine		
Tryptophan			
Tyrosine	iodine		
Tyrosine	iodine		
Tyrosine	iodine	epoxide	
Urea	iodine		
Urea	iodine		
Urea	iodine	epoxide	peroxide
Valine	iodine		
Valine	iodine		
Vitamin K5	iodine		
Vitamin K5	iodine	epoxide	
Xylitol	iodine	epoxide	

TABLE III

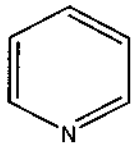
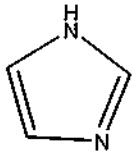
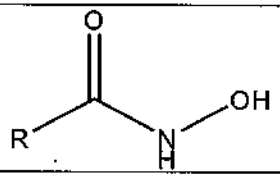
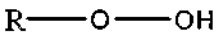
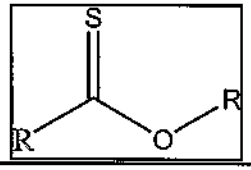
Functional Group	Functional Group Structure	Interacting Group					
pyridine		*alcohol	pyridinium	*amide	nitro	*amine	*carboxilic acid
imidazole		imidazole	chlorine	acetamide	carboxylate	thione	nitro
Hydroxamic acid		hydroxamic acid	alcohol	phosphinic ester	alkane	pyridine	amide
peroxide		ester	peroxide	amide	ether	alkane	N-heterocycle
epoxide		alkane	bromine	alcohol	ester	epoxide	amide
thioester		aromatic	thioester	alkane	sulfamide	hydroxy	bromine

TABLE III

Functional Group									
pyridine	*sulfonamide	*ketone	ether	triazole	alkane	ammonium	oxime	*chlorine	alkyne
imidazole	cyanamide	ketone	cyano	carboxilic acid	alcohol	alkane	thiol	amine	phosphinic acid hemihydrate
Hydroxamic acid	sulfonamide	carboxylate	phosphine	amine	aromatic				
peroxide	aromatic	alcohol	pyrimidinedione	analine	thiazole	peroxy acid	ketone	carboxilic acid	azide
epoxide	alkene	hydrazone	aromatic	thioether	ketone	aldehyde	chlorine	carboxilic acid	alkyne
thioester	iodine	amine	cyano	thioketone	amide		chlorine	nitro	

TABLE III

Functional Group									
pyridine	thiol	n-heterocyclic ring	thionedisulfide	pyrrolidindione	iodine	hydrazone	thiocyanate	*bromine	aromatic
imidazole	chlorine	sulfonyl	sulfoxide	amide	fluorine	sulfonate ester			
Hydroxamic acid									
peroxide	phosphine oxide	sulfonamide	analine						
epoxide		ammonium	fluorine	nitro	amine	cyano			
thioester									

TABLE III

Functional Group	hydroxamic acid	cyano	carboxamide	*sulfonic acid	*phosphoric acid	N-oxide	ester	ether	fluorine	acetate	thione
pyridine											
imidazole											
Hydroxamic acid											
peroxide											
epoxide											
thioester											

TABLE III

Functional Group							
pyridine	dithiadiazocyclopentadienyl						
imidazole							
Hydroxamic acid							
peroxide							
epoxide							
thioester							

TABLE III

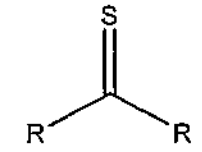
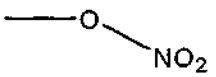
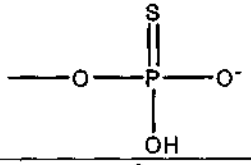
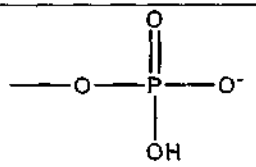
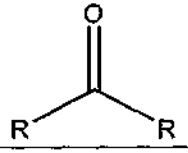
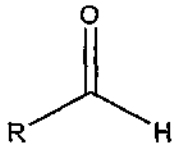
Functional Group	Functional Group Structure	Interacting Group					
thioketone		alkane	thioketone	ketone	SULFAMIDE	AMINE	thiol
nitrate ester		aromatic	amide	alkane	chlorine	nitrate ester	bromine
Thiophosphate ester-O		amine	imidazole	cyclic amide			
Phosphate ester		aromatic	alcohol	phosphate ester	aromatic N-ring	pyridine	analine
Ketone		alcohol	ketone	thiol	amide	amine	analine
Aldehyde		alcohol	ketone	thiol	amide	amine	analine
Thiol		carboxylic acid	sodium	aldehyde	ketone	aromatic-N	cadmium

TABLE III

Functional Group											
thioketone	sulfoxide	oxo	chlorine	bromine	AROMATIC	alkene	sulfone	iodine	AZOXY		
nitrate ester	alcohol	ether	acetate								
Thiophosphate ester-O											
Phosphate ester	amine		sodium	potassium	lithium	carboxylic acid	amide	alkane			
Ketone	phenol	phosphate	sulfate	sulfone	nitrate	pyridine	aromatic	carboxilic acid	metals		
Aldehyde	phenol	phosphate	sulfate	sulfone	nitrate	pyridine	aromatic	carboxilic acid	metals		
Thiol	alkane	arsenic	chlorine	alcohol	potassium	Ru	aromatic	Rb	Sb		

TABLE III

Functional Group									
thioketone	potassium	epoxide	n-oxide	cyano	iron	cobalt	amine	sulfate	
nitrate ester									
Thiophosphate ester-O									
Phosphate ester									
Ketone	aldehyde	ester	ether	cyano		furan	bromine	chlorine	s-heterocyclic
Aldehyde	aldehyde	ester	ether	cyano		furan	bromine	chlorine	s-heterocyclic
Thiol									

TABLE III

Functional Group											
thioketone											
nitrate ester											
Thiophosphate ester-O											
Phosphate ester											
Ketone	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		fluorine	carbamate	imidazole	BF4	alkane
Aldehyde	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		fluorine	carbamate	imidazole	BF4	alkane
Thiol											

TABLE III

Functional Group										
thioketone										
nitrate ester										
Thiophosphate ester-O										
Phosphate ester										
Ketone	aromatic	N-SO2	thiourea	iodine						
Aldehyde	aromatic	N-SO2	thiourea	iodine	epoxide					
Thiol										

TABLE III

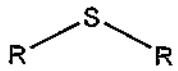
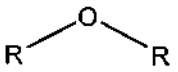
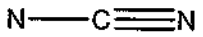
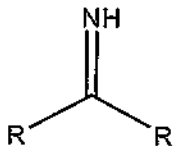
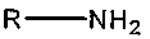
Functional Group	Functional Group Structure	Interacting Group					
Alcohol		alcohol	ketone	thiol	amide	amine	analine
Thioether		aromatic-N	amide	amine	aromatic_s	Sp2 amine	sulfoxide
Ether		aromatic-N	amide	amine	aromatic_s	Sp2 amine	sulfoxide
Cyanamide		cyano	amine	potassium	aromatic-N	bromine	sodium
Thiocyanate		aromatic-S	ester	ether			
sP2 amine		thioether	ether	metals	MoOCl4	BF4	bromine
Amine primary		alcohol	ketone	thiol	amide	amine	analine

TABLE III

Functional Group									
Alcohol	phenol	phosphate	sulfate	sulfone	nitrate	pyridine	aromatic	carboxilic acid	metals
Thioether	chlorate	chlorine	alkyne	cyano	ester	amine	nitro	nitrate	bromine
Ether	chlorate	chlorine	alkyne	cyano	ester	amine	nitro	nitrate	bromine
Cyanamide	imidazole	ether	n-heterocyclic	alcohol	cesium	Ag			
Thiocyanate									
sP2 amine	chlorine		Sp2 amine	sulfate	Osmium				
Amine primary	phenol	phosphate	sulfate	sulfone	nitrate	pyridine	aromatic	carboxilic acid	metals

TABLE III

Functional Group									
Alcohol	aldehyde	ester	ether	cyano		furan	bromine	chlorine	s-heterocyclic
Thioether	aldehyde	ketone	peroxide	epoxide	Ag	Se	heterocyclic-S	iodine	ester
Ether	aldehyde	ketone	peroxide	epoxide	Ag	Se	heterocyclic-S	iodine	ester
Cyanamide									
Thiocyanate									
sP2 amine									
Amine primary	aldehyde	ester	ether	cyano		furan	bromine	chlorine	s-heterocyclic

TABLE III

Functional Group														
Alcohol	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		fluorine	carbamate	imidazole	BF4	alkane			
Thioether	ether	carboxylic acid	sulfate	sulfone	alkane	alcohol		phospphate						
Ether	ether	carboxylic acid	sulfate	sulfone	alkane	alcohol		phospphate	cyanamide					
Cyanamide														
Thiocyanate														
sP2 amine														
Amine primary	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		fluorine	carbamate	imidazole	BF4	alkane			

TABLE III

Functional Group								
	aromatic	N-SO2	thiourea	iodine	epoxide			
Alcohol								
Thioether								
Ether								
Cyanamide								
Thiocyanate								
sP2 amine								
Amine primary	aromatic	N-SO2	thiourea	iodine				

TABLE III

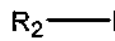
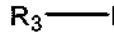
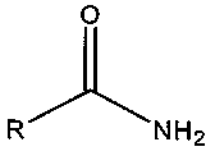
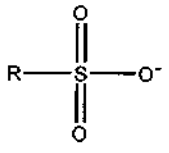
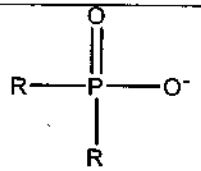
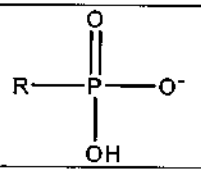
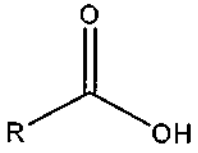
Functional Group	Functional Group Structure	Interacting Group					
Amine secondary		alcohol	ketone	thiol	amide	amine	analine
Amine tertiary		alcohol	ketone	thiol	amide	amine	analine
Amide		alcohol	ketone	thiol	amide	amine	analine
Sulfonic acid		pyridine	ketone	aldehyde	ether	ester	amide
Phosphinic acid		alkane	potassium	lithium	n-heterocyclic	oxime	amide
Phosphonic acid		alkane	potassium	lithium	n-heterocyclic	oxime	amide
Carboxylic acid		alcohol	ketone	thiol	amide	amine	analine

TABLE III

Functional Group										
Amine secondary	phenol	phosphate	sulfate	sulfone	nitrate	pyridine	aromatic	carboxilic acid	metals	
Amine tertiary	phenol	phosphate	sulfate	sulfone	nitrate	pyridine	aromatic	carboxilic acid	metals	
Amide	phenol	phosphate	sulfate	sulfone	nitrate	pyridine	aromatic	carboxilic acid	metals	
Sulfonic acid	carboxilic acid	amine	metals	thioether		sulfate	alcohol			
Phosphinic acid	phenol	aromatic	amine	alcohol		metals				
Phosphonic acid	phenol	aromatic	amine	alcohol		metals	carboxylic acid	Sp2 amine	analine	
Carboxylic acid	phenol	phosphate	sulfate	sulfone	nitrate	pyridine	aromatic	carboxilic acid	metals	

TABLE III

Functional Group										
Amine secondary	aldehyde	ester	ether	cyano		furan	bromine	chlorine	s-heterocyclic	
Amine tertiary	aldehyde	ester	ether	cyano		furan	bromine	chlorine	s-heterocyclic	
Amide	aldehyde	ester	ether	cyano		furan	bromine	chlorine	s-heterocyclic	
Sulfonic acid										
Phosphinic acid										
Phosphonic acid	ether	phosphonic acid	aromatic-N	ketone	aldehyde	imidazole				
Carboxylic acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine	s-heterocyclic	

TABLE III

Functional Group														
Amine secondary	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		fluorine	carbamate	imidazole	BF4	alkane			
Amine tertiary	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		fluorine	carbamate	imidazole	BF4	alkane			
Amide	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		fluorine	carbamate	imidazole	BF4	alkane			
Sulfonic acid														
Phosphinic acid														
Phosphonic acid														
Carboxylic acid	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		fluorine	carbamate	imidazole	BF4	alkane			

TABLE III

Functional Group							
Amine secondary	aromatic	N-SO2	thiourea	iodine			
Amine tertiary	aromatic	N-SO2	thiourea	iodine			
Amide	aromatic	N-SO2	thiourea	iodine	epoxide	peroxide	
Sulfonic acid							
Phosphinic acid							
Phosphonic acid							
Carboxylic acid	aromatic	N-SO2	thiourea	iodine			

TABLE III

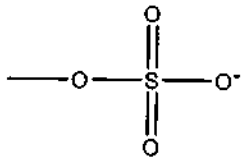
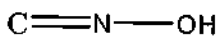
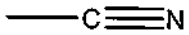
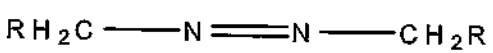
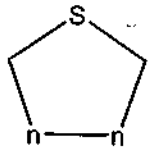
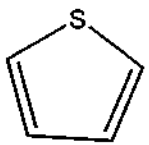
Functional Group	Functional Group Structure	Interacting Group					
Sulfate ester		pyridine	ketone	aldehyde	ether	ester	amide
Oxime		alcohol	alkane	amine	amide	ether	ester
Nitrile		metal	ketone	phenol	alcohol		cyano
Diazo		Oxime					
Nitro	NO_2	pyridine	ketone	aldehyde	ether	ester	amide
S-heterocyclic ring		alcohol	thioketone	thioether	s-heterocyclic	ketone	aromatic
Thiophene		chlorine	fluorine	amide	ketone	NO	SO

TABLE III

Functional Group													
Sulfate ester	carboxilic acid	amine	metals	thioether	sulfate	alcohol							
Oxime	pyridine	n-aromatic	chlorate	chlorine	Sp2-N	diazo	thioketone	cyano	n-oxide				
Nitrile	amine	analine	bromine	amide	alkane	carboxylic acid	chlorine	n-heterocyclic	aromatic				
Diazo													
Nitro	carboxilic acid	amine	metals	thioether	sulfate	alcohol							
S-heterocyclic ring	alkene	amine	chlorine	BF4	sulfate	ester	NO	ether	amide				
Thiophene	CO												

TABLE III

Functional Group											
Sulfate ester											
Oxime	ketone	aldehyde	carboxylic acid	bromine	aromatic	pyridine	BF4				
Nitrile	potassium	aldehyde	thioether	pyridine	n-aromatic	bromine	ether	s-aromatic	thiophene		
Diazo											
Nitro											
S-heterocyclic ring	iodine	carboxylic acid	sodium	cyano	chloride	furan					
Thiophene											

TABLE III

Functional Group										
Sulfate ester										
Oxime										
Nitrile										
Diazo										
Nitro										
S-heterocyclic ring										
Thiophene										

TABLE III

Functional Group								
Sulfate ester								
Oxime								
Nitrile								
Diazo								
Nitro								
S-heterocyclic ring								
Thiophene								

TABLE III

Functional Group	Functional Group Structure	Interacting Group					
		alcohol	thioketone	thioether	s-heterocyclic	ketone	aromatic
N-heterocyclic ring							
O-heterocyclic ring		alcohol	thioketone	thioether	s-heterocyclic	ketone	aromatic
Pyrrole		chlorine	fluorine	amide	ketone	NO	SO
Furan		s-heterocyclic					

TABLE III

Functional Group										
N-heterocyclic ring	alkene	amine	chlorine	BF4	sulfate	ester	NO	ether	amide	
O-heterocyclic ring	alkene	amine	chlorine	BF4	sulfate	ester	NO	ether	amide	
Pyrrole	CO	imidazole	pyridine	n-aromatic	aldehyde	carboxylic acid	sulfate	chlorine	bromine	
Furan										

TABLE III

Functional Group										
N-heterocyclic ring	iodine	carboxylic acid	sodium	cyano	chloride	aldehyde				
O-heterocyclic ring	iodine	carboxylic acid	sodium	cyano	chloride	aldehyde				
Pyrrole	oxime	alcohol	phenol	ester	ether					
Furan										

TABLE III

Functional Group				
N-heterocyclic ring				
O-heterocyclic ring				
Pyrrole				
Furan				

TABLE III

Functional Group						
N-heterocyclic ring						
O-heterocyclic ring						
Pyrrole						
Furan						

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
(-)-amlodipine	3,5-Pyridinedicarboxylic acid, 2-((2-aminoethoxy)methyl)-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-, 3-ethyl-5-methyl ester, (S)- [CAS]	103129-82-4	WO	9310779	Antihypertensive, other	Hypertension, general
(-)-halofenate	(-)-Benzeneacetic acid, 4-chloro-Alpha-[3-(trifluoromethyl)-phenoxy]-, 2-(acetylamino)ethyl ester		US	6262118	Antidiabetic	Diabetes, Type II
(R)-salbutamol	1,3-Benzenedimethanol, Alpha1-(((1,1-dimithylethyl)amino)methyl)-4-hydroxy- [CAS]				Formulation, modified-release, <=24hr	Asthma
(R)-salbutamol	1,3-Benzenedimethanol, Alpha1-(((1,1-dimethylethyl)amino)methyl)-4-hydroxy- [CAS]	34391-04-3	US	5547994	Antiasthma	Asthma
(R,R)-formoterol	Formamide, N-(2-hydroxy-5-(1-hydroxy-2-((2-(4-methoxyphenyl)-1-methylethyl)amino)ethyl)phenyl)- (R-(R*,R*))- [CAS]	67346-49-0	US	5795564	Antiasthma	Asthma
(S)-doxazosin	(S)-1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(1,4-benzodioxan-2-yl carbonyl)piperazine	70918-18-2	WO	9409785	Prostate disorders	Benign prostatic hyperplasia
(S)-fluoxetine	Benzenepropanamide, N-methyl-Gamma-(4-(trifluoromethyl)phenoxy)- (S)				Antimigraine	Migraine
(S)-oxybutynin	Benzeneacetic acid, Alpha-cyclohexyl-Alpha-hydroxy-, 4-(diethylamino)-2-butynyl ester, (S)- [CAS]	119618-22-3			Urological	Incontinence
1,2-Naphthoquinone		524-42-5				
17α-Hydroxyprogesterone		68-96-2				
17-Methyltestosterone		58-18-4				
195mPt-cisplatin	Platinum-195m, diamminedichloro, (SP-4-2)-		US	6074626	Anticancer, alkylating	Cancer, liver
1α-Hydroxycholecalciferol		41294-56-8				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
1-Naphthyl Salicylate		550-97-0				
1-Naphthylamine-4-sulfonic Acid		84-86-6				
1-Theobromineacetic Acid		5614-56-2				
2,4,6-Tribromo-m-cresol		4619-74-3				
2,6-Diamino-2'-butyloxy-3,5'-azopyridine		617-19-6				
21-Acetoxypregnenolone		566-78-9				
2-Amino-4-picoline		695-34-1				
2-Aminothiazole		96-50-4				
2-ethoxybenzoic acid	2-Ethoxybenzoic acid		DE	5134001	Analgesic, NSAID	Pain, general
2-Naphthol		135-19-3				
2-Naphthyl Benzoate		93-44-7				
2-Naphthyl Lactate		93-43-6				
2-Naphthyl Salicylate		613-78-5				
2-p-Sulfanilylanilinoethanol		80-02-4				
2-Thiouracil		141-90-2				
3',3'',5',5''-Tetrabromophenolphthalein		76-62-0				
3-Amino-4-hydroxybutyric Acid		589-44-6				
3-Bromo-d-camphor		76-29-9				
3-Hydroxycamphor		10373-81-6				
3-O-Lauroylpyridoxol Diacetate		1562-13-6				
3-Pentadecylcatechol		492-89-7				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
3-Quinuclidinol		1619-34-7				
4,4'-Oxydi-2-butanol		821-33-0				
4,4'-Sulfinyldianiline		119-59-5				
4-Amino-3-hydroxybutyric Acid		352-21-6				
4-Amino-3-phenylbutyric Acid		1078-21-3				
4-aminosalicylic acid	Benzoic acid, 4-amino-2-hydroxy- [CAS]	65-49-6			GI inflammatory/bowel disorders	Inflammatory bowel disease
4-Chloro-m-cresol		59-50-7				
4-Hexylresorcinol		136-77-6				
4-Salicyloylmorpholine		3202-84-4				
5'-Nitro-2'-propoxyacetanilide		553-20-8				
5-aminolevulinic acid,	Pentanoic acid, 5-amino-4-oxo- [CAS]	106-60-5			Dermatological	Keratosis
5-azacitidine	1,3,5-Triazin-2(1H)-one, 4-amino-1-ß-D-ribofuranosyl- [CAS]	320-67-2			Anticancer, antimetabolite	Myelodysplastic syndrome
5-Bromosalicylhydroxamic Acid		5798-94-7				
5F-DF-203	2-(4-Amino-3-methylphenyl)-6-hydroxybenzothiazole				Anticancer, other	Cancer, breast
5-FU	2,4(1H,3H)-Pyrimidinedione, 5-fluoro [CAS]	51-21-8			Formulation, parenteral, targeted	Cancer, general
5-HT3 antagonists			US	6037360	Male sexual dysfunction	Premature ejaculation
6-Azauridine		54-25-1				
6-Mercaptopurine		50-44-2				
8-Hydroxyquinoline		148-24-3				
9-Aminocamptothecin		91421-43-1				
A-151892	N-[2-(2,2,2-Trifluoro-1-hydroxy-1-trifluoromethyl-ethyl)-naphthalen-1-yl] amide				Urological	Overactive bladder

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
α1-Antitrypsin		9041-92-3				
A-5021	6H-Purin-6-one, 2-amino-9-(((1S,2R)-1,2-bis(hydroxymethyl)cyclopropyl)methyl)-1,9-dihydro- [CAS]	145512-85-2			Antiviral, other	Infection, varicella zoster virus
abacavir	2-Cyclopentene-1-methanol, 4-(2-amino-6-(cyclopropylamino)-9H-purin-9-yl)-, (1S-cis)- [CAS]	136470-78-5 188062-50-2	EP	434450	Antiviral, anti-HIV	Infection, HIV/AIDS
abaperidone	7-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]propoxy]-3-(hydroxymethyl)chromen-4-one	183849-43-6	WO	9632389	Neuroleptic	Schizophrenia
abarelix	D-Alaninamide, N-acetyl-3-(2-naphthalenyl)-D-alanyl-4-chloro-D-phenylalanyl-3-(3-pyridinyl)-D-alanyl-L-seryl-N-methyl-L-tyrosyl-D-asparaginyl-L-leucyl-N6-(1-methylethyl)-L-lysyl-L-prolyl- [CAS]	183552-38-7	US	5843902	Anticancer, hormonal	Cancer, prostate
Abciximab		143653-53-6				
Abecarnil		111841-85-1				
abetimus		169147-32-4	US	5552391	Immunosuppressant	Lupus erythematosus, systemic
abiraterone	Androsta-5,16-dien-3-ol, 17-(3-pyridinyl)-, acetate (ester), (3ß)- [CAS]	154229-18-2	GB	2265624	Anticancer, hormonal	Cancer, prostate
α-Bisabolol		515-69-5				
ABLC	Amphotericin B [CAS]	1397-89-3 30652-87-0			Formulation, conjugate, carbohydrate	Infection, Candida, general
ABT-751	Benzenesulfonamide, N-[2-[(4-hydroxyphenyl)amino]-3-pyridinyl]-4-methoxy- [CAS]	141430-65-1	EP	472053	Anticancer, other	Cancer, general
AC-5216	N-benzyl-N-ethyl-2-(7,8-dihydro-7-methyl-8-oxo-2-phenyl-9H-purin-9-yl)acetamide				Anxiolytic	Anxiety, general
Acadesine		2627-69-2				
acamprosate	1-Propanesulfonic acid, 3-(acetylamino)- [CAS]	77337-76-9	GB	2051789	Dependence treatment	Addiction, alcohol
Acamprosate		77337-73-6				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Acarbose		56180-94-0				
acebrophylline	7H-Purine-7-acetic acid, 1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo-,compd. with trans-4-[[(2-amino-3,5-dibromophenyl)methyl]amino]cyclohexanol (1:1) [CAS]	96989-76-3	DE	3425007	Antiasthma	Asthma
acebutolol	Butanamide, N-[3-acetyl-4-[2-hydroxy-3-[(1-methylethyl)amino]propoxy]phenyl]-, (+/-)- [CAS]	34381-68-5 37517-30-9	US	3726919	Antihypertensive, adrenergic	
Acecainide		32795-44-1				
Acecarbromal		77-66-7				
aceclofenac	Benzeneacetic acid, 2-[(2,6-dichlorophenyl)amino]-, carboxymethyl ester [CAS]	89796-99-6	EP	119932	Anti-inflammatory	Pain, musculoskeletal
Acedapsone		77-46-3				
Acediasulfone		80-03-5				
Acefylline		652-37-9				
Aceglutamide		2490-97-3				
aceglutamide	Aluminum, pentakis(N2-acetyl-L-glutaminato)tetrahydroxytri- [CAS]	12607-92-0	DE	2127176	Antiulcer	Ulcer, GI, general
acemetacin	1H-Indole-3-acetic acid, 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-, carboxymethyl ester [CAS]	53164-05-9	US	3910952	Anti-inflammatory	
Acenocoumarol		152-72-7				
Acetal		105-57-7				
Acetamidoeugenol		305-13-5				
Acetaminophen		103-90-2				
Acetaminosalol		118-57-0				
Acetanilide		103-84-4				
Acetarsone		97-44-9				
Acetazolamide		59-66-5				
Acetiamine		299-89-8				
Acetohexamide		968-81-0				
Acetohydroxamic Acid		546-88-3				
Acetophenazine		2751-68-0				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Acetophenone		98-86-2				
Acetosulfone		128-12-1				
acetoxolone	Olean-12-en-30-oic acid, 3ß-hydroxy-11-oxo-acetate, aluminium salt [CAS]	29728-34-5 6277-14-1	US	3764618	Antiulcer	
Acetrizoate		129-63-5				
Acetyl Sulfamethoxypyrazine		3590-05-4				
Acetylcarnitine		14992-62-2				
Acetylcholine		66-23-9				
Acetylcholine		60-31-1				
Acetylcysteine		616-91-1				
Acetylleucine Monoethanolamine		149-90-6				
Acetylpheneturide		13402-08-9				
acetylsalicylic acid	Benzoic acid, 2-(acetyloxy)- [CAS]	50-78-2 530 75-6			Formulation, optimized, microencapsulate	Pain, general
α-Chloralose		15879-93-3				
aciclovir	6H-Purin-6-one, 2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)methyl]- [CAS]	59277-89-3			Formulation, dermal, topical	Infection, herpes simplex virus
Acifran		72420-38-3				
acipimox	Pyrazinecarboxylic acid, 5-methyl-, 4-oxide [CAS]	51037-30-0	GB	1361967	Hypolipaemic/Antiatherosclerosis	Hyperlipidaemia, general
acitazanolast	Acetic acid, oxo[[3-(1H-tetrazol-5-yl)phenyl]amino]- [CAS]	114607-46-4	EP	256507	Ophthalmological	Conjunctivitis
acitretin	2,4,6,8-Nonatetraenoic acid, 9-(4-methoxy-2,3,6-trimethylphenyl)-3,7-dimethyl-, (all-E)- [CAS]	55079-83-9	GB	1468401	Antipsoriasis	Psoriasis
actarubicin		57576-44-0 75443-99-1	US	3988315	Anticancer, antibiotic	
Aclatonium Napadisilate		55077-30-0				
Aconitine		302-27-2				
Acranil®		1684-42-0				
Acriflavine		8048-52-0				
Acrisorcin		7527-91-5				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
acrivastine	2-Propenoic acid, 3-[6-[1-(4-methylphenyl)-3-(1-pyrrolidinyl)-1-propenyl]-2-pyridinyl]-, (E,E)- [CAS]	87848-99-5	EP	85959	Antipruritic/inflamm, allergic	Rhinitis, allergic, general
acrivastine + pseudoephedrine	Benzenemethanol, Alpha-[1-(methylamino)ethyl]-, hydrochloride, [S-(R*,R*)]-, mixtwith 2-Propenoic acid, 3-[6-[1-(4-methylphenyl)-3-(1-pyrrolidinyl)-1-propenyl]-2-pyridinyl]-, (E,E)-				Antiallergic, non-asthma	Rhinitis, allergic, seasonal
actagardine derivative	3,3-dimethyl-1-propylamide HCl monocarboxamide actagardine				Peptide antibiotic	Infection, general
Actarit		18699-02-0				
ACTH		9002-60-2				
Acyclovir		59277-89-3				
adapalene	2-Naphthalenecarboxylic acid, 6-(4-methoxy-3-tricyclo[3.3.1.13,7]dec-1-yl)phenyl)- [CAS]	106685-40-9	EP	199636	Antiacne	Acne
ADCON-L	GL 402 [CAS]	137802-74-5			Formulation, other	Fibrosis, epidural
Adefovir		106941-25-7				
adefovir dipivoxil	Propanoic acid, 2,2-dimethyl-, (((2-(-6-amino-9H-purin-9-yl)ethoxy)methyl)phosphinylidene)bis(oxy methylene)ester- [CAS]	142340-99-6	EP	205826	Antiviral, other	Infection, hepatitis-B virus
Adenoscan	6-Amino-9-ß-D-ribofuranosyl-9H-purine [CAS]	58-61-7			Imaging agent	Diagnosis, coronary
Adenosine Triphosphate		56-65-5				
ADEPT		156079-88-8			Immunoconjugate, other	Cancer, colorectal
Adinazolam		37115-32-5				
Adiphenine		64-95-9				
ADL-10-0101			WO	9732857	Analgesic, other	Pain, general
Adrafinil		63547-13-7				
Adrenalone		99-45-6				
Adrenochrome		54-06-8				
adrogolide	Benzo(f)thieno(2,3-c)quinoline-9,10-diol, 4,5,5a,6,7,11b-hexahydro-2-propyl-, diacetate (ester), hydrochloride (5aR-trans)- [CAS]	166591-11-3 171752-56-0	US	5597832	Dependence treatment	Addiction, cocaine

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
AEOL-10150			US	6103714	Neuroprotective	Unspecified
AET		56-10-0				
α-Ethylbenzyl Alcohol		93-54-9				
AF-2259	Benzeneacetic acid, Alpha-methyl-4-(2-methylpropyl)-, 2-methoxyphenyl ester [CAS]	66332-77-2	DE	2726435	Anti-inflammatory	Inflammation, general
Afloqualone		56287-74-2				
AG-041R	1H-Indole-3-acetamide, 1-(2,2-diethoxyethyl)-2,3-dihydro-N-(4-methylphenyl)-3-((((4-methylphenyl)amino)carbonyl)amino)-2-oxo-, (3R)- [CAS]	199800-49-2	WO	9419322	Alimentary/Metabolic, other	Unspecified
AG-2037	N-(5-[2-(2-amino-4(3H)-oxo-5,6,7,8-tetrahydropyrido[2,3-d]pyrimidin-6-yl)ethy]-4-methylthieno-2-yl)glutamic acid				Anticancer, antimetabolite	Cancer, general
α-Glucose-1-phosphate		59-56-3				
AGN-194310	Benzoic acid, 4-((4-(4-ethylphenyl)-2,2-dimethyl-2H-1-benzothiopyran-6-yl)ethynyl)- [CAS]	229961-45-9	WO	9709297	Dermatological	Psoriasis
agomelatine	Acetamide, N-(2-(7-methoxy-1-naphthalenyl)ethyl)- [CAS]	138112-76-2	EP	447285	Antidepressant	Sleep disorder, general
Ahistan		518-61-6				
AHL-157			US	5411972	Hypolipaemic/Antiatherosclerosis	Atherosclerosis
AIT-034	9H-Purine-9-propanamide, 1,6-dihydro-6-oxo-N-(3-(2-oxo-1-pyrrolidinyl)propyl)- [CAS]	138117-48-3	US	5447939	Cognition enhancer	Dementia, senile, general
AIT-202	N-[2-(5-Hydroxy-1H-indol-3-yl)ethyl]-3-(6-oxo-6,9-dihydro-1H-purin-9-yl)propionamide		WO	9957120	Antidepressant	Unspecified

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
AJ-9677	Acetic acid, ((3-((2R)-2-(((2R)-2-(3-chlorophenyl)-2-hydroxyethyl)amino)propyl)-1H-indol-7-yl)oxy)- [CAS]	244081-42-3			Antidiabetic	Diabetes, Type II
AJG-049			WO	9733885	Gastroprokinetic	Motility dysfunction, GI, general
Ajmaline		12/07/4360				
Alacepril		74258-86-9				
albaconazole	4(3H)-Quinazolinone, 7-chloro-3-[(1R,2R)-2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]- [CAS]	187949-02-6	WO	9705131	Antifungal	Infection, Candida, general
albendazole	Carbamic acid, [5-(propylthio)-1H-benzimidazol-2-yl]-, methyl ester [CAS]	54029-12-8 54965-21-8	GB	1464326	Anthelmintic	Infection, helminth, general
Albuterol		18559-94-9				
Albutoin		830-89-7				
alclofenac	Benzeneacetic acid, 3-chloro-4-(2-propenyloxy)- [CAS]	22131-79-9	GB	1174535	Anti-inflammatory	
alclometasone	Pregna-1,4-diene-3,20-dione, 7-chloro-11-hydroxy-16-methyl-17,21-bis(1-oxopropoxy)-, (7Alpha,11ß,16Alpha)- [CAS]	66734-13-2 67452-97-5	US	4124707	Antipruritic/inflamm, allergic	Inflammation, dermal
Alcuronium		23214-96-2				
Aldioxa		5579-81-7				
Aldol		107-89-1				
Aldosterone		52-39-1				
alendronate	Phosphonic acid, (4-amino-1-hydroxybutylidene)bis-[CAS]	121268-17-5 129318-43-0	GB	2118042	Osteoporosis treatment	Osteoporosis
Alendronic Acid		66376-36-1				
Alexidine		22573-93-9				
alfacalcidol	9,10-Secocholesta-5,7,10(19)-triene-1,3-diol, (1Alpha,3ß,5Z,7E)- [CAS]	41294-56-8			Osteoporosis treatment	Osteodystrophy
Alfadolone		23930-37-2				
Alfaxalone		23930-19-0				
Alfentanil		71195-58-9				
alfimeprase		259074-76-5			Fibrinolytic	Peripheral vascular disease

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
alfuzosin	2-Furancarboxamide, N-[3-[(4-amino-6,7-dimethoxy-2-quinazolinyl)methylamino]propyl]tetrahydro- [CAS]	81403-68-1 81403-80-7	GB	2013679	Prostate disorders	Benign prostatic hyperplasia
alfuzosin	2-Furancarboxamide, N-[3-[(4-amino-6,7-dimethoxy-2-quinazolinyl)methylamino]propyl]tetrahydro- [CAS]	81403-68-1 81403-80-7			Formulation, modified-release, other	Benign prostatic hyperplasia
Algestone		595-77-7				
Algestone Acetophenide		24356-94-3				
Algin		9005-38-3				
Alglucerase		143003-46-7				
Alibendol		26750-81-2				
aliskiren	(2S,4S,5S,7S)-5-Amino-N-(2-carbamoyl-2-methylpropyl)-4-hydroxy-2-isopropyl-7-[4-methoxy-3-(3-methoxypropoxy)benzyl]-8-methylnonanamide	173334-57-1			Antihypertensive, renin system	Hypertension, general
alitretinoin	9-cis retinoic acid	03/08/5300			Antipruritic/inflamm, allergic	Eczema, general
alizapride	1H-Benzotriazole-5-carboxamide, 6-methoxy-N-[[1-(2-propenyl)-2-pyrrolidinyl]methyl]- [CAS]	59338-93-1	GB	1475234	Antiemetic	Nausea and vomiting, general
Alkannin		517-88-4				
Alkofanone		7527-94-8				
Allantoin		97-59-6				
Allobarbital		52-43-7				
Allopurinol		315-30-0				
Allyl Isothiocyanate		57-06-7				
Allylestrenol		432-60-0				
almagate	Magnesium, [carbonato(2-)]heptahydroxy(aluminum)tri-, dihydrate [CAS]	66827-12-1 72526-11-5	US	4447417	Antacid/Antiflatulent	
alminoprofen	Benzeneacetic acid, Alpha-methyl-4-[(2-methyl-2-propenyl)amino]- [CAS]	39718-89-3	US	3957850	Analgesic, NSAID	

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
almitrine	1,3,5-Triazine-2,4-diamine, 6-[4-[bis(4-fluorophenyl)methyl]-1-piperazinyl]-N,N'-di-2-propenyl-, dimethanesulfonate [CAS]	27469-53-0 29608-49-9	GB	1256513	Respiratory	Bronchitis, chronic
almotriptan	Pyrrolidine, 1-(((3-(2-(dimethylamino)ethyl)-1H-indol-5-yl)methyl)sulfonyl)- [CAS]	154323-57-6	WO	9402460	Antimigraine	Migraine
Aloe-Emodin		481-72-1				
Aloin		5133-19-7				
alosetron	2,3,4,5-Tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one [CAS]	122852-42-0 122852-69-1 132414-02-9	EP	306323	GI inflammatory/bowel disorders	Irritable bowel syndrome
alovudine	Thymidine, 3'-deoxy-3'-fluoro- [CAS]	25526-93-6	EP	470355	Antiviral, anti-HIV	Infection, HIV/AIDS
Aloxiprin		9014-67-9				
Alpha-1 protease inhibitor			US	5780014	Formulation, inhalable, topical	Emphysema, alpha-1 antitrypsin deficiency
Alpha-dihydroergocryptine	Ergocryptine, 9,10-dihydro-methanesulfonate (salt)- [CAS]	29261-93-6			Formulation, other	Parkinson's disease
Alphaprodine		77-20-3				
Alpidem		82626-01-5				
Alpiropride		81982-32-3				
alprazolam	4H-[1,2,4]Triazolo[4,3-a][1,4]benzodiazepine, 8-chloro-1-methyl-6-phenyl-[CAS]	28981-97-7	US	3987052	Anxiolytic	Anxiety, general
Alprenolol		13655-52-2				
alsactide	Alpha1-17-Corticotropin, 1-ß-alanine-17-[N-(4-aminobutyl)-L-lysinamide]- [CAS]	34765-96-3	US	3749704	ACTH	Arthritis, rheumatoid
ALT-711	Thiazolium, 4,5-dimethyl-3-(2-oxo-2-phenylethyl)-, bromide [CAS]	181069-80-7	WO	9622095	Symptomatic antidiabetic	Hypertension, general
Althiazide		5588-16-9				
altinicline	Pyridine, 3-ethynyl-5-((2S)-1-methyl-2-pyrrolidinyl)- [CAS]	179120-92-4	US	5594011	Antiparkinsonian	Parkinson's disease
altretamine	1,3,5-Triazine-2,4,6-triamine, N,N,N',N',N'',N''-hexamethyl- [CAS]	645-05-6	US	3424752	Anticancer, alkylating	Cancer, ovarian
aluminium chloride hexahydrate	Aluminium chloride, hexahydrate	7446-70-0 7784-13-6			Dermatological	Hyperhidrosis

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Aluminon		569-58-4				
Aluminum Acetate Solution		8006-13-1				
Aluminum Chlorate		15477-33-5				
Aluminum Hydroxychloride		1327-41-9				
Aluminum Potassium Sulfate		10043-67-1				
Aluminum Sodium Sulfate		10102-71-3				
alusulf	Aluminum hydroxide sulfate (Al7(OH)17(SO4)2), dodecahydrate [CAS]	61115-28-4	DE	2510663	Urological	Hyperphosphataemia
Alverine		150-59-4				
alvimopan	Glycine, N-[(2S)-2-[[(3R,4R)-4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]methyl]-1-oxo-3-phenylpropyl]- [CAS]	156053-89-3	EP	657428	GI inflammatory/bowel disorders	Ileus
alvocidib	4H-1-Benzopyran-4-one, 2-(2-chlorophenyl)-5,7-dihydroxy-8-(3-hydroxy-1-methyl-4-piperidinyl)-, cis-(-)- [CAS]	131740-09-5 146426-40-6			Anticancer, other	Cancer, renal
ALX-0646			WO	9506638	Antimigraine	Migraine
AM-24	2,4,6-Triiodophenol	609-23-4			GI inflammatory/bowel disorders	Crohn's disease .
AM-36	1-Piperazineethanol, 4-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methyl]-Alpha-(4-chlorophenyl)- [CAS]	199467-52-2			Neuroprotective	Unspecified
AM-477	2-Methoxyoestradiol				Antiasthma	Asthma
Amantadine		768-94-5				
amantanium	1-Decanaminium, N,N-dimethyl-N-[2-[(tricyclo[3.3.1.13,7]dec-1-ylcarbonyl)oxy]ethyl]-, bromide [CAS]	58158-77-3	US	4288609	Antifungal	Infection, general
Ambazone		539-21-9				
Ambenonium		115-79-7				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
ambrisentan	(+)-(2S)-2-[(4,6-dimethylpyrimidin-2-yl)oxy]-3-methoxy-3,3-diphenylpropanoic acid	177036-94-1			Vasodilator, peripheral	Heart failure
ambroxol	Cyclohexanol, 4-[[(2-amino-3,5-dibromophenyl)methyl]amino]-, trans- [CAS]	18683-91-5 23828-92-4	GB	1178034	COPD treatment	Bronchitis, chronic
Ambucaine		119-29-9				
Ambuphylline		5634-34-4				
Ambuside		3754-19-6				
Ambutonium Bromide		115-51-5				
amcinonide	Pregna-1,4-diene-3,20-dione, 21-(acetyloxy)-16,17-[cyclopentylidenebis(oxy)]-9-fluoro-11-hydroxy-, (11ß,16Alpha)- [CAS]	51022-69-6	DE	2437847	Antipsoriasis	
AMD-3100	1,4,8,11-Tetraazacyclotetradecane, 1,11-(1,4-phenylenebis(methylene))bis-, octahydrochloride [CAS]	155148-31-5	US	5612478	Haematological	Chemotherapy-induced injury, bone marrow, leucopenia
Amdinocillin		32887-01-7				
Amdinocillin Pivoxil		32886-97-8				
amdoxovir	1,3-Dioxolane-2-methanol, 4-(2,6-diamino-9H-purin-9-yl)- (2R-cis)- [CAS]	145514-04-1	EP	656778	Antiviral, anti-HIV	Infection, HIV/AIDS
amelubant	Carbamic acid, ((4-((3-((4-(1-(4-hydroxyphenyl)-1-methylethyl)phenoxy)methyl)phenyl)methoxy)phenyl)iminomethyl)- ethyl ester [CAS]	346735-24-8	DE	10000907	COPD treatment	Chronic obstructive pulmonary disease
Americaine	Benzenemethanaminium, N,N-dimethyl-N-[2-[2-[4-(1,1,3,3-tetramethylbutyl)phenoxy]ethoxy]ethyl]-, chloride, mixt. with ethyl 4-aminobenzoate [CAS]	129128-13-8			Formulation, inhalable, other	Pain, general
Amezinium		30578-37-1				
Amfenac		51579-82-9				
Amidephrine		3354-67-4				
Amidinomycin		3572-60-9				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
amifostine	Ethanethiol, 2-[(3-aminopropyl)amino]-, dihydrogen phosphate (ester)- [CAS]	20537-88-6 63717-27-1	EP	131500	Radio/chemoprotective	Chemotherapy-induced injury, renal
amiglumide	Pentanoic acid, 5-(dipentylamino)-4-((2-naphthalenylcarbonyl)amino)-5-oxo- (R)- [CAS]	119363-62-1	WO	8805774	GI inflammatory/bowel disorders	Pancreatitis
amikacin		37517-28-5 39831-55-5			Formulation, optimized, microencapsulate	Infection, general
Amiloride		2609-46-3				
Aminacrine		90-45-9				
amineptine	Heptanoic acid, 7-[(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)amino]- [CAS]	30272-08-3 57574-09-1	US	3758528	Antidepressant	
Aminitrozole		140-40-9				
Amino Acid Preparations						
Aminocaproic Acid						
aminoglutethimide	2,6-Piperidinedione, 3-(4-aminophenyl)-3-ethyl- [CAS]	125-84-8	US	3944671	Anticancer, hormonal	Cancer, breast
Aminoguanidine		79-17-4				
Aminohippurate						
Aminometradine		642-44-4				
Aminopentamide		60-46-8				
aminophylline	1H-Purine-2,6-dione, 3,7-dihydro-1,3-dimethyl-, compd. with 1,2-ethanediamine (2:1) [CAS]	317-34-0			Formulation, modified-release, other	Asthma
Aminopromazine		58-37-7				
Aminopyrine		58-15-1				
Aminoquinuride		3811-56-1				
Aminorex		2207-50-3				
amiodarone	Methanone, (2-butyl-3-benzofuranyl)[4-[2-(diethylamino)ethoxy]-3,5-diiodophenyl]- [CAS]	1951-25-3 19774-82-4	US	3248401	Antiarrhythmic	Arrhythmia, general
Amiphenazole		490-55-1				
Amiprilose		56824-20-5				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
amisulpride	Benzamide, 4-amino-N-[(1-ethyl-2-pyrrolidinyl)methyl]-5-(ethylsulfonyl)-2-methoxy- [CAS]	71675-85-9	US	4401822	Neuroleptic	Schizophrenia
Amitriptyline		50-48-6				
amitriptyline+ketamine	1-Propanamine,3-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-N,N-dimethyl + cyclohexanone,2-(2-chlorophenyl)-2-(methylamino)				Formulation, fixed-dose combinations	Pain, neuropathic
Amitriptylinoxide		4317-14-0				
amlexanox	5H-[1]Benzopyrano[2,3-b]pyridine-3-carboxylic acid, 2-amino-7-(1-methylethyl)-5-oxo- [CAS]	68302-57-8	US	4299963	Antiasthma	Asthma
amlodipine	3,5-Pyridinedicarboxylic acid, 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-, 3-ethyl 5-methyl ester [CAS]	111470-99-6 88150-42-9 88150-47-4	EP	89167	Antianginal	Hypertension, general
Ammoniacum		03/07/9000				
Ammonium Benzoate		1863-63-4				
Ammonium Mandelate		530-31-4				
Ammonium Salicylate		528-94-9				
Ammonium Valerate		42739-38-8				
Amobarbital		57-43-2				
Amocarzine		36590-19-9				
Amodiaquin		86-42-0				
amorolfine	Morpholine, 4-[3-[4-(1,1-dimethylpropyl)phenyl]-2-methylpropyl]-2,6-dimethyl-, cis- [CAS]	78613-35-1 78613-38-4	EP	24334	Antifungal	Infection, fungal, general
Amoscanate		26328-53-0				
amosulalol	Benzenesulfonamide, 5-[1-hydroxy-2-[[2-(2-methoxyphenoxy)ethyl]amino]ethyl]-2-methyl-, (+/-)- [CAS]	70958-86-0 85320-68-9	EP	136103	Antihypertensive, adrenergic	Hypertension, general
Amotriphene		5585-64-8				
amoxapine	Dibenz[b,f][1,4]oxazepine, 2-chloro-11-(1-piperazinyl)- [CAS]	14028-44-5	GB	1192812	Antidepressant	Depression, general

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
amoxicillin	4-Thia-1-azobicyclo[3,2,0]heptane-2-carboxylic acid, 6-[[amino(4-hydroxyphenyl)acetyl]amino]-3,3-dimethyl-7-oxo-,[2S-[2Alpha,5Alpha,6ß(S*)]] [CAS]	26787-78-0 61336-70-7			Formulation, modified-release, other	Infection, general
amoxicillin+potassium clavulan		74469-00-4	GB	1508977	Formulation, fixed-dose combinations	Infection, respiratory tract, general
AMPAlex	Piperidine, 1-(6-quinoxalinylcarbonyl)- [CAS]	154235-83-3	US	5650409	Psychostimulant	Attention deficit disorder
Amphetamine		300-62-9				
Amphetaminil		17590-01-1				
amphotericin B	Amphotericin B compd. with (3ß)-cholest-5-en-3-yl hydrogen sulfate (1:1) [CAS]	120895-52-5 1397-89-3	US	4822777	Formulation, optimized, liposomes	Infection, general
ampicillin	4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 6-[(aminophenylacetyl)amino]-3,3-dimethyl-7-oxo-, [2S-[2Alpha,5Alpha,6ß(S*)]]	69-53-4 7177-48-2			Formulation, fixed-dose combinations	Infection, general
Ampiroxicam		99464-64-9				
Ampligen		38640-92-5				
amprenavir	Carbamic acid, (3-(((4-aminophenyl)sulfonyl)(2-methylpropyl)amino)-2-hydroxy-1-(phenylmethyl)propyl)-, tetrahydro-3-furanyl ester, (3S-(3R*(1R*,2S*)))- [CAS]	161814-49-9	US	5783701	Antiviral, anti-HIV	Infection, HIV/AIDS
amrinone	[3,4'-Bipyridin]-6(1H)-one, 5-amino- [CAS]	60719-84-8 75898-90-7	US	4004012	Cardiostimulant	
amrubicin	5,12-Naphthacenedione, 9-acetyl-9-amino-7-[(2-deoxy-ß-D-erythro-pentopyranosyl)oxy]-7,8,9,10-tetrahydro-6,11-dihydroxy-, hydrochloride, (7S-cis)- [CAS]	92395-36-3	EP	107486	Anticancer, antibiotic	Cancer, lung, non-small cell
amsacrine	Methanesulfonamide, N-[4-(9-acridinylamino)-3-methoxyphenyl]- [CAS]	51264-14-3			Anticancer, other	Cancer, leukaemia, acute lymphocytic

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
amtolmetin guacil	Glycine, N-[[1-methyl-5-(4-methylbenzoyl)-1H-pyrrol-2-yl]acetyl]-, 2-methoxyphenyl ester [CAS]	87344-06-7	GB	2115417	Analgesic, NSAID	Arthritis, rheumatoid
Amylocaine		532-59-2				
AN-152			WO	9719954	Anticancer, antibiotic	Cancer, prostate
anabolic steroids			WO	9848812	Cardiovascular	Heart failure
Anagestone		2740-52-5				
anagrelide	Imidazo[2,1-b]quinazolin-2(3H)-one, 6,7-dichloro-1,5-dihydro-, monohydrochloride [CAS]	58579-51-4 68475-42-3	GB	1418822	Haematological	Thrombocytosis
anastrozole	1,3-Benzenediacetonitrile, Alpha,Alpha,Alpha,Alpha'-tetramethyl-5-(1H-1,2,4-triazol-1-ylmethyl)- [CAS]	120511-73-1	EP	296749	Anticancer, hormonal	Cancer, breast
Anazolene		3861-73-2				
Ancitabine		31698-14-3				
Ancrod		9046-56-4				
andolast	N-4'-[5-Tetrazolyl]-phenyl-4-(5-tetrazolyl)-benzamide	132640-22-3	EP	460083	Antiasthma	Asthma
Androisoxazole		360-66-7				
Androstenediol		521-17-5				
anecortave	21-(Acetyloxy)-17-hydroxypregna-4,9(11)-diene-3,20-dione	7753-60-8			Ophthalmological	Macular degeneration
Anethole		4180-23-8; 104-46-1 (unspecified)				
Anethole Trithione		532-11-6				
Angiogenix			US	6417205	Cardiovascular	Cardiomyopathy, ischaemic
Angiotensin		1407-47-2				
anhydrovinblastine	Vincaleukoblastine, 3',4'-didehydro-4'-deoxy- [CAS]	38390-45-3	US	6011041	Anticancer, other	Cancer, general
anidulafungin	Echinocandin B, 1-((4R,5R)-4,5-dihydroxy-N2-((4''-(pentyloxy)(1,1':4',1''-terphenyl)-4-yl)carbonyl)-L-ornithine)- [CAS]	166663-25-8	US	6384013	Antifungal	Infection, Candida, general

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Anileridine		144-14-9				
Aniracetam		72432-10-1				
Anisindione		117-37-3				
Anisomycin		22862-76-6				
Anisotropine Methylbromide		80-50-2				
anistreplase	Anistreplase [CAS]	81669-57-0	EP	28489	Fibrinolytic	Infarction, myocardial
Antazoline		91-75-8				
Anthiolimine		305-97-5				
Anthralin		1143-38-0				
Anthramycin		4803-27-4				
Anthrarobin		577-33-3				
anthrax inhibitor			US	6436933	Anti-infective, other	Infection, anthrax
antiangiogenic dendrimers			US	6426067	Anticancer, other	Cancer, general
Anticort	L-Ascorbic acid, mixt with 2-(diethylamino)ethyl 4-aminobenzoate monohydrochloride, disodium hydrogen phosphate, potassium benzoate and zinc sulfate (1:1) [CAS]	186646-39-9	WO	9640038	Anabolic	Cachexia
antidepressants			US	5898036	Antidepressant	Depression, general
anti-invasins			US	6303302	Antifungal	Infection, fungal, general
Antimony Potassium Tartrate		28300-74-5				
Antimony Sodium Thioglycollate		539-54-8				
Antimony Thioglycollamide		6533-78-4				
Antiprogestin	19-Norpregna-4,9-dien-3-one,(acetylphenyl)-20,20,21,21,21-pentafluoro-17-hydroxy-(11ß,17Alpha) [CAS]	211254-73-8	DE	19706061	Anticancer, hormonal	Cancer, breast
Antipyrine		60-80-0				
Antipyrine Salicylate		520-07-0				
antithrombin III	Antithrombin, III [CAS]	9000-94-6 90170-80-2			Blood fraction	Antithrombin III deficiency

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
anxiolytics			US	5756538	Anxiolytic	Anxiety, general
AP-521	N-Piperonyl-2-amino-1,2,3,4-tetrahydrobenzo(b)thieno(2,3-c)pyridine-3-carbamide	151227-08-6	WO	9321189	Anxiolytic	Anxiety, general
AP-5280			US	5965118	Anticancer, alkylating	Cancer, general
Apalcillin		63469-19-2				
apaziquone	1H-Indole-4,7-dione, 5-(1-aziridinyl)-3-(hydroxymethyl)-2-(3-hydroxy-1-propenyl)-1-methyl-, (E)- [CAS]	114560-48-4	WO	8706227	Anticancer, alkylating	Cancer, breast
Apazone		13539-59-8				
α-Phenylbutyramide		90-26-6				
Apocodeine		641-36-1				
apomine	Phosphonic acid, (2-(3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl)ethylidene)bis- tetrakis(1-methylethyl) ester [CAS]	126411-13-0			Anticancer, other	Cancer, prostate
apomorphine	4H-Dibenzo[de,g]quinoline-10,11-diol, 5,6,6a,7-tetrahydro-6-methyl-, hydrochloride	314-19-2 58-00-4			Formulation, transmucosal, nasal	Impotence
apraclonidine	1,4-Benzenediamine, 2,6-dichloro-N1-(4,5-dihydro-1H-imidazol-2-yl)- [CAS]	66711-21-5 73218-79-8	US	4517199	Antiglaucoma	Glaucoma
aprepitant	3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- [CAS]	170729-80-3	US	5719147	Antiemetic	Chemotherapy-induced nausea and vomiting
aprindine	1,3-Propanediamine, N-(2,3-dihydro-1H-inden-2-yl)-N',N'-diethyl-N-phenyl-[CAS]	33237-74-0 37640-71-4	GB	1321424	Antiarrhythmic	
Aprobarbital		77-02-1				
Apronalide		528-92-7				
Aprotinin		9087-70-1				
Aptiganel		137159-92-3				
AQ4N	9,10-Anthracenedione, 1,4-bis((2-(dimethyloxidoamino)ethyl)amino)-5,8-dihydroxy-[CAS]	136470-65-0	US	5132327	Anticancer, other	Cancer, general
Aquavan			US	6204257	Anaesthetic, injectable	Anaesthesia

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
AR-116081			US	6107324	Neuroleptic	Unspecified
AR-A2	(R)-N-[5-methyl-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinobenzamide				Anxiolytic	Anxiety, general
Arachidonic Acid		506-32-1				
aranidipine	3,5-Pyridinedicarboxylic acid, 1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-, methyl 2-oxopropyl ester- [CAS]	86780-90-7	GB	2111978	Antihypertensive, other	Hypertension, general
arbekacin	D-Streptamine, O-3-amino-3-deoxy-Alpha-D-glucopyranosyl-(1-6)-O-[2,6-diamino-2,3,4,6-tetradeoxy-Alpha-D-erythro-hexopyranosyl-(1-4)]-N1-(4-amino-2-hydroxy-1-oxobutyl)-2-deoxy-, (S)- [CAS]	51025-85-5 75282-65-4	US	4001208	Aminoglycoside antibiotic	Infection, general
Arbidol	1H-Indole-3-carboxylic acid, 6-bromo-4-((dimethylamino)methyl)-5-hydroxy-1-methyl-2-((phenylthio)methyl)-, ethylester, monohydrochloride [CAS]	131707-23-8	WO	9008135	Immunostimulant, other	Infection, influenza virus
arbutamine	1,2-Benzenediol, 4-[1-hydroxy-2-[[4-(4-hydroxyphenyl)butyl]amino]ethyl]-, (R)- [CAS]	128470-16-6	WO	9220324	Diagnostic	Diagnosis, coronary
Arcitumomab		154361-48-5				
ardeparin	Heparin [CAS]	9005-49-6			Anticoagulant	Thrombosis, venous
arecoline	1,2,5,6-Tetrahydro-1-methyl-3-pyridine carboxylic acid methyl ester				Formulation, transdermal, patch	Alzheimer's disease
argatroban	2-Piperidinecarboxylic acid, 1-[5-[(aminoiminomethyl)amino]-1-oxo-2-[[(1,2,3,4-tetrahydro-3-methyl-8-quinolinyl)sulfonyl]amino]pentyl]-4-methyl- [CAS]	74863-84-6	EP	8746	Anticoagulant	Thrombosis, arterial
Arginine		74-79-3				
Ariflo®		153259-65-5				
aripiprazole	2(1H)-Quinolinone, 7-[4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydro- [CAS]	129722-12-9	EP	367141	Neuroleptic	Schizophrenia

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
arofylline	1H-Purine-2,6-dione, 3-(4-chlorophenyl)-3,7-dihydro-1-propyl- [CAS]	136145-07-8	EP	435811	COPD treatment	Chronic obstructive pulmonary disease
arotinolol	2-Thiophenecarboxamide, 5-[2-[[3-[(1,1-dimethylethyl)amino]-2-hydroxypropyl]thio]-4-thiazolyl]-, (±)- [CAS]	104766-23-6 68377-92-4	US	3932400	Antihypertensive, adrenergic	Hypertension, general
Arsacetin		618-22-4				
arsenic trioxide	Arsenic oxide (As2O3) [CAS]	1327-53-3			Anticancer, other	Cancer, leukaemia, acute myelogenous
Arsphenamine		139-93-5				
Arsthinol		119-96-0				
Arteether		75887-54-6				
Arteflene		123407-36-3 (Z-form)				
Artemether		71963-77-4				
Artemisinin		63968-64-9				
artemotil	3,12-Epoxy-12H-pyrano[4,3-j]-1,2-benzodioxepin, 10-ethoxydecahydro-3,6,9-trimethyl-, [3R-(3Alpha,5aß,6ß,8aß,9aAlpha,10Alpha,12ß,12aR*)]- [CAS]	75887-54-6			Antimalarial	Infection, malaria
artesunate	Butanedioic acid mono-[(3R,5aS,6R,8aS,9R,10R,12R,12aR)-decahydro-3,6,9-trimethyl-3,12-epoxy-12H-pyrano[4,3-j]-1,2-benzodioxepin-10-yl]ester	88495-63-0			Formulation, transmucosal, systemic	Infection, malaria
arzoxifene	Benzo(b)thiophene-6-ol, 2-(4-methoxyphenyl)-3-(4-(2-(1-piperidinyl)ethoxy)phenoxy)- [CAS]	182133-27-3	WO	9609041	Anticancer, hormonal	Cancer, breast
AS-3201	Spiro(pyrrolidine-3,4'(1'H)-pyrrolo(1,2-a)pyrazine)-1',2,3',5(2'H)-tetrone, 2'-((4-bromo-2-fluorophenyl)methyl)-, (3'R)- [CAS]	147254-64-6	EP	520320	Symptomatic antidiabetic	Diabetic complication, general
ASA	Benzoic acid, 2-(acetyloxy)- [CAS]	50-78-2 56449-07-1			Formulation, modified-release, other	Pain, general

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
α-Santonin		481-06-1				
Ascaridole		512-85-6				
Ascorbic Acid		50-81-7				
asenapine	1H-Dibenz[2,3:6,7]oxepino[4,5-c]pyrrole, 5-chloro-2,3,3a,12b-tetrahydro-2-methyl-, trans-, (Z)-2-butenedioate (1:1) [CAS]	85650-56-2	WO	9523600	Neuroleptic	Psychosis, general
asimadoline	Benzeneacetamide, N-[2-(3-hydroxy-1-pyrrolidinyl)-1-phenylethyl]-N-methyl-Alpha-phenyl-, [S-(R*,R*)]- [CAS]	153205-46-0	DE	4215213	GI inflammatory/bowel disorders	Irritable bowel syndrome
asoprisnil	11ß-[4-(Hydroxyiminomethyl)phenyl]-17ß-methoxy-17Alpha-(methoxymethyl)estra-4,9-dien-3-one	199396-76-4	EP	0648778	Menstruation disorders	Endometriosis
Asoxime		34433-31-3				
Aspartic Acid		56-84-8				
Aspidin		584-28-1				
Aspidinol		519-40-4				
Aspirin		50-78-2				
Aspirin, Dipyridamole						
aspoxicillin	Glycinamide, N-methyl-D-asparaginyl-N-(2-carboxy-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-6-yl)-D-2-(4-hydroxyphenyl)-, [2S-(2Alpha,5Alpha,6ß)]- [CAS]	63358-49-6	GB	1533413	Penicillin, injectable	Infection, respiratory tract, general
AST-120	AST 120 [CAS]	90597-58-3			Urological	Renal failure
Astemizole		68844-77-9				
asulacrine	4-Acridinecarboxamide, 9-[[2-methoxy-4-[(methylsulfonyl)amino]phenyl]amino]-N,5-dimethyl- [CAS]	80841-47-0 80841-48-1	EP	39224	Anticancer, other	Cancer, general
AT-1015	(N-[2-[4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-piperdino]ethyl]-1-formyl-4-piperidinecarboxamide monohydrochloride monohydrate				Antithrombotic	Thrombosis, general
atamestane	Androsta-1,4-diene-3,17-dione, 1-methyl- [CAS]	96301-34-7	DE	3338212	Anticancer, hormonal	Cancer, breast

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
atazanavir	2,5,6,10,13-Pentaazatetradecanedioic acid, 3,12-bis(1,1-dimethylethyl)-8-hydroxy-4,11-dioxo-9-(phenylmethyl)-6-((4-(2-pyridinyl)phenyl)methyl)- dimethyl ester, (3S,8S,9S,12S)-, sulfate (1:1) (salt) [CAS]	229975-97-7			Antiviral, anti-HIV	Infection, HIV/AIDS
atenolol	Benzeneacetamide, 4-[2-hydroxy-3-[(1-methylethyl)amino]propoxy]- [CAS]	29122-68-7 73677-19-7	GB	1285038	Antihypertensive, adrenergic	Hypertension, general
atenolol + chlorthalidone	Benzeneacetamide, 4-[2-hydroxy-3-[(1-methylethyl)amino]propoxy]-, mixt. with 2-chloro-5-(2,3-dihydro-1-hydroxy-3-oxo-1H-isoindol-1-yl)benzenesulfonamide [CAS]	73677-19-7	US	3836671	Formulation, fixed-dose combinations	Hypertension, general
atenolol + nifedipine	Benzeneacetamide, 4-[2-hydroxy-3-[(1-methylethyl)amino]propoxy]- + 4-(2'-nitrophenyl)-2,6-dimethyl-3,5-dicarbomethoxy-1,4-dihydropyridine				Formulation, fixed-dose combinations	Hypertension, general
α-Terpineol		98-55-5				
Atevirdine		136816-75-6				
atipamezole	1H-Imidazole, 4-(2-ethyl-2,3-dihydro-1H-inden-2-yl)- [CAS]	104054-27-5	EP	183492	Reproductive/gonadal, general	Sexual dysfunction, female
atiprimod dimaleate	2-Azaspiro[4.5]decane-2-propanamine, N,N-diethyl-8,8-dipropyl, dimaleate	130065-61-1	US	5744495	Antiarthritic, immunological	Arthritis, rheumatoid
ATL-146e			US	6232297	Imaging agent	Unspecified
α-Tocopherol		59-02-9				
atomoxetine	Benzenepropanamine, N-methyl-Gamma-(2-methylphenoxy)-, (R)- [CAS]	82248-59-7 83015-26-3	EP	52492	Neurological	Attention deficit disorder
atorvastatin	1H-Pyrrole-1-heptanoic acid, 2-(4-fluorophenyl)-ß,delta-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]- [CAS]	134523-03-8 134523-00-5	EP	409281	Hypolipaemic/Antiatherosclerosis	Hypercholesterolaemia
atosiban	Oxytocin, 1-(3-mercaptopropanoic acid)-2-(O-ethyl-D-tyrosine)-4-L-threonine-8-L-ornithine- [CAS]	90779-69-4	EP	112809	Labour inhibitor	Labour, preterm

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
atovaquone	1,4-Naphthalenedione, 2-[4-(4-chlorophenyl)cyclohexyl]-3-hydroxy-, trans- [CAS]	95233-18-4	EP	123238	Antifungal	Infection, Pneumocystis jiroveci
atovaquone + proguanil	1,4-Naphthalenedione,2-[4-(4-chlorophenyl)cyclohexyl]-3-hydroxy-,trans + N-(4-chloro-phenyl)-N-(1-methylethyl)imidiodicarbonimidic diamide				Antimalarial	Infection, malaria
atracurium	Isoquinolinium, 2,2'-[1,5-pentanediylbis[oxy(3-oxo-3,1-propanediyl)]]bis[1-[(3,4-dimethoxyphenyl)methyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl- [CAS]	64228-81-5	US	4179557	Muscle relaxant	Surgery adjunct
atrasentan	3-Pyrrolidinecarboxylic acid, 4-(1,3-benzodioxol-5-yl)-1-[2-(dibutylamino)-2-oxoethyl]-2-(4-methoxyphenyl)-, (2R,3R,4S)- [CAS]	173937-91-2	WO	9730045	Anticancer, other	Cancer, prostate
Atrial Natriuretic Peptide		85637-73-6				
Atrolactamide		2019-68-3				
Atropine		51-55-8				
Augmentin		74469-00-4			Formulation, modified-release, other	Infection, respiratory tract, general
auranofin	Gold, (1-thio-ß-D-glucopyranose 2,3,4,6-tetraacetato-S)(triethylphosphine)-[CAS]	34031-32-8	US	3708579	Antiarthritic, other	Arthritis, rheumatoid
Aurothioglucose		12192-57-3				
avasimibe	Sulfamic acid, [[2,4,6-tris(1-methylethyl)phenyl]acetyl]-, 2,6-bis(1-methylethyl)phenyl ester [CAS]	166518-60-1	US	5491172	Hypolipaemic/Antiatherosclerosis	Atherosclerosis
Avobenzone		70356-09-1				
AWD-12-281	AWD 12-281 [CAS]	257892-33-4			Antiallergic, non-asthma	Rhinitis, allergic, general
Azacitidine		320-67-2				
Azacyclonol		115-46-8				
azanidazole	2-Pyrimidinamine, 4-[2-(1-methyl-5-nitro-1H-imidazol-2-yl)ethenyl]-,(E)- [CAS]	62973-76-6	US	3882105	Antibacterial, other	Infection, trichomoniasis

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
azapropazone	1H-Pyrazolo[1,2-a][1,2,4]benzotriazine-1,3(2H)-dione, 5-(dimethylamino)-9-methyl-2-propyl- [CAS]	13539-59-8	FR	1440629	Anti-inflammatory	
Azaserine		115-02-6				
azasetron	2H-1,4-Benzoxazine-8-carboxamide, N-1-azabicyclo[2.2.2]oct-3-yl-6-chloro-3,4-dihydro-4-methyl-3-oxo-, monohydrochloride- [CAS]	123040-16-4 123040-94-8 123040-96-0 123040-69-7	EP	313393	Antiemetic	Nausea and vomiting, general
Azatadine		3964-81-6				
azathioprine	6-[(1-Methyl-4-nitro-1H-imidazol-5-yl)thio]-1H-purine	446-86-6			Formulation, oral, other	Transplant rejection, bone marrow
AZD-4282	glycine				Analgesic, other	Pain, neuropathic
AZD-6140	3,4 Difluorophenylcyclopropylamine				Antithrombotic	Thrombosis, arterial
azelaic acid	Nonanedioic acid [CAS]	123-99-9			Antiacne	Acne
azelastine	1(2H)-Phthalazinone, 4-[(4-chlorophenyl)methyl]-2-(hexahydro-1-methyl-1H-azepin-4-yl)-, monohydrochloride [CAS]	58581-89-8 79307-93-0	GB	1377231	Antiasthma	Asthma
azelnidipine	3,5-Pyridinedicarboxylic acid, 2-amino-1,4-dihydro-6-methyl-4-(3-nitrophenyl)-, 3-[1-(diphenylmethyl)-3-azetidinyl] 5-(1-methylethyl)ester, (+/-)- [CAS]	123524-52-7	EP	266922	Antihypertensive, other	Hypertension, general
Azidamfenicol		13838-08-9				
Azidocillin		17243-38-8				
Azimilide		149908-53-2				
Azintamide		1830-32-6				
azithromycin	9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin-A	76801-85-9 83905-01-5 92395-24-9	US	4328334	Macrolide antibiotic	Infection, respiratory tract, lower
azlocillin	4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[[[[(2-oxo-1-imidazolidinyl)carbonyl]amino]phenylacetyl]amino]-, [2S-[2.alpha.,5Alpha,6ß(S*)]]- [CAS]	37091-65-9 37091-66-0	GB	1392849	Penicillin, injectable	Infection, general

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Azosemide		27589-33-9				
aztreonam	Propanoic acid, 2-[[[1-(2-amino-4-thiazolyl)-2-[(2-methyl-4-oxo-1-sulfo-3-azetidinyl)amino]-2-oxoethylidene]amino]oxy]-2-methyl-, [2S-[2Alpha,3ß(Z)]]-[CAS]	104184-69-2 78110-38-0	GB	2071650	Beta-lactam antibiotic	Infection, general
azulene	Sodium 5-isopropyl-3,8-dimethyl-1-azulene sulfonate	6223-35-4	EP	88958	Formulation, modified-release, other	Inflammation, general
bacampicillin	4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 6-[(aminophenylacetyl)amino]-3,3-dimethyl-7-oxo-, 1-[(ethoxycarbonyl)oxy]ethyl ester, [2S-[2Alpha,5Alpha,6ß(S*)]]- [CAS]	37661-08-8 50972-17-3	GB	1363506	Penicillin, oral	*Infection, general*
Bacitracin		1405-87-4				
baclofen	ß-(Aminomethyl)-4-chlorobenzenepropanoic acid [CAS]	1134-47-0			Formulation, implant	Spastic paralysis
Baicalein		491-67-8				
balofloxacin	3-Quinolinecarboxylic acid, 1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-[3-(methylamino)-1-piperidinyl]-4-oxo- [CAS]	127294-70-6	EP	342675	Quinolone antibacterial	Infection, urinary tract
balsalazide	Benzoic acid, 5-[[4-[[(2-carboxyethyl)amino]carbonyl]phenyl]azo]-2-hydroxy-, (E)- [CAS]	80573-04-2	US	4412992	GI inflammatory/bowel disorders	Colitis, ulcerative
bambuterol	Carbamic acid, dimethyl-, 5-[2-[(1,1-dimethylethyl)amino]-1-hydroxyethyl]-1,3-phenylene ester, monohydrochloride [CAS]	81732-46-9 81732-65-2	EP	43807	Antiasthma	Asthma
Bamethan		3703-79-5				
Bamifylline		2016-63-9				
Bamipine		4945-47-5				
Barbital		57-44-3				
barnidipine	3,5-Pyridinedicarboxylic acid, 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-, methyl-1-(phenylmethyl)-3-pyrrolidinyl ester, [S-(R*,R*)]-	104713-75-9 104757-53-1 71863-56-4	US	4220649	Antihypertensive, other	Hypertension, general

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
BAS-118	N-Methyl-3-[2-(2-napthyl)acetylamino]benzamide				Antibacterial, other	Infection, Helicobacter pylori
Basic Aluminum Carbonate Gel		1339-92-0				
Basiliximab		179045-86-4				
Batimastat		130370-60-4				
Batroxobin		9039-61-6				
Bay-41-2272	5-cyclopropyl-2-[1(2-fluoro-benzyl)-1H-pyrazolo[3,4-b]pyridine-3-yl]pyrimidin-4ylamine				Male sexual dysfunction	Sexual dysfunction, male, general
Bay-41-8543	2-[1-(2-Fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]-5-(4-mopholinyl)pyrimidine-4,6-diamine				Cardiovascular	Unspecified
BAY-43-9006	N-(4-chloro-3-(trifluoromethyl)phenyl)-N'-(4-(2-(N-methylcarbamoyl)-4-pyridyloxy)phenyl)urea				Anticancer, other	Cancer, liver
BAY-57-1293	N-[5(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)phenyl]acetamide				Antiviral, other	Infection, herpes simplex virus
bazedoxifen	TSE 424 [CAS]	198481-33-3	EP	802183	Osteoporosis treatment	Osteoporosis
β-Benzalbutyramide		7236-47-7				
BBR-3464	Platinum(4+), hexaaminedichlorobis(μ-(1,6-hexanediamine-N:N'))tri- stereoisomer, tetranitrate [CAS]	172903-00-3	US	5744497	Anticancer, alkylating	Cancer, lung, non-small cell
BBR-3576			US	5519029	Anticancer, antibiotic	Cancer, prostate
BBR-3610			US	6060616	Anticancer, alkylating	Cancer, general
β-Carotene		7235-40-7				
BCH-1868	(-)-2-R-dihydroxyphosphinyol-5-(S)-(guanin-9'-yl-methyl)tetrahydrofuran				Anticancer, antimetabolite	Cancer, general
Bebeerine		477-60-1				
Beclamide		501-68-8				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
beclometasone	Pregna-1,4-diene-3,20-dione, 9-chloro-11ß,17,21-trihydroxy-16ß-methyl, [CAS]	5534-09-8 4419-39-0	WO	0006132	Formulation, inhalable, solution	Asthma
Befloxatone		134564-82-2				
befunolol	Ethanone, 1-[7-[2-hydroxy-3-[(1-methylethyl)amino]propoxy]-2-benzofuranyl]-[CAS]	39543-79-8 39552-01-7			Antiglaucoma	
Bemegride		64-65-3				
Benactyzine		302-40-9				
benazepril	1H-1-Benzazepine-1-acetic acid, 3-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-2,3,4,5-tetrahydro-2-oxo-, [S-(R*,R*)]-[CAS]	86541-74-4 86541-75-5 86541-78-8	EP	72352	Antihypertensive, renin system	Hypertension, general
bencyclane	1-Propanamine, N,N-dimethyl-3-[[1-(phenylmethyl)cycloheptyl]oxy]-, (E)-2-butenedioate (1:1) [CAS]	14286-84-1 2179-37-5	WO	9829409	Vasodilator, peripheral	
bendazac	L-Lysine, mono[[[1-(phenylmethyl)-1H-indazol-3-yl]oxy]acetate] [CAS]	81919-14-4 20187-55-7	GB	2081708	Ophthalmological	
Bendroflumethiazide		73-48-3				
Benexate		78718-25-9				
benfluorex	Ethanol, 2-[[1-methyl-2-[3-(trifluoromethyl)phenyl]ethyl]amino]-, benzoate (ester) [CAS]	23602-78-0 23642-66-2	GB	1175516	Hypolipaemic/Antiatherosclerosis	
Benfotiamine		22457-89-2				
Benfurodil		3447-95-8				
benidipine	3,5-Pyridinedicarboxylic acid, 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-, methyl 1-(phenylmethyl)-3-piperidinyl ester, monohydrochloride (R*,R*)-(+/-)-[CAS]	105979-17-7 91599-74-5	EP	63365	Antihypertensive, other	Hypertension, general
Benorylate		5003-48-5				
Benoxaprofen		67434-14-4				
Benoxinate		99-43-4				
Benperidol		2062-84-2				
Benproperine		2156-27-6				
Benserazide		322-35-0				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
bentazepam	2H-[1]Benzothieno[2,3-e]-1,4-diazepin-2-one, 1,3,6,7,8,9-hexahydro-5-phenyl[CAS]	29462-18-8	DE	2005276	Anxiolytic	
Bentiromide		37106-97-1				
Bentoquatam		1340-69-8				
Benzalkonium		8001-54-5				
Benzarone		1477-19-6				
benzbromarone	Methanone, (3,5-dibromo-4-hydroxyphenyl)(2-ethyl-3-benzofuranyl)- [CAS]	3562-84-3	US	3012042	Antigout	
Benzethonium		121-54-0				
Benzetimide		14051-33-3				
Benzilonium		1050-48-2				
Benzlodarone		68-90-6				
benznidazole	N-benzyl-2-nitroimidazole-1-acetamide	22994-85-0	GB	1138529	Protozoacide	
benzocaine	Benzoic acid, 4-amino-, ethyl ester	94-09-7			Formulation, fixed-dose combinations	Pain, musculoskeletal
Benzoctamine		17243-39-9				
Benzonatate		104-31-4				
Benzoxonium Chloride		19379-90-9				
benzoyl peroxide	Peroxide, dibenzoyl [CAS]	94-36-0			Formulation, other	Acne
Benzoylpas		13898-58-3				
Benzphetamine		156-08-1				
Benzpiperylon		53-89-4				
Benzquinamide		63-12-7				
Benzthiazide		91-33-8				
Benztropine		132-17-2				
benzydamine	1-Propanamine, N,N-dimethyl-3-[[1-(phenylmethyl)-1H-indazol-3-yl]oxy]- [CAS]	132-69-4 642-72-8			Stomatological, reproductive/gonadal, anti-inflammatory	
Benzyl Benzoate		120-51-4				
Benzylhydrochlorothiazide		1824-50-6				
Benzylmorphine		14297-87-1				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Bephenium Hydroxynaphthoate		3818-50-6				
bepotastine	1-Piperidinebutanoic acid, 4-((4-chlorophenyl)-2-pyridinylmethoxy)-, (S)-, monobenzenesulfonate [CAS]	190786-44-8 190786-43-7	WO	9829409	Antiallergic, non-asthma	Allergy, general
bepridil	1-Pyrrolidineethanamine, ß-[(2-methylpropoxy)methyl]-N-phenyl-N-(phenylmethyl)- [CAS]	64706-54-3 74764-40-2 74764-75-3	EP	146155	Antianginal	Angina, general
beraprost	1H-Cyclopenta[b]benzofuran-5-butanoic acid, 2,3,3a,8b-tetrahydro-2-hydroxy-1-(3-hydroxy-4-methyl-1-octen-6-ynyl)- [CAS]	88475-69-8 88430-50-6	US	4474802	Prostaglandin	Peripheral vascular disease
Berberine		2086-83-1				
Bergapten		484-20-8				
Bermoprofen		78499-27-1				
Besipirdine		119257-34-0				
betahistine	2-Pyridineethanamine, N-methyl-, dihydrochloride	5579-84-0 5638-76-6			Formulation, modified-release, <=24hr	Meniere's disease
betaine	Betaine- [CAS]	107-43-7			Metabolic and enzyme disorders	Homocystinuria
betamethasone	Pregna-1,4-diene-3,20-dione, 9-fluoro-11,17,21-trihydroxy-16-methyl-, (11ß,16ß)- [CAS]	378-44-9			Formulation, dermal, topical	Psoriasis
Betamipron		3440-28-6				
Betasine		3734-24-5				
betaxolol	2-Propanol, 1-[4-[2-(cyclopropylmethoxy)ethyl]phenoxy]-3-[(1-methylethyl)amino]- [CAS]	63659-18-7 63659-19-8	US	4252984	Antihypertensive, adrenergic	Hypertension, general, glaucoma
Betazole		105-20-4				
Bethanechol		590-63-6				
Bethanidine		55-73-2				
Betoxycaine		3818-62-0				
β-Eucaine		500-34-5				
bevantolol	2-Propanol, 1-[[2-(3,4-dimethoxyphenyl)ethyl]amino]-3-(3-methylphenoxy)- [CAS]	42864-78-8 59170-23-9	US	3857891	Antihypertensive, adrenergic	Hypertension, general
Bevonium		5205-82-3				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
bexarotene	Benzoic acid, 4-(1-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)ethenyl)- [CAS]	153559-49-0	WO	9321146	Anticancer, other	Cancer, lymphoma, T-cell
bezafibrate	Propanoic acid, 2-[4-[2-[(4-chlorobenzoyl)amino]ethyl]phenoxy]-2-methyl- [CAS]	41859-67-0	GB	1359264	Hypolipaemic/Antiatherosclerosis	
Bezitramide		15301-48-1				
BG-9928		166374-48-7			Cardiostimulant	Heart failure
BIA-2-024	10,11-dihydro-10-hydroxyimino-5H-dibenz/b,f/azepine-5-carboxamide	199997-15-4	WO	9745416	Antiepileptic	Epilepsy, general
BIA-2-093	(S)-(-)-10-acetoxy-10,11-dihydro-5H-dibenzo/b,f/azepine-5-carboxamide- [CAS]	236395-14-5			Antiepileptic	Epilepsy, general
BIA-3-202	1-(3,4-dihydroxy-5-nitrophenyl)-2-phenyl-ethanone	274925-86-9	EP	1010688	Antiparkinsonian	Parkinson's disease
Bialamicol		493-75-4				
biapenem	5H-Pyrazolo[1,2-a][1,2,4]triazol-4-ium, 6-[[2-carboxy-6-(1-hydroxyethyl)-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-en-3-yl]thio]-6,7-dihydro-, hydroxide, inner salt, [4R-[4Alpha,5ß,6ß(R*)]]- [CAS]	120410-24-4	EP	289801	Beta-lactam antibiotic	Infection, beta-lactamase resistant
Bibenzonium		15585-70-3				
Bibrocathol		6915-57-7				
bicalutamide	Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl-, (+/-)- [CAS]	90357-06-5	EP	100172	Anticancer, hormonal	Cancer, prostate
bicifadine	3-Azabicyclo[3.1.0]hexane, 1-(4-methylphenyl)-, (+/-)- [CAS]	66504-75-4 71195-57-8	DE	2740562	Analgesic, other	Pain, general
bicyclic monoterpene diols			US	6294585	Dermatological	Unspecified
Bidisomide		116078-65-0				
Bietamiverine		479-81-2				
Bietanautine		6888-11-5				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Bietaserpine		53-18-9				
bifemelane	1-Butanamine, N-methyl-4-[2-(phenylmethyl)phenoxy]-, hydrochloride [CAS]	62232-46-6 90293-01-9	GB	1512880	Cognition enhancer	Attention deficit disorder
Bifluranol		34633-34-6				
bifonazole	1H-Imidazole, 1-([1,1'-biphenyl]-4-ylphenylmethyl)- [CAS]	60628-96-8 60629-08-5 60629-09-6	US	4118487	Antifungal	Infection, fungal, general
bimatoprost	5-Heptenamide, 7-(3,5-dihydroxy-2-(3-hydroxy-5-phenyl-1-pentenyl)cyclopentyl)-N-ethyl (1R-(1Alpha(Z)2ß(1E,3S,3Alpha,5Alpha)) [CAS]	155206-00-1	US	5688819	Prostaglandin	Glaucoma
bimoclomol	N-[2-hydroxy-3-(1-piperidinyl)propoxy]-3-pyridinecarboximidoyl chloride, (Z)-2-butanedioate (1:1)	130493-04-8	US	5147874	Symptomatic antidiabetic	Neuropathy, diabetic
bimosiamose	(1,1'-Biphenyl)-3-acetic acid, 3',3'''-(1,6-hexanediyl)bis(6'-Alpha-D-mannopyranosyloxy)-, [CAS]	187269-40-5	US	5444050	Antiasthma	Asthma
Binifibrate		69047-39-8				
binodenoson	Adenosine, 2-((cyclohexylmethylene)hydrazino)- [CAS]	144348-08-3			Vasodilator, coronary	Diagnosis, coronary
Biomed-101			US	6423744	Anticancer, other	Cancer, renal
Biotin		58-85-5				
Biperiden		514-65-8				
biricodar	2-Piperidinecarboxylic acid, 1-(oxo(3,4,5-trimethoxyphenyl)acetyl)-,4-(3-pyridinyl)-1-(3-(3-pyridinyl)propyl)butyl ester, (S)-, 2-hydroxy-1,2,3-propanetricarboxylate (1:2) [CAS]	174254-13-8 159997-94-1			Radio/chemosensitizer	Cancer, breast
biriperone	1-Butanone, 1-(4-fluorophenyl)-4-(3,4,6,7,12,12a-hexahydropyrazino[1',2':1,6]pyrido[3,4-b]indol-2(1H)-yl)- [CAS]	42021-34-1	DE	2333922	Neuroleptic	
Bisacodyl		603-50-9				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Bisantrene		78186-34-2				
Bisbentiamine		2667-89-2				
Bisdequalinium		52951-36-7				
Bismuth Aluminate		12284-76-3				
Bismuth Butylthiolaurate		53897-25-9				
Bismuth Ethyl Camphorate		52951-37-8				
Bismuth Iodosubgallate		138-58-9				
Bismuth Sodium Iodide		53778-50-0				
Bismuth Sodium Triglycollamate		5798-43-6				
Bismuth Subcarbonate		5892-10-4				
Bismuth Subgallate		22650-86-8				
Bismuth Subnitrate		1304-85-4				
Bismuth Subsalicylate		14882-18-9				
Bismuth Tribromophenate		5175-83-7				
bisoprolol	2-Propanol, 1-[4-[[2-(1-methylethoxy)ethoxy]methyl]phenoxy]-3-[(1-methylethyl)amino]- [CAS]	104344-23-2 66722-44-9	GB	1532380	Antihypertensive, adrenergic	Heart failure
bisoprolol + HCTZ	2-Propanol, 1-[4-[[2-(1-methylethoxy)ethoxy]methyl]phenoxy]-3-[(1-methylethyl)amino] mixt. with 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide				Formulation, fixed-dose combinations	Hypertension, general
bisoprolol+trichloromethiazide	2-Propanol, 1-[4-[[2-(1-methylethoxy)ethoxy]methyl]phenoxy]-3-[(1-methylethyl)amino] mixt. with 6-chloro-3-(dichloromethyl)-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide				Formulation, fixed-dose combinations	Hypertension, general

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Bisoxatin		14008-48-1				
Bithionol		97-18-7				
Bitolterol		30392-40-6				
Bitoscanate		4044-65-9				
BL-3875			WO	0218378	Anti-inflammatory	Unspecified
bleomycin	Bleomycin [CAS]	11056-06-7 9041-93-4			Formulation, transdermal, enhanced	Cancer, head and neck
blonanserin	Cycloocta[b]pyridine, 2-(4-ethyl-1-piperazinyl)-4-(4-fluorophenyl)-5,6,7,8,9,10-hexahydro- [CAS]	132810-10-7	EP	385237	Neuroleptic	Schizophrenia
BMS-184476			EP	639577	Anticancer, other	Cancer, breast
BMS-387032	cis-(+/-)-2-(Ethylthio)-5,7-dihydroxy-8-(3-hydroxy-1-methyl-4-piperidinyl)-4H-1-benzopyran-4-one		WO	9742949	Anticancer, other	Cancer, general
BN-82451	4-[2-(aminomethyl)-1,3-thiazol-4-yl]-2,6-di-tert-butylphenol, dihydrochloride				Neuroprotective	Unspecified
BNP-7787	Ethanesulfonic acid, 2,2'-dithiobis-, disodium salt [CAS]	16208-51-8			Radio/chemoprotective	Chemotherapy-induced nausea and vomiting
BO-653	5-Benzofuranol, 4,6-bis(1,1-dimethylethyl)-2,3-dihydro-2,2-dipentyl- [CAS]	157360-23-1	WO	9408930	Hypolipaemic/Antiatherosclerosis	Atherosclerosis
Bolandiol		19793-20-5				
Bolasterone		1605-89-6				
Boldenone		846-48-0				
bopindolol	2-Propanol, 1-[(1,1-dimethylethyl)amino]-3-[(2-methyl-1H-indol-4-yl)oxy]-, benzoate (ester), (+/-)- [CAS]	62658-63-3 82857-38-3	US	4340541	Antihypertensive, adrenergic	Hypertension, general
Bornyl Chloride		464-41-5				
Bornyl Salicylate		560-88-3				
bortezomib	Boronic acid, [(1R)-3-methyl-1-[[(2S)-1-oxo-3-phenyl-2-[(pyrazinylcarbonyl)amino]propyl]amino]butyl]- [CAS]	179324-69-7	US	6271199	Anticancer, other	Cancer, myeloma

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
bosentan	Benzenesulfonamide, 4-(1,1-dimethylethyl)-N-[6-(2-hydroxyethoxy)-5-(2-methoxyphenoxy)[2,2'-bipyrimidin]-4-yl]- [CAS]	147536-97-8	EP	633259	Vasodilator, peripheral	Hypertension, pulmonary
BP2.94	Phenol, 2-[[[(1R)-2-(1H-imidazol-4-yl)-1-methylethyl]imino]phenylmethyl]- [CAS]	139191-80-3	WO	9117146	Respiratory	Rhinitis, general
BP4.897	N-[4-[4-(2-methoxyphenyl)-1-piperazinyl]butyl]naphthalene-2-carboxamide		EP	779284	Dependence treatment	Addiction, cocaine
β-Propiolactone		57-57-8				
Bradycor		140661-97-8				
Brain Natriuretic Peptide		114471-18-0				
Brallobarbital		561-86-4				
brasofensine	8-Azabicyclo(3.2.1)octane-2-carboxaldehyde, 3-(3,4-dichlorophenyl)-8-methyl-, O-methyloxime, (1R-(1Alpha,2ß(E),3Alpha,5Alpha))- [CAS]	171655-91-7	WO	9528401	Antiparkinsonian	Parkinson's disease
Brequinar		96187-53-0				
Bretylium		61-75-6				
Brilliant Green		633-03-4				
brimonidine	6-Quinoxalinamine, 5-bromo-N-(4,5-dihydro-1H-imidazol-2-yl)- [CAS]	59803-98-4	DE	2538620	Antiglaucoma	Glaucoma
brinzolamide	2H-Thieno(3,2-e)-1,2-thiazine-6-sulfonamide, 4-(ethylamino)-3,4-dihydro-2-(3-methoxypropyl)-, 1,1-dioxide, (R)- [CAS]	138890-62-7	US	5378703	Antiglaucoma	Glaucoma
brivudin	Uridine, 5-(2-bromoethenyl)-2'-deoxy, (E)- [CAS]	69304-47-8			Antiviral, other	Infection, varicella zoster virus
Brodimoprim		56518-41-3				
Bromazepam		1812-30-2				
bromfenac	Benzeneacetic acid, 2-amino-3-(4-bromobenzoyl)- [CAS]	91714-93-1 91714-94-2			Formulation, mucosal, topical	Inflammation, ocular
Bromhexine		3572-43-8				
Bromindione		1146-98-1				
Bromisovalum		496-67-3				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Bromocriptine		25614-03-3				
Bromodiphenhydramine		118-23-0				
Bromoform		75-25-2				
Bromopride		4093-35-0				
Bromosalicylchloranilide		3679-64-9				
bromperidol	1-Butanone, 4-[4-(4-bromophenyl)-4-hydroxy-1-piperidinyl]-1-(4-fluorophenyl)- [CAS]	10457-90-6	US	3438991	Neuroleptic	Psychosis, general
Brompheniramine		86-22-6				
Broparoestrol		479-68-5				
Bropirimine		56741-95-8				
brostallicin	4-(2-Bromoacrylamido)-N'''-(2-guanidinoethyl)-1,1',1",1'''-tetramethyl-N,4':N',4":N",4'''-quater-[pyrrole-2-carboxamide] [CAS]				Anticancer, other	Cancer, general
brotizolam	6H-Thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepine, 2-bromo-4-(2-chlorophenyl)-9-methyl- [CAS]	57801-81-7	US	4094984	Hypnotic/Sedative	
Brovincamine		57475-17-9				
Broxuridine		59-14-3				
Broxyquinoline		521-74-4				
Brucine		357-57-3				
β-Sitosterol		83-46-5				
Bucetin		1083-57-4				
Bucillamine		65002-17-7				
Bucindolol		71119-11-4				
bucladesine	Adenosine, N-(1-oxobutyl)-, cyclic 3',5'-(hydrogen phosphate) 2'-butanoate [CAS]	362-74-3	JP	51113896	Cardiostimulant	Wound healing
Buclizine		82-95-1				
Buclosamide		575-74-6				
Bucolome		841-73-6				
bucricaine	9-Acridinamine, N-butyl-1,2,3,4-tetrahydro-, monohydrochloride [CAS]	82636-28-0			Anaesthetic, focal	

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Bucumolol		58409-59-9				
budesonide	Pregna-1,4-diene-3,20-dione, 16,17-[butylidenebis(oxy)]-11,21-dihydroxy-, (11ß,16Alpha)- [CAS]	51333-22-3	GB	1429922	Antiasthma	Asthma
budesonide + formoterol	Pregna-1,4-diene-3,20-dione, 16,17-[butylidenebis(oxy)]-11,21-dihydroxy-,(11ß,1bAlpha) + formamide, N-[2-hydroxy-5-[1-hydroxy-2-[[2-(4-methoxyphenol)-1-methylethyl]amino]ethyl]phenyl]-(R*,R*)-(±)				Formulation, fixed-dose combinations	Asthma
budipine	Piperidine, 1-(1,1-dimethylethyl)-4,4-diphenyl- [CAS]	57982-78-2 63661-61-0	DE	2825322	Antiparkinsonian	Parkinson's disease
Budralazine		36798-79-5				
Bufeniode		22103-14-6				
Bufetolol		53684-49-4				
bufexamac	p-butoxyacetohydroxamic acid	2438-72-4	US	3479396	Anti-inflammatory	
buflomedil	1-Butanone, 4-(1-pyrrolidinyl)-1-(2,4,6-trimethoxyphenyl)- [CAS]	35543-24-9 55837-25-7	GB	1325192	Vasodilator, peripheral	
Buformin		692-13-7				
Bufuralol		54340-62-4				
Bumadizon		3583-64-0				
bumetanide	Benzoic acid, 3-(aminosulfonyl)-5-(butylamino)-4-phenoxy- [CAS]	28395-03-1	US	3806534	Antihypertensive, diuretic	Hypertension, general
bunaftine	1-Naphthalenecarboxamide, N-butyl-N-[2-(diethylamino)ethyl]- [CAS]	32421-46-8	DE	2009894	Antiarrhythmic	
Bunamiodyl Sodium		1923-76-8				
bunazosin	1H-1,4-Diazepine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)hexahydro-4-(1-oxobutyl)- [CAS]	52712-76-2 80755-51-7	GB	1398455	Antihypertensive, adrenergic	Hypertension, general
bunitrolol	Benzonitrile, 2-[3-[(1,1-dimethylethyl)amino]-2-hydroxypropoxy]- [CAS]	34915-68-9	US	3940489	Antihypertensive, adrenergic	
bupivacaine	2-Piperidinecarboxamide, 1-butyl-N-(2,6-dimethylphenyl)- [CAS]	38396-39-3 2180-92-9			Formulation, modified-release, >24hr	Anaesthesia
Bupranolol		14556-46-8				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
buprenorphine	6,14-Ethenomorphinan-7-methanol, 17-(cyclopropylmethyl)-Alpha-(1,1-dimethylethyl)-4,5-epoxy-18,19-dihydro-3-hydroxy-6-methoxy-Alpha-methyl-, [5Alpha,7Alpha(S)]- [CAS]	52485-79-7 53152-21-9	US	3433791	Analgesic, other	
bupropion	1-Propanone, 1-(3-chlorophenyl)-2-[(1,1-dimethylethyl)amino]-, (+/-)- [CAS]	31677-93-7 34911-55-2	US	4425363	Antidepressant	Depression, general
Buramate		4663-83-6				
buserelin	Luteinizing hormone-releasing factor (pig), 6-[O-(1,1-dimethylethyl)-D-serine]-9-(N-ethyl-L-prolinamide)-10-deglycinamide- [CAS]	57982-77-1 68630-75-1	GB	1523623	Releasing hormones	Cancer, prostate
buspirone	8-Azaspiro[4.5]decane-7,9-dione, 8-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]-[CAS]	36505-84-7	EP	276536	Anxiolytic	Anxiety, general
busulfan	1,4-Butanediol, dimethanesulfonate [CAS]	55-98-1			Formulation, optimized, microparticles	Cancer, general
busulfan	1,4-Butanediol, dimethanesulfonate- [CAS]	55-98-1			Formulation, parenteral, other	Cancer, leukaemia, acute myelogenous
Butabarbital		143-81-7				
Butacaine		149-16-6				
Butacetin		2109-73-1				
Butalamine		22131-35-7				
Butalbital		77-26-9				
Butallylonal		1142-70-7				
butamben	4-Aminobenzoic acid butyl ester [CAS]	94-25-7			Formulation, modified-release, other	Pain, cancer
butamirate	Benzeneacetic acid, Alpha-ethyl-, 2-[2-(diethylamino)ethoxy]ethylester, 2-hydroxy-1,2,3-propanetricarboxylate (1:1) [CAS]	18109-80-3 18109-81-4			Antitussive	Cough
Butanilicaine		3785-21-5				
Butaperazine		653-03-2				
Butaverine		55837-14-4				
Butazolamide		16790-49-1				
Butedronic Acid		51395-42-7				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
butenafine	1-Naphthalenemethanamine, N-((4-(1,1-dimethylethyl)phenyl)methyl)-N-methyl- [CAS]	101827-46-7 101828-21-1	EP	164697	Antifungal	Infection, dermatological
Butethal		77-28-1				
Butethamate		14007-64-8				
Butethamine		2090-89-3				
Buthalital		510-90-7				
Buthiazide		2043-38-1				
Butibufen		55837-18-8				
Butidrine		1506-12-3				
butobendine	benzoic acid, 3,4,5-trimethoxy-, 1,2-ethanediylbis[(methylimino)(2-ethyl-2,1-ethanediyl)] ester, [S-(R*,R*)]- [CAS]	55769-64-7 55769-65-8	US	4021473	Antiarrhythmic	Arrhythmia, general
butoconazole	1H-Imidazole, 1-[4-(4-chlorophenyl)-2-[(2,6-dichlorophenyl)thio]butyl]-, (+/-)- [CAS]	64872-76-0 64872-77-1	GB	1567431	Antifungal	Infection, Candida, general
Butoctamide		32838-26-9				
Butofilolol		64552-17-6				
butorphanol	Morphinan-3,14-diol, 17-(cyclobutylmethyl)-, [S-(R*,R*)]-2,3-dihydroxybutanedioate (1:1) (salt) [CAS]	42408-82-2 58786-99-5	GB	1412129	Analgesic, other	
Butoxycaine		3772-43-8				
Butriptyline		35941-65-2				
Butropium		29025-14-7				
Buzepide		3691-21-2				
BVT-5182			WO	0208178	Anorectic/Antiobesity	Obesity
BXT-51072	2H-1,2-Benzoselenazine, 3,4-dihydro-4,4-dimethyl- [CAS]	173026-17-0			GI inflammatory/bowel disorders	Colitis, ulcerative
C-1311	6H-Imidazo[4,5,1-de]acridin-6-one, 5-[[2-(diethylamino)ethyl]amino]-8-hydroxy-, 2HCl, 2H2O				Anticancer, other	Cancer, general
cabergoline	Ergoline-8-carboxamide, N-[3-(dimethylamino)propyl]-N-[(ethylamino)carbonyl]-6-(2-propenyl)-, (8ß)- [CAS]	81409-90-7 85329-89-1	GB	2103603	Antiprolactin	Galactorrhoea

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Cabergoline		81409-90-7				
Cacodylic Acid		75-60-5				
Cactinomycin		8052-16-2				
cadexomer iodine	Cadexomer iodine [CAS]	94820-09-4			Anti-infective, other	Ulcer, venostasis
Cadmium Salicylate		19010-79-8				
Cadralazine		64241-34-5				
Cafaminol		30924-31-3				
caffeine	1,2,3,-Propanetricarboxylic acid, 2-hydroxy-, mixt. with 3,7-dihydro-1,3,7-trimethyl-1H-purine-2,6-dione [CAS]	69-22-7 58-08-2			Respiratory	Apnoea
Calcifediol		19356-17-3				
Calcipotriene		112965-21-6				
calcipotriol	9,10-Secochola-5,7,10(19),22-tetraene-1,3,24-triol, 24-cyclopropyl-,(1Alpha,3ß,5Z,7E,22E)- [CAS]	112965-21-6	WO	8700834	Antipsoriasis	Psoriasis
calcipotriol+beclometasone	9,10-Secochola-5,7,10(19),22-tetraene-1,3,24-triol, 24-cyclopropyl-,(1Alpha,3ß,5Z,7E,22E) + Pregna-1,4-diene-3,20-dione, 9-chloro-11ß,17,21-trihydroxy-16ß-methyl, 17,21-dipropionate				Formulation, fixed-dose combinations	Psoriasis
calcitriol	9,10-Secocholesta-5,7,10(19)-triene-1,3,25-triol, (1Alpha,3ß,5Z,7E)- [CAS]	32222-06-3			Antipsoriasis	Psoriasis
Calcium 3-Aurothio-2-propanol-1-sulfonate		5743-29-3				
Calcium Acetylsalicylate		69-46-5				
Calcium Bromolactobionate		33659-28-8				
Calcium Carbonate		471-34-1				
Calcium Gluconate		299-28-5				
Calcium Glycerophosphate		27214-00-2				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
calcium hopantothenate	Calcium D-(+)-4-(2,4-dihydroxy-3,3-dimethylbutyramido)butyrate (hemihydrate) [CAS]	17097-76-6	EP	117260	Neurological	Attention deficit disorder
Calcium Iodobehenate		1319-91-1				
Calcium Iodostearate		1301-16-2				
Calcium Lactate		814-80-2				
Calcium Levulinate		591-64-0				
Calcium Mesoxalate		21085-60-9				
Calcium N-Carbamoylaspartate		16649-79-9				
calcium polycarbophil	Polycarbophil, calcium salt- [CAS]	126040-58-2 9003-97-8			GI inflammatory/bowel disorders	Irritable bowel syndrome
Calcium Propionate		4075-81-4				
Calcium Succinate		140-99-8				
caldaret	5-methyl-2-(1-piperazinyl)-benzenesulfonic acid monohydrate	133804-44-1			Cardiostimulant	Heart failure
Calusterone		17021-26-0				
Camazepam		36104-80-0				
camostat	Benzeneacetic acid, 4-[[4-[(aminoiminomethyl)amino]benzoyl]oxy]-, 2-(dimethylamino)-2-oxoethyl ester, monomethanesulfonate [CAS]	59721-28-7 59721-29-8 71079-09-9	US	4021472	GI inflammatory/bowel disorders	Pancreatitis
Camphor		76-22-2				
Camphotamide		4876-45-3				
camptothecin	4-Ethyl-4-hydroxy-1H-pyrano-[l3'4':6,7]indolizinol[1,2-b;]quinoline-3,14(4H,12H)-dione				Formulation, optimized, microemulsion	Cancer, general
Candesartan		139481-59-7				
candesartan cilexetil	1H-Benzimidazole-7-carboxylic acid, 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, 1-[[(cyclohexyloxy)carbonyl]oxy]ethyl ester, (+/-)- [CAS]	145040-37-5	EP	520423	Antihypertensive, renin system	Hypertension, general
Candoxatril		123122-55-4				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
canertinib	N-[4-(3-(Chloro-4-fluoro-phenylamino)-7-(3-morpholin-4-yl-propoxy)-quinazolin-6-yl]-acrylamide	289499-45-2			Anticancer, other	Cancer, lung, *non-small cell*
Canrenone		976-71-6				
Cantharidin		56-25-7				
cantuzumab mertansine	Maytansine, N2-deacetyl-N2-(3-mercapto-1-oxopropyl)-, conjugated humanized C242 monoclonal antibody	139504-50-0			Immunotoxin	Cancer, colorectal
capecitabine	Cytidine, 5-deoxy-5-fluoro-N-[(pentyloxy)carbonyl]- [CAS]	154361-50-9	EP	602454	Anticancer, antimetabolite	Cancer, breast
Capobenic Acid		21434-91-3				
capravirine	1H-imidazole-2-methanol, 5-(3,5-dichlorophenyl)thio-4-(1-methylethyl)-1-(4-pyridinyl)methyl carbamate (ester) [CAS]	178979-85-6			Antiviral, anti-HIV	Infection, HIV/AIDS
Capromab		151763-64-3				
capsaicin cream	N-[(4-hydroxy-3-methoxyphenyl)methyl]-8-methyl-, (E)- [CAS]	404-86-4			Formulation, dermal, topical	Pain, post-herpetic
Captodiamine		486-17-9				
captopril	L-Proline, 1-(3-mercapto-2-methyl-1-oxopropyl)-, (S)- [CAS]	62571-86-2	US	4105776	Antihypertensive, renin system	Hypertension, general
captopril + HCTZ	L-Proline, 1-(3-mercapto-2-methyl-1-oxopropyl)-, (S)-, mixt. with 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide [CAS]	110075-07-5	US	4217347	Antihypertensive, renin system	
Capuride		5579-13-5				
carabersat	Benzamide, N-(6-acetyl-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-4-yl)-4-fluoro, (3R-trans)- [CAS]	184653-84-7	WO	9811890	Antiepileptic	Epilepsy, general
Caramiphen		77-22-5				
carazolol	2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[(1-methylethyl)amino]- [CAS]	57775-29-8	DE	2240599	Antihypertensive, adrenergic	
Carbachol		51-83-2				
carbamazepine	5H-Dibenz[b,f]azepine-5-carboxamide [CAS]	298-46-4			Formulation, modified-release, other	Epilepsy, general

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Carbamide Peroxide		124-43-6				
Carbarsone		121-59-5				
Carbaryl		63-25-2				
Carbazochrome		13051-01-9 51460-26-5				
carbendazim	Methyl-2-benzimidazolecarbamate				Anticancer, other	Cancer, general
Carbenicillin		4697-36-3				
Carbenoxolone		5697-56-3				
Carbetapentane		77-23-6				
Carbicarb	Carbonic acid disodium salt, mixt. with monosodium salt- [CAS]	72227-05-5			Alimentary/Metabolic, other	Acidosis
Carbidopa		28860-95-9				
carbidopa+levodopa-1	S-Alpha Hydrazino-3,4-dihydroxy-Alpha methyl benzene propanoic acid monohydrate +3-hydroxy-L-tyrosine				Formulation, fixed-dose combinations	Parkinson's disease
Carbimazole		22232-54-8				
Carbinoxamine		486-16-8				
Carbocloral		541-79-7				
carbocysteine		151756-26-2 638-23-3	EP	546272	Cystic fibrosis treatment	Cystic fibrosis
Carbon Tetrachloride		56-23-5				
carboplatin	Platinum, diammine[1,1-cyclobutanedicarboxylato(2-)]-, (SP-4-2)- [CAS]	41575-94-4			Anticancer, alkylating	Cancer, ovarian
Carboprost		35700-23-3				
carboprost trometamol	Prosta-5,13-dien-1-oic acid, 9,11,15-trihydroxy-15-methyl-, (5Z,9.alpha.,11Alpha,13E,15S)-, compd. with 2-amino-2-(hydroxymethyl)-1,3-propanediol(1:1) [CAS]	58551-69-2 74849-93-7	US	3728382	Prostaglandin	Abortion
Carboquone	2,5-Cyclohexadiene-1,4-dione, 2-[2-[(aminocarbonyl)oxy]-1-methoxyethyl]-3,6-bis(1-aziridinyl)-5-methyl- [CAS]	24279-91-2	DE	1905224	Anticancer, antibiotic	
Carbromal		77-65-6				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Carbubarb		960-05-4				
Carbutamide		339-43-5				
Carbuterol		34866-47-2				
Carfimate		3567-38-2				
carglumic acid	N-Carbamoyl-L-glutamic acid	1188-38-1			Metabolic and enzyme disorders	Hyperammonaemia
Cargutocin		33605-67-3				
Carindacillin		35531-88-5				
cariporide	Benzamide, N-(aminoiminomethyl)-4-(1-methylethyl)-3-(methylsulfonyl)- [CAS]	159138-80-4 159138-81-5	EP	589336	Antianginal	Angina, general
Cariporide		159138-80-4				
Carisoprodol		78-44-4				
carmofur	1(2H)-Pyrimidinecarboxamide, 5-fluoro-N-hexyl-3,4-dihydro-2,4-dioxo- [CAS]	61422-45-5	US	4071519	Anticancer, antimetabolite	
Carmoxirole		98323-83-2				
carmustine	Urea, N,N'-bis(2-chloroethyl)-N-nitroso- [CAS]	154-93-8			Formulation, implant	Cancer, brain
Carnitine		461-06-3				
Caroverine		23465-76-1				
Caroxazone		18464-39-6				
Carphenazine		2622-30-2				
Carpipramine		5942-95-0				
carprofen	9H-Carbazole-2-acetic acid, 6-chloro-Alpha-methyl-, (+/-)- [CAS]	53716-49-7	US	3896145	Anti-inflammatory	
Carsalam		2037-95-8				
carteolol	2(1H)-Quinolinone, 5-[3-[(1,1-dimethylethyl)amino]-2-hydroxypropoxy]-3,4-dihydro-, monohydrochloride [CAS]	51781-06-7 51781-21-6	US	3910924	Antihypertensive, adrenergic	Glaucoma
Carticaine		23964-58-1				
Carubicin		50935-04-1				
Carumonam		87638-04-8				
Carvacrol		499-75-2				
carvedilol	2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-[CAS]	72956-09-3	EP	4920	Antihypertensive, adrenergic	Hypertension, general

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Carvone		99-49-0				
Cascarillin		10118-56-6				
caspofungin	Pneumocandin B0, 1-((4R,5S)-5-((2-aminoethyl)amino)-N2-(10,12-dimethyl-1-oxotetradecyl)-4-hydroxy-L-ornithine)-5-(threo-3-hydroxy-L-ornithine)-, diacetate (salt) [CAS]	162808-62-0 179463-17-3	WO	9421677	Antifungal	Infection, Aspergillus
Catechin		154-23-4				
cathepsin K inhibitors	N-(1-benzothien-2-ylcarbonyl)-N-[2-(2-fluorophenyl)-4-oxo-1,2,3,4-tetrahydropyrimidin-5-yl]-L-leucinamide		WO	9613523	Osteoporosis treatment	Osteoporosis
cathepsin S inhibitors	N-(1-benzothien-2-ylcarbonyl)-N-[2-(2-fluorophenyl)-4-oxo-1,2,3,4-tetrahydropyrimidin-5-yl]-L-leucinamide				Antiasthma	Asthma
CC-401			US	6342595	Immunosuppressant	Arthritis, rheumatoid
CCI-779	Rapamycin 42-(3-hydroxy-2-(hydroxymethyl)-2-methylpropanoate) [CAS]	162635-04-3			Anticancer, antibiotic	Cancer, renal
CCR5 antagonists			WO	9732019	Antiviral, anti-HIV	Infection, HIV/AIDS
CDC-394			US	634061	Anticancer, other	Cancer, myeloma
CDC-801			US	5605914	GI inflammatory/bowel disorders	Crohn's disease
CEE-03-310	1H-3-Benzazepin-7-ol, 5-(2,3-dihydro-7-benzofuranyl)- 2,3,4,5,-tetrahydro-3-methyl-8-nitro, (5S)- [CAS]	128022-68-4	EP	347672	Dependence treatment	Addiction, alcohol
cefaclor	5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[(aminophenylacetyl)amino]-3-chloro-8-oxo-, [6R-[6Alpha,7ß(R*)]]- [CAS]	53994-73-3 70356-03-5	GB	1461323	Cephalosporin, oral	Infection, Haemophilus influenzae prophylaxis
cefadroxil	5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[[amino(4-hydroxyphenyl)acetyl]amino]-3-methyl-8-oxo-, [6R-[6Alpha,7ß(R*)]]- [CAS]	50370-12-2 66592-87-8	GB	1240687	Cephalosporin, oral	Infection, general
cefalexin	5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[(aminophenylacetyl)amino]-3-methyl-8-oxo-, [CAS]	105879-42-3 15686-71-2	US	4775751	Cephalosporin, oral	Infection, respiratory tract, upper

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
cefalexin pivoxil	5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[(aminophenylacetyl)amino]-3-methyl-8-oxo-, (2,2-dimethyl-1-oxopropoxy)methyl ester, monohydrochloride, [6R-[6Alpha,7ß(R*)]]- [CAS]	27726-31-4			Cephalosporin, oral	Infection, general
cefamandole	7-D-mandelamido-3[[(1-methyl-1H-tetrazol-5-yl)thio]methyl]-3-cephem-4-carboxylic acid	34444-01-4	US	3641021	Cephalosporin, injectable	Infection, general
cefatrizine	5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[[amino(4-hydroxyphenyl)acetyl]amino]-8-oxo-3-[(1H-1,2,3-triazol-4-ylthio)methyl]-, [6R-[6Alpha,7ß(R*)]]- [CAS]	51627-14-6	GB	1460914	Cephalosporin, oral	Infection, general
Cefazedone		56187-47-4				
Cefazolin		25953-19-9				
Cefbuperazone		76610-84-9				
cefcapene pivoxil	7ß-[(Z)-2-(2-amino-4-thiazolyl)-2-pentenoylamino]-3-carbamoyloxymethyl-3-cephem-4-carboxylic acid, pivaloyloxymethyl ester HCl- [CAS]	105889-45-0 105889-46-1	GB	2173194	Cephalosporin, oral	Infection, respiratory tract, general
Cefclidin		105239-91-6				
cefdinir	5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[[(2-amino-4-thiazolyl)(hydroxyimino)acetyl]amino]-3-ethenyl-8-oxo-, [6R-[6Alpha,7ß(Z)]]- [CAS]	91832-40-5	EP	105459	Cephalosporin, oral	Infection, dermatological
cefditoren pivoxil	5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[[(2-amino-4-thiazolyl)(methoxyimino)acetyl]amino]-3-[2-(4-methyl-5-thiazolyl)ethenyl]-8-oxo-, (2,2-dimethyl-1-oxopropoxy)methyl ester, [6R-[3(Z),6Alpha,7ß(Z)]]- [CAS]	104145-95-1 104146-53-4 117467-28-4	JP	61178991	Cephalosporin, oral	Infection, general

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
cefepime	Pyrrolidinium, 1-[[7-[[(2-amino-4-thiazolyl)(methoxyimino)acetyl]amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-1-methyl-, hydroxide, inner salt, [6R-[6Alpha,7ß(Z)]]- [CAS]	107648-80-6 123171-59-5 88040-23-7	EP	531981	Cephalosporin, injectable	Infection, respiratory tract, lower
Cefetamet		65052-63-3				
cefetamet pivoxil	5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[[(2-amino-4-thiazolyl)(methoxyimino)acetyl]amino]-3-methyl-8-oxo-, (2,2-dimethyl-1-oxopropoxy)methyl ester, monohydrochloride, [6R-[6Alpha,7ß(Z)]]- [CAS]	111696-23-2	GB	1581854	Cephalosporin, oral	Infection, general
cefixime	5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[[(2-amino-4-thiazolyl)[(carboxymethoxy)imino]acetyl]amino]-3-ethenyl-8-oxo-, [6R-[6Alpha,7ß(Z)]]- [CAS]	79350-37-1	EP	30630	Cephalosporin, oral	Infection, general
cefmenoxime	5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[[(2-amino-4-thiazolyl)(methoxyimino)acetyl]amino]-3-[[(1-methyl-1H-tetrazol-5-yl)thio]methyl]-8-oxo-, [6R-[6Alpha,7ß(Z)]]- [CAS]	65085-01-0 75738-58-8	GB	1536281	Cephalosporin, injectable	Infection, ocular
cefmetazole	5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[[[(cyanomethyl)thio]acetyl]amino]-7-methoxy-3-[[(1-methyl-1H-tetrazol-5-yl)thio]methyl]-8-oxo-, (6R-cis)- [CAS]	56796-20-4 56796-39-5	GB	1449420	Cephalosporin, injectable	Infection, general
cefminox	5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[[[(2-amino-2-carboxyethyl)thio]acetyl]amino]-7-methoxy-3-[[(1-methyl-1H-tetrazol-5-yl)thio]methyl]-8-oxo-, [6R-[6Alpha,7Alpha,7(S*)]]- [CAS]	84305-41-9	EP	24879	Cephalosporin, injectable	Infection, urinary tract

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
cefodizime	5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[[(2-amino-4-thiazolyl)(methoxyimino)acetyl]amino]-3-[[[5-(carboxymethyl)-4-methyl-2-thiazolyl]thio]methyl]-8-oxo-, [6R-[6Alpha,7ß(Z)]]- [CAS]	69739-16-8 86329-79-5	US	4590267	Cephalosporin, injectable	Infection, respiratory tract, lower
cefonicid	5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[(hydroxyphenylacetyl)amino]-8-oxo-3-[[[1-(sulfomethyl)-1H-tetrazol-5-yl]thio]methyl]-, disodium salt, [6R-[6Alpha,7ß(R*)]]- [CAS]	61270-78-8 61270-58-4	GB	1547473	Cephalosporin, injectable	Infection, general
cefoperazone	5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[[[[(4-ethyl-2,3-dioxo-1-piperazinyl)carbonyl]amino](4-hydroxyphenyl)acetyl]amino]-3-[[(1-methyl-1H-tetrazol-5-yl)thio]methyl]-8-oxo-, [6R-[6Alpha,7ß(R*)]]- [CAS]	62893-19-0	GB	1508071	Cephalosporin, injectable	Infection, general
cefoperazone + sulbactam		92739-15-6	US	4234579	Antibiotic, other	Infection, general
Ceforanide		60925-61-3				
cefoselis	5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[[(2-amino-4-thiazolyl)(methoxyimino)acetyl]amino]-3-[[2,3-dihydro-2-(2-hydroxyethyl)-3-imino-1H-pyrazol-1-yl]methyl]-8-oxo-, [6R-[6Alpha,7ß(Z)]]	122841-12-7 122841-10-5	EP	307804	Cephalosporin, injectable	Infection, general
cefotaxime	(6R,7R)-7-[[(2-amino-4-thiazolyl)(methoxyimino)acetyl]amino]cephalosporanic acidsodium salt	64485-93-4 63527-52-6	GB	1580621	Cephalosporin, injectable	Infection, general
Cefotetan		69712-56-7				
cefotiam	5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[[(2-amino-4-thiazolyl)acetyl]amino]-3-[[[1-[2-(dimethylamino)ethyl]-1H-tetrazol-5-yl]thio]methyl]-8-oxo-, (6R-trans)- [CAS]	61622-34-2 66309-69-1	US	4080498	Cephalosporin, injectable	Infection, general

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
cefotiam hexetil	1-(cyclohexyloxycarbonyloxy)ethyl 7ß-[2-(2-aminothiazol-4-yl)acetamido]-3-[[[1-(2-dimethylaminoethyl)-1H-tetrazol-5-yl]thio]methyl]ceph-3-em-4-carboxylate 2HCl [CAS]	95789-30-3	EP	128029	Cephalosporin, oral	Infection, respiratory tract, lower
cefoxitin	5-Thia-1-azabicyclo(4.2.0)oct-2-ene-2-carboxylic acid, 3-(((aminocarbonyl)oxy)methyl)-7-methoxy-8-oxo-7-((2-thienylacetyl)amino)-, monosodium salt, (6R-cis)- [CAS]	33564-30-6 35607-66-0	GB	1348984	Cephalosporin, oral	Infection, general
cefozopran	Imidazo[1,2-b]pyridazinium, 1-[[7-[[(5-amino-1,2,4-thiadiazol-3-yl)(methoxyimino)acetyl]amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-, hydroxide, inner salt, [6R-[6Alpha,7ß(Z)]]- [CAS]	113359-04-9	EP	203271	Cephalosporin, injectable	Infection, general
cefpimizole	Pyridinium, 1-[[2-carboxy-7-[[[[(5-carboxy-1H-imidazol-4-yl)carbonyl]amino]phenylacetyl]amino]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-4-(2-sulfoethyl)-, hydroxide, inner salt, [6R-[6Alpha,7ß(R*)]]- [CAS]	84880-03-5 85287-61-2	EP	60028	Cephalosporin, injectable	Infection, respiratory tract, general
cefpiramide	5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[[[[(4-hydroxy-6-methyl-3-pyridinyl)carbonyl]amino](4-hydroxyphenyl)acetyl]amino]-3-[[(1-methyl-1H-tetrazol-5-yl)thio]methyl]-8-oxo-, [6R-[6Alpha,7ß(R*)]]- [CAS]	70797-11-4	US	4156724	Cephalosporin, injectable	Infection, general
cefpirome	5H-1-Pyrindinium, 1-[[7-[[(2-amino-4-thiazolyl)(methoxyimino)acetyl]amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-6,7-dihydro-,hydroxide, inner salt, [6R-[6Alpha,7ß(Z)]]- [CAS]	84957-29-9 98753-19-6	EP	64740	Cephalosporin, injectable	Infection, respiratory tract, lower
Cefpodoxime Proxetil		87239-81-4				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
cefprozil	5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[[amino(4-hydroxyphenyl)acetyl]amino]-8-oxo-3-(1-propenyl)-, [6R-[6Alpha,7ß(R*)]]- [CAS]	92665-29-7 121123-17-9	GB	2173798	Cephalosporin, oral	Infection, dermatological
cefroxadine	5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[(amino-1,4-cyclohexadien-1-ylacetyl)amino]-3-methoxy-8-oxo-, [6R-[6Alpha,7ß(R*)]]- [CAS]	51762-05-1	GB	1435111	Cephalosporin, oral	Infection, general
cefsulodin	Pyridinium, 4-(aminocarbonyl)-1-[[2-carboxy-8-oxo-7-[(phenylsulfoacetyl)amino]-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-, hydroxide, inner salt, [6R-[6Alpha,7ß(R*)]]- [CAS]	52152-93-9 62587-73-9	GB	1387656	Cephalosporin, injectable	Infection, pseudomonal
ceftazidime	Pyridinium, 1-[[7-[[(2-amino-4-thiazolyl)[(1-carboxy-1-methylethoxy)imino]acetyl]amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-, hydroxide, inner salt, [6R-[6Alpha,7ß(Z)]]- [CAS]	72558-82-8	GB	2025398	Cephalosporin, injectable	Infection, respiratory tract, upper
Cefteram		82547-58-8				
Ceftezole		26973-24-0				
ceftibuten	5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[[2-(2-amino-4-thiazolyl)-4-carboxy-1-oxo-2-butenyl]amino]-8-oxo-, [6R-[6Alpha,7ß(Z)]]- [CAS]	97519-39-6	EP	136721	Cephalosporin, oral	Infection, respiratory tract, lower
ceftizoxime	5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[[(2-amino-4-thiazolyl)(methoxyimino)acetyl]amino]-8-oxo-, [6R-[6Alpha,7ß(Z)]]- [CAS]	68401-81-0 68401-82-1	GB	1600735	Cephalosporin, injectable	Infection, general

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
ceftizoxime alapivoxil	5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[[[2-[(2-amino-1-oxopropyl)amino]-4-thiazolyl](methoxyimino)acetyl]amino]-8-oxo-, (2,2-dimethyl-1-oxopropoxy)methyl ester, monohydrochloride, [6R-[6Alpha,7ß(Z(S*))]]- [CAS]	113812-94-5 135767-36-1	JP	62209112	Cephalosporin, oral	Infection, general
ceftriaxone	5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[[(2-amino-4-thiazolyl)(methoxyimino)acetyl]amino]-8-oxo-3-[[(1,2,5,6-tetrahydro-2-methyl-5,6-dioxo-1,2,4-triazin-3-yl)thio]methyl]-, [6R-[6Alpha,7ß(Z)]]- [CAS]	73384-59-5 74578-69-1	GB	2022090	Cephalosporin, injectable	Infection, respiratory tract, lower
cefuroxime axetil	5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 3-[[(aminocarbonyl)oxy]methyl]-7-[[2-furanyl(methoxyimino)acetyl]amino]-8-oxo-, 1-(acetyloxy)ethyl ester, [6R-[6Alpha,7ß(Z)]]- [CAS]	15686-71-2 64544-07-6	GB	1571683	Cephalosporin, oral	Infection, respiratory tract, upper
cefuroxime	5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 3-[[(aminocarbonyl)oxy]methyl]-7-[[2-furanyl(methoxyimino)acetyl]amino]-8-oxo-, [6R-[6Alpha,7ß(Z)]]- [CAS]	55268-75-2 56238-63-2	GB	1453049	Cephalosporin, injectable	Infection, general
Cefuzonam		82219-78-1				
celecoxib	Benzenesulfonamide, 4-(5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)- [CAS]	169590-42-5	US	5760068	Antiarthritic, other	Arthritis, rheumatoid
celgosivir	Butanoic acid, octahydro-1,7,8-trihydroxy-6-indolizinyl ester, [1S-(1Alpha,6ß,7Alpha,8ß,8aß)]- [CAS]	121104-96-9	US	5017563	Antiviral, other	Infection, hepatitis virus, general
celiprolol	Urea, N'-[3-acetyl-4-[3-[(1,1-dimethylethyl)amino]-2-hydroxypropoxy]phenyl]-N,N-diethyl- [CAS]	56980-93-9 57470-78-7	GB	1441359	Antihypertensive, adrenergic	Angina, unstable
Cellulose Ethyl Hydroxyethyl Ether		9004-58-4				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Centchroman		31477-60-8				
CEP-1347	9,12-Epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocine-10-carboxylic acid, 5,16-bis((ethylthio)methyl)-2,3,9,10,11,12-hexahydro-10-hydroxy-9-methyl-1-oxo-, methyl ester, (9S,10R,12R)-[CAS]	156177-65-0	WO	9731002	Antiparkinsonian	Parkinson's disease
CEP-701	9,12-Epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocin-1-one, 2,3,9,10,11,12-hexahydro-10-hydroxy-10-(hydroxymethyl)-9-methyl-, (9S,10S,12R)-[CAS]	111358-88-4			Anticancer, antimetabolite	Cancer, prostate
Cephacetrile		23239-41-0				
Cephaeline		483-17-0				
Cephalexin		15686-71-2				
Cephaloglycin		3577-1-3				
Cephaloridine		50-59-9				
Cephalosporin C		61-24-5				
Cephalothin		153-61-7				
Cephapirin		24356-60-3				
Cephradine		38821-53-3				
Cerivastatin		145599-86-6				
Ceronapril		111223-26-8				
certoparin	Heparin [CAS]	9005-49-6			Anticoagulant	Thrombosis, venous
Ceruletide		17650-98-5				
Cerviprost	Prosta-5,13-dien-1-oic acid, 11,15-dihydroxy-9-oxo-, (5Z,11Alpha,13E,-15S)-[CAS]	363-24-6			Formulation, dermal, topical	
Cetalkonium		122-18-9				
Cetamolol		34919-98-7				
Cethexonium		1794-74-7				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
cethromycin	2H-Oxacyclotetradecino(4,3-d)oxazole-2,6,8,14(1H,7H,9H)-tetrone 4-ethyloctahydro-3a,7,9,11,13,15-hexamethyl-11-((3-(3-quinolinyl)-2-propenyl)oxy)-10-((3,4,6-trideoxy-3-(dimethylamino)-ß-D-xylo-hexapyranosyl)oxy)-,(3a S,4R,7R,9R,10R,11R,13R,15R,15aR)-[CAS]	205110-48-1	EP	929563	Macrolide antibiotic	Infection, respiratory tract, general
Cetiedil		14176-10-4				
Cetirizine		83881-51-0				
cetirizine	Acetic acid, [2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-, [CAS]	83881-51-0 83881-52-1	EP	58146	Antiallergic, non-asthma	Allergy, general
cetirizine+pseudoephedrine	Acetic acid, [2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-, dihyrochloride, Benzenemethanol, Alpha-[1-(methylamino)ethyl]-, hydrochloride, [S-(R*R*)]-	83881-52-1 90-82-4			Formulation, optimized, microencapsulate	Allergy, general
Cetotiamine		137-76-8				
Cetoxime		25394-78-9				
cetraxate	Benzenepropanoic acid, 4-[[[4-(aminomethyl)cyclohexyl]carbonyl]oxy]-, trans-[CAS]	27724-96-5 34675-84-8	JP	48075547	Antiulcer	
Cetrimonium		57-09-0				
Cetrorelix		120287-85-6				
Cetyldimethylethylammonium		124-03-8				
Cetylpyridinium		123-03-5				
cevimeline	Spiro[1-azabicyclo[2.2.2]octane-3,5'-[1,3]oxathiolane], 2'-methyl-, cis- [CAS]	107220-27-9 107233-08-9	EP	205247	Stomatological	Sjogren's syndrome
CG-1521	7-phenyl-2,4,6-heptatrienoylhydroxamic acid				Anticancer, other	Cancer, general
Chaulmoogric Acid		29106-32-9				
Chenodiol		474-25-9				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
CHF-3381			EP	951465	Analgesic, other	Pain, neuropathic
Chlophedianol		791-35-5				
Chloracizine		800-22-6				
chloral	1,1-Ethanediol, 2,2,2-trichloro- [CAS]	302-17-0 2218-68-0 515-82-2			Formulation, transmucosal, systemic	Insomnia
Chlorambucil		305-03-3				
Chloramine-B		127-52-6				
Chloramine-T		127-65-1				
Chloraminophenamide		121-30-2				
Chloramphenicol		56-75-7				
Chlorazanil		500-42-5				
Chlorbenzoxamine		522-18-9				
Chlorbetamide		97-27-8				
Chlorcyclizine		82-93-9				
Chlordantoin		5588-20-5				
Chlordiazepoxide		58-25-3				
Chlorguanide		500-92-5				
Chlorhexadol		3563-58-4				
chlorhexidine	2,4,11,13-Tetraazatetradecanediimidamide, N,N''-bis(4-chlorophenyl)-3,12-diimino- [CAS]	55-56-1			Formulation, other	Xerostomia, Periodontitis
Chlorisondamine		69-27-2				
Chlormadinone		302-22-7				
Chlormerodrin		62-37-3				
Chlormezanone		80-77-3				
Chlormidazole		3689-76-7				
Chlornaphazine		494-03-1				
Chloroazodin		502-98-7				
Chlorophyll		1406-65-1				
Chloroprednisone		52080-57-6				
Chloroprocaine		3858-89-7				
Chloropyramine		59-32-5				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Chloroquine		54-05-7				
Chlorothen		148-65-2				
Chlorothiazide		58-94-6				
Chlorotrianisene		569-57-3				
Chloroxine		773-76-2				
Chloroxylenol		88-04-0				
Chlorozotocin		54749-90-5				
chlorphenamine	2-Pyridinepropanamine, Gamma-(4-chlorophenyl)-N,N-dimethyl- [CAS]	132-22-9			Formulation, modified-release, other	Allergy, general
Chlorphenesin		104-29-0 886-74-8				
Chlorpheniramine		132-22-9				
Chlorphenoxamide		3576-64-5				
Chlorphenoxamine		77-38-3				
Chlorphentermine		461-78-9				
Chlorproethazine		84-01-5				
Chlorproguanil		537-21-3				
chlorproguanil + dapsone	4,4'-Sulfonyldianiline + 1-(3,4-Dichlorophenyl)5-isopropylbiguanide	537-21-3 80-08-0			Antimalarial	Infection, malaria
Chlorpromazine		50-53-3				
Chlorpropamide		94-20-2				
Chlorprothixene		113-59-7				
Chlorquinaldol		72-80-0				
Chlortetracycline		57-62-5				
Chlorthalidone		77-36-1				
Chlorthenoxazin(e)		132-89-8				
Chlorzoxazone		95-25-0				
Cholic Acid		81-25-4				
Choline		67-48-1 2016-36-6 28319-77-9				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
choline theophyllinate	Ethanaminium, 2-hydroxy-N,N,N-trimethyl-, salt with 3,7-dihydro-1,3-dimethyl-1H-purine-2,6-dione (1:1) [CAS]	4499-40-5			Formulation, modified-release, other	
choline-L-alfoscerate	Ethanaminium, 2-[[(2,3-dihydroxypropoxy)hydroxyphosphinyl]oxy]-N,N,N-trimethyl-, hydroxide, inner salt, (R)- [CAS]	28319-77-9	JP	55028955	Cognition enhancer	Amnesia
Chromocarb		4940-39-0				
Chromonar		804-10-4				
Chrysoidine		532-82-1				
CHS-828	Guanidine, N-[6-(4-chlorophenoxy)hexyl]-N'-cyano-N"-4-pyridinyl- [CAS]	200484-11-3	US	5696140	Anticancer, other	Cancer, general
CI-1031	Glycine, N-[2-[5-(aminoiminomethyl)-2-hydroxyphenoxy]-6-[3-(4,5-dihydro-1-methyl-1H-imidazol-2-yl)phenoxy]-3,5-difluoro-4-pyridinyl]-N-methyl- [CAS]	183305-24-0	WO	9638421	Antianginal	Angina, unstable
CI-1040	Benzamide, 2-[(2-chloro-4-iodophenyl)amino]-N-(cyclopropylmethoxy)-3,4-difluoro- [CAS]	212631-79-3	WO	9837881	Anticancer, other	Cancer, general
cibenzoline	1H-Imidazole, 2-(2,2-diphenylcyclopropyl)-4,5-dihydro- [CAS]	53267-01-9	GB	1417174	Antiarrhythmic	Arrhythmia, general
ciclesonide	Pregna-1,4-diene-3,20-dione 16,17-((cyclohexylmethylene)bis(oxy))-11-hydroxy-21-(2-methyl-1-oxopropoxy) (11ß,16Alpha) [CAS]	126544-47-6	DE	4129535	Antiasthma	Asthma
cicletanine	Furo[3,4-c]pyridin-7-ol, 3-(4-chlorophenyl)-1,3-dihydro-6-methyl-, (+/-)- [CAS]	82747-56-6 89943-82-8	US	4383998	Antihypertensive, other	
ciclonicate	3-Pyridinecarboxylic acid, 3,3,5-trimethylcyclohexyl ester, trans- [CAS]	53449-58-4	DE	1910481	Vasodilator, peripheral	Cancer, lung, small cell
ciclopirox	2(1H)-Pyridinone, 6-cyclohexyl-1-hydroxy-4-methyl-, [CAS]	41621-49-2 29342-05-0	US	3883545	Antifungal	Infection, fungal, general
Ciclosidomine		66564-16-7				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
ciclosporin A	Cyclosporin A- [CAS]	59865-13-3			Formulation, optimized, microemulsion	Transplant rejection, general
cidofovir	Phosphonic acid, [[2-(4-amino-2-oxo-1(2H)-pyrimidinyl)-1-(hydroxymethyl)ethoxy]methyl]-, (S)- [CAS]	113852-37-2	EP	253412	Antiviral, other	Infection, cytomegalovirus
Cifenline		53267-01-9				
cilansetron	4H-Pyrido[3,2,1-jk]carbazol-11(8H)-one, 5,6,9,10-tetrahydro-10-[(2-methyl-1H-imidazol-1-yl)methyl]-, (R)- [CAS]	120635-74-7	EP	297651	GI inflammatory/bowel disorders	Irritable bowel syndrome
Cilastatin		82009-34-5				
cilazapril	6H-Pyridazino[1,2-a][1,2]diazepine-1-carboxylic acid, 9-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]octahydro-10-oxo-, [1S-[1Alpha,9Alpha(R*)]]- [CAS]	88768-40-5 90139-06-3	GB	2128984	Antihypertensive, renin system	Hypertension, general
cilengitide	Cyclo(L-arginylglycyl-L-Alpha-aspartyl-D-phenylalanyl-N-methyl-L-valyl) [CAS]	188968-51-6	EP	770622	Anticancer, other	Cancer, lung, non-small cell
cilnidipine	3,5-Pyridinedicarboxylic acid, 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-, 2-methoxyethyl 3-phenyl-2-propenyl ester- [CAS]	102106-21-8 132203-70-4	EP	161877	Antihypertensive, other	Hypertension, general
cilomilast	Cis-4-cyano-4-[3-(cyclopentyloxy)-4-methoxyphenyl]cyclohexane-1-carboxylic acid	153259-65-5	US	5602157	COPD treatment	Chronic obstructive pulmonary disease
cilostazol	2(1H)-Quinolinone, 6-[4-(1-cyclohexyl-1H-tetrazol-5-yl)butoxy]-3,4-dihydro-[CAS]	73963-72-1	GB	2033893	Antithrombotic	Peripheral vascular disease
Cimetidine		51481-61-9				
cimetropium	3-Oxa-9-azoniatricyclo[3.3.1.02,4]nonane, 9-(cyclopropylmethyl)-7-(3-hydroxy-1-oxo-2-phenylpropoxy)-9-methyl-, [7(S)-(1Alpha,2ß,4ß,5Alpha,7ß)]-[CAS]	51598-60-8	US	3853886	Antispasmodic	Muscle spasm, general
cinacalcet	1-napthalenemethanamine,Alpha-methyl-N-[3-[3-(trifluoromethyl)phenyl]propyl]-, (AlphaR)-,	364782-34-3			Hormone	Hyperparathyroidism

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Cinchonidine		485-71-2				
Cinchonine		118-10-5				
Cinchophen		132-60-5				
Cinepazet		23887-41-4				
Cinepazide		23887-46-9				
cinepazide	Piperazine, 1-[2-oxo-2-(1-pyrrolidinyl)ethyl]-4-[1-oxo-3-(3,4,5-trimethoxyphenyl)-2-propenyl]-, (Z)-2-butenedioate (1:1) [CAS]	26328-04-1	GB	1218591	Vasodilator, peripheral	Peripheral vascular disease
Cinitapride		66564-14-5				
Cinmetacin		20168-99-4				
Cinnamedrine		90-86-8				
Cinnarizine		298-57-7				
cinolazepam	1H-1,4-Benzodiazepine-1-propanenitrile, 7-chloro-5-(2-fluorophenyl)-2,3-dihydro-3-hydroxy-2-oxo- [CAS]	75696-02-5	DE	2950235	Hypnotic/Sedative	Insomnia
cinoxacin	[1,3]Dioxolo[4,5-g]cinnoline-3-carboxylic acid, 1-ethyl-1,4-dihydro-4-oxo-[CAS]	28657-80-9	GB	1296753	Quinolone antibacterial	Infection, urinary tract
Cinoxate		104-28-9				
Cinromide		58473-74-8				
Cioteronel		89672-11-7				
cipamfylline	1H-Purine-2,6-dione, 8-amino-1,3-bis(cyclopropylmethyl)-3,7-dihydro- [CAS]	132210-43-6	EP	389282	Antipruritic/inflamm, allergic	Eczema, atopic
cipralisant	1H-Imidazole, 4-[(1R,2R)-2-(5,5-dimethyl-1-hexynyl)cyclopropyl]- [CAS]	213027-19-1	US	6008240	Psychostimulant	Attention deficit disorder
ciprofibrate	Propanoic acid, 2-[4-(2,2-dichlorocyclopropyl)phenoxy]-2-methyl- [CAS]	52214-84-3	GB	1385828	Hypolipaemic/Antiatherosclerosis	Hyperlipidaemia, general
ciprofloxacin	3-Quinolinecarboxylic acid, 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)- [CAS]	85721-33-1	US	4670444	Quinolone antibacterial	Infection, general

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
ciprofloxacin+fluocinolone,SAL	3-Quinolinecarboxylic acid, 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)- + (6Alpha, 11ß, 16Alpha)-6,9-Difluoro-11,21-dihydroxy-16,17-[(1-methylethylidene)bis-(oxy)]-pregna-1,4-diene-3,20-dione				Formulation, fixed-dose combinations	Otitis
Ciramadol		63269-31-8				
cisapride	Benzamide, 4-amino-5-chloro-N-[1-[3-(4-fluorophenoxy)propyl]-3-methoxy-4-piperidinyl]-2-methoxy-, cis- [CAS]	81098-60-4	EP	76530	Gastroprokinetic	
cisatracurium	Isoquinolinium, 2,2'-[1,5-pentanediylbis[oxy(3-oxo-3,1-propanediyl)]]bis[1-[(3,4-dimethoxyphenyl)methyl]]-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-, [1R-[1Alpha,2Alpha(1'R*,2'R*)]]-, [CAS]	96946-42-8	US	5453510	Muscle relaxant	Surgery adjunct
cisplatin	Platinum, diamminedichloro-, (SP-4-2)- [CAS]	15663-27-1	US	4177263	Anticancer, alkylating	
citalopram	5-Isobenzofurancarbonitrile, 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro- [CAS]	59729-32-7 59729-33-8	GB	1526331	Antidepressant	Depression, general
citicoline	Cytidine 5'-(trihydrogen diphosphate), P'-[2-(trimethylammonio)ethyl]ester, hydroxide, inner salt [CAS]	987-78-0	JP	39006541	Cognition enhancer	Infarction, cerebral
Citiolone		1195-16-0				
Citric Acid		77-92-9				
Citrulline		372-75-8				
cizolirtine	Ethanamine, N,N-dimethyl-2-[(1-methyl-1H-pyrazol-5-yl)phenylmethoxy]-, 2-hydroxy-1,2,3-propanetricarboxylate [CAS]	142155-44-0			Urological	Incontinence
CJ-13610	4-(3-[4-(2-Methyl-imidazol-1-yl)-phenylsulfanyl]-phenyl)-tetrahydro-pyran-4-carboxylic acid amide				COPD treatment	Chronic obstructive pulmonary disease

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
CKD-602	1H-Pyrano[3',4':6,7]indolizino[1,2-b]quinoline-3,14(4H,12H)-dione, 4-ethyl-4-hydroxy-11-[2-[(1-methylethyl)amino]ethyl]-, monohydrochloride, (4S)- [CAS]	213819-48-8	WO	9902530	Anticancer, other	Cancer, ovarian
cladribine	Adenosine, 2-chloro-2'-deoxy- [CAS]	4291-63-8	EP	173059	Anticancer, antimetabolite	Cancer, leukaemia, hairy cell
Clanobutin		30544-61-7				
clarithromycin	Erythromycin, 6-O-methyl- [CAS]	81103-11-9	EP	41355	Macrolide antibiotic	Infection, respiratory tract, lower
Clavulanate, Disodium						
Clavulanic Acid		58001-44-8				
Clebopride		55905-53-8				
Clemastine		15686-51-8				
Clemizole		442-52-4				
Clenbuterol		37148-27-9				
Clentiazem		96125-53-0				
clevidipine	3,5-Pyridinedicarboxylic acid, 4-(2,3-dichlorophenyl)-1,4-dihydro-2,6-dimethyl-, methyl (1-oxobutoxy)methyl ester (±) [CAS]	167221-71-8	WO	9512578	Antihypertensive, other	Hypertension, general
clevudine	2,4(1H,3H)-Pyrimidinedione, 1-(2-deoxy-2-fluoro-ß-L-arabinofuranosyl)-5-methyl- [CAS]	163252-36-6			Antiviral, other	Infection, hepatitis-B virus
Clidanac		28968-07-2				
Clidinium		3485-62-9				
Clinafloxacin		105956-97-6				
Clindamycin		18323-44-9				
clindamycin + tretinoin	L-threo-Alpha-D-galacto-Octopyranoside, methyl 7-chloro-6,7,8-trideoxy-6-[[(1-methyl-4-propyl-2-pyrrolidinyl)carbonyl]amino]-1-thio-, (2S-trans)- + retinoic acid				Formulation, fixed-dose combinations	Acne

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
clindamycin	L-Threo-Alpha-D-galacto-octopyranoside, methyl 7-chloro-6,7,8-trideoxy-6-[[(1-methyl-4-propyl-2-pyrrolidinyl)carbonyl]amino]-1-thio-, 2-(dihydrogen phosphate), (2S-trans)-	18323-44-9 24729-96-2			Formulation, parenteral, other	Infection, gynaecological
Clinofibrate		30299-08-2				
Clinprost		88931-51-5				
clobazam	1H-1,5-Benzodiazepine-2,4(3H,5H)-dione, 7-chloro-1-methyl-5-phenyl- [CAS]	22316-47-8	GB	1214662	Anxiolytic	
Clobenfurol		3611-72-1				
Clobenoside		29899-95-4				
Clobenzepam		1159-93-9				
Clobenzorex		13364-32-4				
Clobenztropine		5627-46-3				
clobetasol	Pregna-1,4-diene-3,20-dione, 21-chloro-9-fluoro-11,17-dihydroxy-16-methyl-, (11ß,16ß)- [CAS]	25122-41-2			Formulation, dermal, topical	Psoriasis
clobetasone	Pregna-1,4-diene-3,11,20-trione, 21-chloro-9-fluoro-16-methyl-17-(1-oxobutoxy)-, (16ß)- [CAS]	25122-57-0 54063-32-0	GB	1253831	Antipruritic/inflamm, allergic	
Clobutinol		14860-49-2				
Clocapramine		47739-98-0				
Clocinizine		298-55-5				
Cloconazole		77175-51-0				
Clocortolone		4828-27-7				
clodronate	Phosphonic acid, (dichloromethylene)bis- [CAS]	22560-50-5			Osteoporosis treatment, Anticancer, hormonal	Pain, cancer, Hypercalcaemia of malignancy
Clodronic Acid		10596-23-3				
clofarabine	2-chloro-9-(2-deoxy-2-fluoro-ß-D-arabinofurasonyl)adenine				Anticancer, antimetabolite	Cancer, leukaemia, chronic lymphocytic

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
clofazimine	3-(p-chloroanilo)-10-(p-chlorophenyl)-2,10-dihydro-2-(isopropylimino)-phenazine	2030-63-9			Formulation, optimized, microencapsulate	Infection, tuberculosis
Clofenamide		671-95-4				
Clofibrate		637-07-0				
Clofibric Acid		882-09-7				
Cloflucarban		369-77-7				
Clofoctol		37693-01-9				
Cloforex		14261-75-7				
Clomacran		5310-55-4				
Clomestrone		4091-75-2				
Clometacin		25803-14-9				
Clomethiazole		533-45-9				
Clometocillin		1926-49-4				
Clomiphene		911-45-5				
Clomipramine		303-49-1				
Clomocycline		1181-54-0				
clonazepam	2H-1,4-Benzodiazepin-2-one, 5-(2-chlorophenyl)-1,3-dihydro-7-nitro- [CAS]	1622-61-3	US	4316897	Antiepileptic	Epilepsy, general
clonidine	1H-Imidazol-2-amine, N-(2,6-dichlorophenyl)-4,5-dihydro- [CAS]	4205-90-7	US	4060084	Formulation, transdermal, patch	Hypertension, general
Clonitazene		3861-76-5				
Clonitrate		2612-33-1				
Clonixin		17737-65-4				
Clopamide		636-54-4				
Clopenthixol		982-24-1				
Cloperastine		3703-76-2				
clopidogrel	Thieno[3,2-c]pyridine-5(4H)-acetic acid, Alpha-(2-chlorophenyl)-6,7-dihydro-, methyl ester, (S)- [CAS]	120202-48-4 90055-48-4 113665-84-2	EP	99802	Antithrombotic	Infarction, myocardial
Clopirac		42779-82-8				
Cloprednol		5251-34-3				
cloranolol	2-Propanol, 1-(2,5-dichlorophenoxy)-3-[(1,1-dimethylethyl)amino]- [CAS]	39563-28-5 54247-25-5	US	4310549	Antihypertensive, adrenergic	

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Clorazepic Acid		23887-31-2				
Clorexolone		2127-1-7				
cloricromene	Acetic acid, [[8-chloro-3-[2-(diethylamino)ethyl]-4-methyl-2-oxo-2H-1-benzopyran-7-yl]oxy]-, ethyl ester [CAS]	68206-94-0	US	4349566	Vasodilator, coronary	Peripheral vascular disease
Clorindione		1146-99-2				
Clorprenaline		3811-25-4				
Clortermine		10389-73-8				
Clospirazine		24527-27-3				
Clostebol		1093-58-9				
Clothiapine		2058-52-8				
clotiazepam	2H-Thieno[2,3-e]-1,4-diazepin-2-one, 5-(2-chlorophenyl)-7-ethyl-1,3-dihydro-1-methyl- [CAS]	33671-46-4	US	3849405	Anxiolytic	Anxiety, general
clotrimazole	1-[(2-chlorophenyl)diphenylmethyl]-1H-imidazole	23593-75-1	US	3705172	Antifungal	
clotrimazole + betamethasone	Pregna-1,4-diene-3,20-dione, 9-fluoro-11-hydroxy-16-methyl-17,21-bis(1-oxopropoxy)-, (11ß,16ß)-, mixt. with 1-[(2-chlorophenyl)diphenylmethyl]-1H-imidazole [CAS]	92522-91-3			Formulation, fixed-dose combinations	Infection, fungal, general
Cloxacillin		61-72-3				
cloxazolam	Oxazolo[3,2-d][1,4]benzodiazepin-6(5H)-one, 10-chloro-11b-(2-chlorophenyl)-2,3,7,11b-tetrahydro- [CAS]	24166-13-0	US	3772371	Anxiolytic	
Cloxotestosterone		53608-96-1				
Cloxyquin		130-16-5				
clozapine	5H-Dibenzo[b,e][1,4]diazepine, 8-chloro-11-(4-methyl-1-piperazinyl)- [CAS]	5786-21-0	US	3539573	Neuroleptic	Schizophrenia
CMI-392	Trans-2-[3-methoxy-4-(2-p-chlorophenylthio)ethoxy-5-(N'-methyl-N'-hydroxyureidyl)methylphenyl]-5-(3,4,5-trimethoxyphenyl)tetrahydrofuran	193739-23-0	US	5648486	Antipsoriasis	Psoriasis

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
CMT-3	2-Naphthacenecarboxamide, 1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-, (4aS,5aR,12aS)- [CAS]	15866-90-7	US	5837696	Anticancer, other	Cancer, sarcoma, Kaposi's
CNI-1493	Decanediamide, N,N'-bis[3,5-bis[1-[(aminoiminomethyl)hydrazono]ethyl]phenyl]-, tetrahydrochloride [CAS]	164301-51-3	US	5750573	Anti-inflammatory	Psoriasis
CNS-5161	N'-[2-chloro-5-(methylthio)phenyl]-N-methyl-N-[3-(methylthio)phenyl]guanidine [CAS]	160754-76-7	WO	9427591	Analgesic, other	Pain, neuropathic
Cobamamide		13870-90-1				
Cocaethylene		529-38-4				
Cocaine		50-36-2				
Codeine		76-57-3 52-28-8				
CoFactor	5,10 methylene - tetrahydrofolate				Anticancer, antimetabolite	Cancer, colorectal
Colchicine		64-86-8				
colesevelam	1-Hexanaminium, N,N,N-trimethyl-6-(2-propenylamino)-, polymer with (chloromethyl)oxirane, 2-propen-1-amine and N-2-propenyl-1-decanamine, hydrochloride [CAS]	182815-44-7	US	5607669	Hypolipaemic/Antiatherosclerosis	Hyperlipidaemia, general
colestilan	1H-Imidazole, 2-methyl-, polymer with (chloromethyl)oxirane [CAS]	95522-45-5	JP	59155421	Hypolipaemic/Antiatherosclerosis	Hypercholesterolaemia
Colestipol		26658-42-4				
colforsin daropate	6-(3-dimethylaminopropionyl)forskolin-[CAS]	138605-00-2	EP	222413	Cardiostimulant	Heart failure
colfosceril	3,5,9-Trioxa-4-phosphapentacosan-1-aminium, 4-hydroxy-N,N,N-trimethyl-10-oxo-7-[(1-oxohexadecyl)oxy]-, hydroxide, inner salt, 4-oxide, (R)- [CAS]	63-89-8 99732-49-7	US	4826821	Lung Surfactant	Respiratory distress syndrome, infant
Collagraft		138331-02-9			Formulation, implant	Regeneration, bone
Colocynthin		1398-78-3				
Colpormon		1247-71-8				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
coluracetam	1-Pyrrolidineacetamide, 2-oxo-N-(5,6,7,8-tetrahydro-2,3-dimethylfuro[2,3-b]quinolin-4-yl)- [CAS]	135463-81-9	EP	427636	Cognition enhancer	Alzheimer's disease
combretastatin A-4 prodrug	disodium combretastatin-A-4-3-O-phosphate				Anticancer, other	Cancer, thyroid
compound B, Pharmacor			US	6362165	Antiviral, anti-HIV	Infection, HIV/AIDS
conivaptin	[1,1'-Biphenyl]-2-carboxamide, N-[4-[(4,5-dihydro-2-methylimidazo[4,5-d][1-benzazepin-6(1H)-yl)carbonyl]phenyl]-, [CAS]	168626-94-6	WO	9503305	GI inflammatory/bowel disorders	Hyponatraemia
Connettivina	Hyaluronic acid [CAS]	9004-61-9			Vulnerary	
Convallatoxin		508-75-8				
Coparaffinate		8001-60-3				
Corticorelin Ovine Triflutate						
Corticosterone		50-22-6				
Cortisone		53-06-5				
Cortivazol		1110-40-3				
Cosyntropin		16960-16-0				
Cotarnine		82-54-2				
Cotinine		486-56-6				
co-trimazine	Benzenesulfonamide, 4-amino-N-2-pyrimidinyl-, mixt. with 5-[(3,4,5-trimethoxyphenyl)methyl]-2,4-pyrimidinediamine [CAS]	39474-58-3			Trimethoprim and analogues	Infection, urinary tract
Coumetarol		4366-18-1				
CP-248	1H-Indene-3-acetamide, 5-fluoro-2-methyl-N-(phenylmethyl)-1-[(3,4,5-trimethoxyphenyl)methylene]-, (1Z)- [CAS]	200803-37-8	WO	9747303	Anticancer, other	Barrett's oesophagus
CP-461			US	5948779	Anticancer, other	Cancer, prostate
CPC-211	Acetic acid, dichloro-, sodium salt [CAS]	2156-56-1			Neuroprotective	Acidosis, lactic
CPI-1189	CPI 1189 [CAS]	210475-67-5	WO	9631462	Cognition enhancer	Dementia, AIDS-related
CRA-0450			WO	0202549	Anxiolytic	Unspecified

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
creatinol-O-phosphate	Guanidine, N-methyl-N-[2-(phosphonooxy)ethyl]- [CAS]	6903-79-3			Antianginal	
CRL-5861	Oxirane, methyl-, polymer with oxirane, block [CAS]	106392-12-5	US	4837014	Antisickling	Anaemia, sickle cell
crobenetine	(2R,6S)-3-[2(S)-Benzyloxypropyl]-6,11,11-trimethyl-1,2,3,4,5,6,-hexahydro-2,6-methano-3-benzazocin-10-ol		WO	9914199	Neuroprotective	Ischaemia, cerebral
croconazole	1H-Imidazole, 1-[1-[2-[(3-chlorophenyl)methoxy]phenyl]ethenyl]- [CAS]	77175-51-0	DE	3021467	Antifungal	Infection, fungal, general
cromoglicic acid	4H-1-Benzopyran-2-carboxylic acid, 5,5'-[(2-hydroxy-1,3-propanediyl)bis(oxy)]bs4-oxo- [CAS]	53736-52-0			Formulation, mucosal, topical	Conjunctivitis
cromolyn	4H-1-Benzopyran-2-carboxylic acid, 5,5'-[(2-hydroxy-1,3-propanediyl)bis(oxy)]bis[4-oxo-, [CAS]	15826-37-6 16110-51-3			Formulation, inhalable, solution	Asthma
Cropropamide		633-47-6				
Crotamiton		483-63-6				
Crotethamide		6168-76-9				
Crystacide			US	4557935	Formulation, dermal, topical	Infection, dermatological
CS-502	□		EP	799823	Analgesic, other	Pain, general
CS-758	4-[(1E,3E)-4-[trans-5-[[1R,2R)-2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]thio]-1,3-dioxan-2-yl]-1,3-butadienyl]-3-fluorobenzonitrile				Antifungal	Infection, fungal, general
CS-834	1-Azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid, 6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-3-[[(3R)-5-oxo-3-pyrrolidinyl]thio]-, (2,2 dimethyl-1-oxopropoxy)methyl ester, (4R,5S,6S)- [CAS]	157542-49-9	EP	599512	Beta-lactam antibiotic	Infection, general

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
CT-052923	[(2H-benzo[d]1,3-dioxalan-5-methyl)amino][4-(6,7-dimethoxyquinazolin-4-yl)piperazinyl]methane-1-thione				Cardiovascular	Restenosis
CT-32228	N-(4-bromophenyl)-6-(5-chloro-2-methylphenyl)-[1,3,5]triazine-2,4-diamine				Anticancer, other	Cancer, general
Cupric Citrate		866-82-0				
Cuproxoline		13007-93-7				
CVT-2584	Ethanol, 2,2'-[[6-[[(4-methoxyphenyl)methyl]amino]-9-(1-methylethyl)-9H-purin-2-yl]imino]bis- [CAS]	199986-75-9	WO	9805335	Cardiovascular	Restenosis
CX-659S	((S)-6-amino-5-(6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxamido)-3-methyl-1-phenyl-2,4-(1H,3H)-pyrmidinedione				Dermatological	Eczema, general
Cyacetacide		140-87-4				
Cyamemazine		3546-03-0				
Cyanidin		528-58-5				
CYC400			WO	00172745	Anticancer, other	Cancer, general
Cyclacillin		3485-14-1				
Cyclandelate		456-59-7				
Cyclazocine		3572-80-3				
Cyclexanone		15301-52-7				
Cyclexedrine		532-52-5				
cyclidrol	3-Cyclohexene-1-methanol, 5-hydroxy-Alpha,Alpha,4-trimethyl- [CAS]	498-71-5			COPD treatment, Respiratory	Bronchitis, chronic
cyclin D1 inhibitors			US	6033843	Anticancer, hormonal	Cancer, breast
Cyclizine		82-92-8				
Cyclobarbital		52-31-3				
Cyclobendazole		31431-43-3				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
cyclobenzaprine	1-Propanamine, 3-(5H-dibenzo[a,d]cyclohepten-5-ylidene)-N,N-dimethyl-[CAS]	303-53-7			Formulation, modified-release, other	Muscle spasm, general
Cyclobutyrol		512-16-3				
Cyclocumarol		518-20-7				
Cyclodrine		52109-93-0				
Cyclofenil		2624-43-3				
Cycloguanil		516-21-2				
Cyclomethycaine		139-62-8				
Cyclonium Iodide		6577-41-9				
Cyclopentamine		102-45-4				
Cyclopenthiazide		742-20-1				
Cyclopentobarbital		76-68-6				
Cyclopentolate		512-15-2				
cyclophosphamide	N,N-Bis(2-chloroethyl)tetrahydro-2H-1,3,2-oxazaphosphorin-2-amine-2-oxide monohydrate	50-18-0 6055-19-2			Formulation, parenteral, targeted	Cancer, general
cyclopiroxalamine	2(1H)-Pyridinone, 6-cyclohexyl-1-hydroxy-4-methyl-, cmpd with 2-aminoethanol(1:1) [CAS]	41621-49-2			Formulation, transdermal, other	Vaginitis
Cycloserine		68-41-7				
Cyclothiazide		2259-96-3				
Cyclovalone		579-23-7				
Cymarin		508-77-0				
cymserine	Carbamic acid, [4-(1-methylethyl)phenyl]-, (3aS,8aR)-1,2,3,3a,8,8a-hexahydro-1,3a,8-trimethylpyrrolo[2,3-b]indol-5-yl ester [CAS]	145209-39-8	WO	9902154	Cognition enhancer	Alzheimer's disease
Cynarin(e)		30964-13-7				
CYP26 inhibitors			US	6063606	Dermatological	Unspecified
Cyproheptadine		129-03-3				
cyproterone	(1ß,2ß)-6-Chloro-1,2-dihydro-17-hydroxy-3'H-cyclopropa[1,2]pregna-1,4,6-triene-3,20-dione [CAS]	2098-66-0			Radio/chemoprotective	Chemotherapy-induced injury, general

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Cysteamine		60-23-1				
cystic fibrosis ther	[[4-[[3-[[4-[1-(4-hydroxyphenyl)-1-methyl-ethyl]phenoxy]methyl]phenyl]methoxy]-phenyl]iminomethyl]-, ethyl ester				Cystic fibrosis treatment	Cystic fibrosis
cytarabine	2(1H)-Pyrimidinone, 4-amino-1-[5-O-[hydroxy(octadecyloxy)phosphinyl]-ß-D-arabinofuranosyl]-, [CAS]	65093-40-5 147-94-4	EP	239015	Anticancer, antimetabolite	Myelodysplastic syndrome
D-24851	N-(Pyridin-4-yl)-(1-(4-chlorobenzyl)-indol-3-yl)-glyoxyl-amide)				Anticancer, other	Cancer, general
D-4418	8-Methoxyquinoline-5-[N-(2,5-dichloropyridin-3-yl)]carboxamide				Antiasthma	Asthma
DA-5018	Benzeneacetamide, 4-(2-aminoethoxy)-N-(3-(3,4-dimethylphenyl)propyl)-3-methoxy-, monohydrochloride [CAS]	174661-97-3	US	5242944	Analgesic, other	Pain, musculoskeletal
DA-6034			US	6025387	GI inflammatory/bowel disorders	Crohn's disease
DA-7867			KR	9957803	Antibacterial, other	Infection, general
DA-7911			KR	56034	Antiarthritic, other	Arthritis, rheumatoid
DA-8159	3-(1-Methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo-[4,3-d]pyrimidin-5-yl)-N-[2-(1-methylpyrrolidin-2-yl)ethyl]-4-propoxybenzenesulfonamide		KR	353014	Male sexual dysfunction	Sexual dysfunction, male, general
Dacarbazine		4342-3-4				
Daclizumab		152923-56-3				
Dactinomycin		50-76-0				
dalbavancin	5,31-Dichloro-38-de(methoxycarbonyl)-7-demethyl-19-deoxy-56-O-[2-deoxy-2-(10-methylundecanamido)-ß-D-glucopyranurosyl]-38-[N-[3-(dimethylamino)propyl]carbamoyl]-42-O-Alpha-D-mannopyranosyl-N15-methylristomycin A aglycone	171500-79-1			Peptide antibiotic	Infection, dermatological

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Dalfopristin		112362-50-2				
dalfopristin + quinupristin	Virginiamycin M1, 26-((2-(diethylamino)ethyl)sulfonyl)-26,27-dihydro-, (26R,27S)-, mixt with 4-(4-(dimethylamino)-N-methyl-L-phenylalanine)-5-(5-((1-azabicyclo(2.2.2)oct-3-ylthio)methyl)-4-oxo-L-2-piperidinecarboxylic acid) virginiamycin S1- [CAS]	126602-89-9	EP	248703	Antibiotic, other	Infection, respiratory tract, general
dalteparin	Heparin-, [CAS]	9041-08-1	US	4303651	Anticoagulant	Thromboprophylaxis
Daltroban		79094-20-5				
δ-Aminolevulinic Acid		106-60-5				
danaparoid			EP	66908	Anticoagulant	Thrombosis, venous
danazol	Pregna-2,4-dien-20-yno[2,3-d]isoxazol-17-ol, (17Alpha)- [CAS]	17230-88-5	GB	905844	Menstruation disorders	
Danthron		117-10-2				
Dantrolene		7261-97-4				
dapiprazole	1,2,4-Triazolo[4,3-a]pyridine, 5,6,7,8-tetrahydro-3-[2-[4-(2-methylphenyl)-1-piperazinyl]ethyl]- [CAS]	72822-12-9 72822-13-0	US	4252721	Ophthalmological	Glaucoma
dapivirine	4-[[4-(2,4,6-trimethylphenyl)amino]pyrimidin-2-yl]amino]benzonitrile	244767-67-7			Antiviral, anti-HIV	Infection, HIV/AIDS
dapoxetine	(+)-(S)-N,N-dimethyl-Alpha-[2-(1-naphthyl-oxy)ethyl]benzylamine HCl	119356-77-3	EP	288188	Male sexual dysfunction	Premature ejaculation
dapsone	4,4'-Sulfonyldianiline	80-08-0			Formulation, dermal, topical	Acne
daptomycin	Daptomycin [CAS]	103060-53-3	EP	178152	Peptide antibiotic	Infection, dermatological
Darbepoetin Alfa						
darifenacin	3-Pyrrolidineacetamide, 1-[2-(2,3-dihydro-5-benzofuranyl)ethyl]-Alpha,Alpha-diphenyl-, (S)- [CAS]	133099-04-4	EP	388054	Urological	Overactive bladder

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
daunorubicin	5,12-Naphthacenedione, 8-acetyl-10-[(3-amino-2,3,6-trideoxy-Alpha-L-lyxo-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-, (8S-cis)- [CAS]	20830-81-3	US	5441745	Formulation, optimized, liposomes	Cancer, sarcoma, Kaposi's
DAX, SciClone	3-diallyl-8-cyclohexylxanthine				Cystic fibrosis treatment	Cystic fibrosis
DB-67	7-tert-Butyldimethylsilyl-10-hydroxycamptothecin				Anticancer, other	Cancer, general
d-Camphocarboxylic Acid		18530-30-8				
DCF-987	Dextran		US	5514665	Formulation, other	Cystic fibrosis
DDT		50-29-3				
Deaminooxytocin		113-78-0				
Deanol		108-01-0				
Debrisoquin		1131-64-2				
Decamethonium		541-22-0				
Decimemide		14817-09-5				
decitabine	1,3,5-Triazin-2(1H)-one, 4-amino-1-(2-deoxy-ß-D-erythro-pentofuranosyl)-[CAS]	23339-46-0 2353-33-5			Anticancer, antimetabolite	Myelodysplastic syndrome
declopramide	Benzamide, 4-amino-3-chloro-N-(2-(diethylamino)ethyl)- [CAS]	891-60-1	WO	9732582	Anticancer, other	Cancer, colorectal
Deferiprone		30652-11-0				
Deferoxamine		70-51-9				
deflazacort	5'H-Pregna-1,4-dieno[17,16-d]oxazole-3,20-dione, 21-(acetyloxy)-11-hydroxy-2'-methyl-, (11ß,16ß)- [CAS]	14484-47-0 74712-90-6	GB	1077393	Hormone	Asthma
Defosfamide		3733-81-1				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
degarelix	N-acetyl-3-(naphtalen-2-yl)-D-alanyl-4-chloro-D-phenylalanyl-3-(pyridin-3-yl)-D-alanyl-L-seryl-4-[[[(4S)-2,6-dioxohexahydropyrimidin-4-yl]carbonyl]amino]-L-phenylalanyl-4-(carbamoylamino)-D-phenylalanyl-L-leucyl-N6-(1-methylethyl)-L-lysyl-L-prolyl-D-alaninamide	214766-78-6			Anticancer, hormonal	Cancer, prostate
dehydroascorbic acid	L-threo-2,3-Hexodiulosonic acid gamma-lactone	490-83-5			Cognition enhancer	Alzheimer's disease
Dehydrocholic Acid		81-23-2				
Dehydroemetine		4914-30-1				
delapril	Glycine, N-(2,3-dihydro-1H-inden-2-yl)-N-[N-[1-(ethoxycarbonyl)-3-phenylpropyl]-L-alanyl]-, (S)- [CAS]	83435-66-9 83435-67-0	EP	51391	Antihypertensive, renin system	Hypertension, general
delapril+manidipine	Glycine, N-(2,3-dihydro-1H-inden-2-yl)-N-[N-[1-(ethoxycarbonyl)-3-phenylpropyl]-L-alanyl]-, (S)-3,5-Pyridinedicarboxylic acid, 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-, 2-[4-(diphenylmethyl)-1-piperazinyl]ethyl methyl ester [CAS]		FR	2733911	Formulation, fixed-dose combinations	Hypertension, general
delavirdine	Piperazine, 1-[3-[(1-methylethyl)amino]-2-pyridinyl]-4-[[5-[(methylsulfonyl)amino]-1H-indol-2-yl]carbonyl]- [CAS]	136817-59-9	WO	9109849	Antiviral, anti-HIV	Infection, HIV/AIDS
Delmadinone		13698-49-2				
Delmopinol		79874-76-3				
delorazepam	2H-1,4-Benzodiazepin-2-one, 7-chloro-5-(2-chlorophenyl)-1,3-dihydro- [CAS]	2894-67-9	CH	408029	Anxiolytic	
delucemine	3,3-Bis-(m-fluorophenyl)-N-methylpropylamine [CAS]	186495-99-8			Neuroprotective	Ischaemia, cerebral
Demanyl		6909-62-2				
Demecarium		56-94-0				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
demeclocycline	2-Naphthacenecarboxamide, 7-chloro-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-1,11-dioxo-, [4S-(4Alpha,4aAlpha,5aAlpha,6ß,12aAlpha)]-[CAS]	127-33-3			Formulation, modified-release, <=24hr	Infection, general
Demecolcine		477-30-5				
Demegestone		10116-22-0				
Demexiptiline		24701-51-7				
denaverine	Benzeneacetic acid, Alpha-(2-ethylbutoxy)-Alpha-phenyl-, 2-(dimethylamino)ethyl ester, [CAS]	3321-06-0	DE	4133785	Analgesic, NSAID	Pain, musculoskeletal
Denileukin Diftitox		173146-27-5				
Denopamine		71771-90-9				
Denopterin		22006-84-4				
Deoxycholic Acid		83-44-3				
Deoxycorticosterone		64-85-7 56-47-3				
Deoxydihydrostreptomycin		26086-49-7				
Deoxyepinephrine		501-15-5				
Depreotide		161982-62-3				
depsipeptide	L-Valine, N-[(3S,4E)-3-hydroxy-7-mercapto-1-oxo-4-heptenyl]-D-valyl-D-cysteinyl-(2Z)-2-amino-2-butenoyl-, (4-1)-lactone, cyclic (1-2)-disulfide [CAS]	128517-07-7	EP	352646	Anticancer, antibiotic	Cancer, general
Deptropine		604-51-3				
Dequalinium		522-51-0				
dersalazine	Benzoic acid, 2-hydroxy-5-[[4-[3-[4-(2-methyl-1H-imidazol[4,5-c]pyridin-1-yl]methyl]-1-piperidinyl]-3-oxo-1-phenyl-1-propenyl]phenyl]azo] (Z) [CAS]	188913-57-7 188913-58-8	US	5747477	Anti-inflammatory	Colitis, ulcerative
Deserpidine		131-01-1				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
desferrioxamine	Butanediamide, N'-[5-[[4-[[5-(acetylhydroxyamino)pentyl]amino]-1,4-dioxobutyl]hydroxyamino]pentyl]-N-(5-aminopentyl)-N-hydroxy- [CAS]	70-51-9			Antidote	Poisoning, metal
Desflurane		57041-67-5				
Desipramine		50-47-5				
Deslanoside		17598-65-1				
desloratadine	5H-Benzo(5,6)cyclohepta(1,2-b)pyridine, 8-chloro-6,11-dihydro-11-(4-piperidinylidene)- [CAS]	100643-71-8	US	5595997	Antiallergic, non-asthma	Rhinitis, allergic, perennial
deslorelin	Luteinizing hormone-releasing factor (pig), 6-D-tryptophan-9-(N-ethyl-L-prolinamide)-10-deglycinamide- [CAS]	57773-65-6	US	4034082	Releasing hormones	Cancer, prostate
desmopressin	Vasopressin, 1-(3-mercaptopropanoic acid)-8-D-arginine- [CAS]	16679-58-6	DE	2948345	Hormone	Enuresis
Desogestrel		54024-22-5				
desogestrel + estradiol	Estra-1,3,5(10)-triene-3,17-diol (17ß)-, mixt. with (17Alpha)-13-ethyl-11-methylene-18,19-dinorpregn-4-en-20-yn-17-ol [CAS]	122364-17-4			Menopausal disorders	Hormone replacement therapy
desogestrel, Akzo Nobel	18,19-Dinorpregn-4-en-20-yn-17-ol, 13-ethyl-11-methylene-, (17Alpha)- [CAS]	54024-55-5			Formulation, oral, other	Contraceptive, female
desogestrel+ethinylestrad (1)	18,19-Dinorpregn-4-en-20-yn-17-ol, 13-ethyl-11-methylene-, (17Alpha)- [CAS]	54024-22-5 71138-35-7	US	3927046	Formulation, oral, other	Contraceptive, female
Desomorphine		427-00-9				
Desonide		638-94-8				
Desoximetasone		382-67-2				
Detaxtran		9015-73-0				
Devacade			WO	9308176	Analgesic, other	Pain, general
dexamethasone	Pregna-1,4-diene-3,20-dione,9-fluoro-11,17,21-trihydroxy-16-methyl-, (11ß,16Alpha)- [CAS]	50-02-2 2392-39-4 312-93-6			Formulation, other	Inflammation, ocular
dexanabinol	6H-Dibenzo[b,d]pyran-9-methanol, 3-(1,1-dimethylheptyl)-6a,7,10,10a-tetrahydro-1-hydroxy-6,6-dimethyl-, (6aS-trans)- [CAS]	112924-45-5	EP	427518	Neuroprotective	Head trauma

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
dexecadotril	Glycine, N-[2-[(acetylthio)methyl]-1-oxo-3-phenylpropyl]-, phenylmethyl ester, (R)- [CAS]	112573-72-5	EP	318377	Alimentary/Metabolic, other	Unspecified
dexefaroxan	1H-Imidazole, 2-(2-ethyl-2,3-dihydro-2-benzofuranyl)-4,5-dihydro- [CAS]	89197-00-2 89197-32-0	EP	71368	Cognition enhancer	Alzheimer's disease
Dexetimide		21888-98-2				
dexibuprofen	Benzeneacetic acid, Alpha-methyl-4-(2-methylpropyl)-, (AlphaS)- [CAS]	51146-56-6			Analgesic, NSAID	Pain, general
dexketoprofen	Benzeneacetic acid, 3-benzoyl-Alpha-methyl-, (S)- [CAS]	22161-81-5			Anti-inflammatory	Inflammation, general
dexloxiglumide	Pentanoic acid, 4-[(3,4-dichlorobenzoyl)amino]-5-[(3-methoxypropyl)pentylamino]-5-oxo-, (R)- [CAS]	119817-90-2	EP	0344184	GI inflammatory/bowel disorders	Irritable bowel syndrome
dexmedetomidine	1H-Imidazole, 4-[1-(2,3-dimethylphenyl)ethyl]-, (R)- [CAS]	113775-47-6 86347-15-1	EP	187471	Hypnotic/Sedative	Anaesthesia
dexmethylphenidate	2-Piperidineacetic acid, Alpha-phenyl-, methyl ester, (AlphaR,2R)-	19262-68-1			Psychostimulant	Attention deficit disorder
Dexpanthenol		81-13-0				
dexrazoxane	2,6-Piperazinedione, 4,4'-(1-methyl-1,2-ethanediyl)bis-, (S)- [CAS]	24584-09-6	DE	1910283	Radio/chemoprotective	Chemotherapy-induced injury, general
Dextran-1	Dextran [CAS]	9004-54-0			Plasma substitute	
Dextranomer		56087-11-7				
Dextroamphetamine		51-64-9				
dextromethorphan	Morphinan, 3-methoxy-17-methyl-, (9Alpha,13Alpha,14Alpha)-,	6700-34-1 125-71-3	US	4221788	Formulation, oral, other	Cough, Emotional lability
Dextromoramide		357-56-2				
dextropropoxyphene	Benzeneethanol, Alpha-[2-(dimethylamino)-1-methylethyl]-Alpha-phenyl-, propanoate (ester), [S-(R*,S*)]- [CAS]	469-62-5			Formulation, modified-release, other	Pain, general
Dezocine		53648-55-8				
DF-1012	N-Tropyl 7-azaindol-3-ylcarboxamide	163220-65-3	WO	9504742	Respiratory	Respiratory disease, general
DFA-IV	di-D-fructofuranose 2,6':6,2' dianhydride		US	5700832	Antianaemic	Anaemia, aplastic

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
d-Fenchone		4695-62-9				
D-Glucuronolactone		32449-92-6				
Diab II	Diab II	309956-85-2	US	6153632	Antidiabetic	Diabetes, Type II
diacerein	2-Anthracenecarboxylic acid, 4,5-bis(acetyloxy)-9,10-dihydro-9,10-dioxo- [CAS]	13739-02-1	US	4244968	Antiarthritic, other	Arthritis, rheumatoid
Diampromide		552-25-0				
Diamthazole		136-96-9				
Diathymosulfone		5964-62-5				
Diatrizoate		737-31-5				
diazepam	2H-1,4-Benzodiazepin-2-one, 7-chloro-1,3-dihydro-1-methyl-5-phenyl- [CAS]	439-14-5			Formulation, transmucosal, systemic	Anxiety, epilepsy, general
Diaziquone		57998-68-2				
Diazoxide		364-98-7				
dibekacin	D-Streptamine, O-3-amino-3-deoxy-Alpha-D-glucopyranosyl-(1-6)-O-[2,6-diamino-2,3,4,6-tetradeoxy-Alpha-D-erythro-hexopyranosyl-(1-4)]-2-deoxy-, sulfate (salt)[CAS]	34493-98-6 58580-55-5	GB	1349302	Aminoglycoside antibiotic	Infection, general
Dibenzepin		4498-32-2				
Dibromopropamidine		496-00-4				
Dibucaine		61-12-1				
Dichloralphenazone		480-30-8				
Dichloramine T		473-34-7				
Dichlorisone		7008-26-6				
Dichlorobenzyl Alcohol		1777-82-8				
Dichlorophen		97-23-4				
Dichlorophenarsine		536-29-8				
Dichlorphenamide		120-97-8				
diclofenac + HA	Hyaluronic acid + benzeneacetic acid, 2-[(2,6-dichlorophenyl)amino]- [CAS]				Formulation, transdermal, systemic	Keratosis
diclofenac	Benzeneacetic acid, 2-[(2,6-dichlorophenyl)amino]-, [CAS]	15307-79-6 15307-86-5 15307-81-0			Formulation, modified-release, <=24hr	Pain, general

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Dicloxacillin		3116-76-5				
Dicumarol		66-76-2				
Dicyclomine		77-19-0				
didanosine	Inosine, 2',3'-dideoxy- [CAS]	69655-05-6	US	4861759	Antiviral, anti-HIV	Infection, HIV/AIDS
Dideoxyadenosine		4097-22-7				
didox	Benzamide, N,3,4-trihydroxy- [CAS]	69839-83-4	US	4263322	Anticancer, antimetabolite	Cancer, general
Dienestrol		84-17-3				
dienogest	19-Norpregna-4,9-diene-21-nitrile, 17-hydroxy-3-oxo-, (17Alpha)- [CAS]	65928-58-7	GB	1524917	Menstruation disorders	Endometriosis
dienogest+estradiol	19-Norpregna-4,9-diene-21-nitrile, 17-hydroxy-3-oxo-,(17Alpha) + Estra-1,3,5(10)-triene-3,17-diol(17ß)				Formulation, fixed-dose combinations	Contraceptive, female
Diethadione		702-54-5				
Diethazine		60-91-3				
Diethylbromoacetamide		511-70-6				
Diethylcarbamazine		90-89-1				
diethylpropion	1-Propanone, 2-(diethylamino)-1-phenyl- [CAS]	90-84-6			Formulation, modified-release, <=24hr	Obesity
Diethylstilbestrol		56-53-1				
Difemerine		80387-96-8				
Difenamizole		20170-20-1				
Difenoxin		28782-42-5				
Difenpiramide		51484-40-3				
diflomotecan	(5R)-5-Ethyl-9,10-difluoro-1,4,5,13-tetrahydro-5-hydroxy-3H,15H-oxepino[3',4':6,indolizino[1,2-b]quinoline-3,15-dione	220997-97-7			Anticancer, other	Cancer, general
diflorasone	Pregna-1,4-diene-3,20-dione, 17,21-bis(acetyloxy)-6,9-difluoro-11-hydroxy-16-methyl-, (6Alpha,11ß,16ß)- [CAS]	33564-31-7 2557-49-5	US	3980778	Antipsoriasis	
Difloxacin		98106-17-3				
Diflucortolone		2607-6-9				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
diflunisal	2',4'-difluoro-4-hydroxy[1,1'-biphenyl]-3-carboxylic acid	23674-86-4 22494-42-4	GB	1175212	Analgesic, NSAID	Pain, post-operative
Difluprednate		23674-86-4				
Digitalin		752-61-4				
Digitoxin		71-63-6				
digoxin	Card-20(22)-enolide, 3-[(O-2,6-dideoxy-ß-D-ribo-hexopyranosyl-(1-4)-O-2,6-dideoxy-ß-D-ribo-hexopyranosyl-(1-4)-2,6-dideoxy-ß-D-ribo-hexopyranosyl)oxy]-12,14-dihydroxy-, (3ß,5ß,12ß)- [CAS]	20830-75-5	US	4088750	Formulation, oral, enteric-coated	Heart failure
Dihexyverine		561-77-3				
Dihydralazine		484-23-1				
Dihydrocodeine		125-28-0				
Dihydrocodeinone Enol		466-90-0				
dihydroergocryptine	Ergocryptine, dihydro- [CAS]	25447-66-9			Formulation, other	Depression, general
dihydroergotamine	Ergotaman-3',6',18-trione, 9,10-dihydro-12'-hydroxy-2'-methyl-5'-(phenylmethyl)-, (5'Alpha,10Alpha)- [CAS]	511-12-6		6495535	Formulation, modified-release, other	Migraine
Dihydromorphine		509-60-4				
Dihydrostreptomycin		128-46-1				
Dihydrotachysterol		67-96-9				
Dihydroxyaluminum		13682-92-3 539-68-4				
Diisopromine		5966-41-6				
Diisopropyl Paraoxon		3254-66-8				
Diisopropylamine		660-27-5				
dilazep	Benzoic acid, 3,4,5-trimethoxy-, (tetrahydro-1H-1,4-diazepine-1,4(5H)-diyl)di-3,1-propanediyl ester [CAS]	35898-87-4	JP	51095086	Vasodilator, coronary	
Dilevalol		75659-07-3				
diloxanide	2-Furancarboxylic acid, 4-[(dichloroacetyl)methylamino]phenyl ester [CAS]	3736-81-0 579-38-4			Amoebicide	

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
diltiazem	1,5-Benzothiazepin-4(5H)-one, 3-(acetyloxy)-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-, (2S-cis)- [CAS]	33286-22-5 42399-41-7	US US EP	4721619 5529791 322277	Antianginal	Angina, hypertension, general
Dimecrotic Acid		7706-67-4				
Dimefline		1165-48-6				
Dimemorfan		36309-01-0				
Dimenhydrinate		523-87-5				
Dimenoxadol		509-78-4				
Dimepheptanol		545-90-4				
Dimercaprol		59-52-9				
Dimetacrine		4757-55-5				
Dimethadione		695-53-4				
Dimethazan		519-30-2				
Dimethindene		5636-83-9				
Dimethisoquin		86-80-6				
Dimethisterone		79-64-1				
Dimethocaine		94-15-5				
Dimethoxanate		477-93-0				
Dimethyl Sulfoxide		67-68-5				
Dimethylthiambutene		524-84-5				
Dimetofrine		22950-29-4				
Dimorpholamine		119-48-2				
dinoprostone	Prosta-5,13-dien-1-oic acid, 11,15-dihydroxy-9-oxo-, (5Z,11Alpha,13E,15S)- [CAS]	363-24-6			Formulation, modified-release, <=24hr	Labour, induction
diosmectite	Smecta- [CAS]	110070-78-5	FR	2770778	Antidiarrhoeal	Diarrhoea, general
diosmin	4H-1-Benzopyran-4-one, 7-[[6-O-(6-deoxy-Alpha-L-mannopyranosyl)-.beta.-D-glucopyranosyl]oxy]-5-hydroxy-2-(3-hydroxy-4-methoxyphenyl)- [CAS]	520-27-4	DE	2602314	Vasoprotective, systemic	
Dioxadrol		6495-46-1				
Dioxaphetyl		467-86-7				
Dioxethedrine		497-75-6				
Dioxybenzone		131-53-3				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Diphemanil		62-97-5				
Diphenadione		82-66-6				
Diphencyprone		886-38-4				
Diphenhydramine		58-73-1				
Diphenidol		972-02-1				
Diphenoxylate		915-30-0				
Diphenylpyraline		147-20-6				
Diphetarsone		515-76-4				
Diphtheria & Tetanus Toxoids And Acellular Pertussis Vaccine Adsorbed						
Dipipanone		467-83-4				
dipivefrin	Propanoic acid, 2,2-dimethyl-, 4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene ester, (+/-)- [CAS]	52365-63-6	US	3809714	Antiglaucoma	Glaucoma
Dipyridamole		58-32-2				
Dipyrocetyl		486-79-3				
Dipyrone		5907-38-0				
diquafosol	Uridine 5'-(pentahydrogen tetraphosphate)-5'-ester with uridine, [CAS]	211427-08-6			Ophthalmological	Dry eye syndrome
dirithromycin	Erythromycin, 9-deoxo-11-deoxy-9,11-[imino[2-(2-methoxyethoxy)ethylidene]oxy]-, [9S(R)]- [CAS]	62013-04-1	DE	2515075	Macrolide antibiotic	Tonsillitis
disodium pamidronate	Phosphonic acid, (3-amino-1-hydroxypropylidene)bis-, disodium salt [CAS]	57248-88-1	EP	177443	Osteoporosis treatment	Hypercalcaemia of malignancy
Disofenin		65717-97-7				
disopyramide	2-Pyridineacetamide, Alpha-[2-[bis(1-methylethyl)amino]ethyl]-Alpha-phenyl- [CAS]	3737-09-5			Formulation, modified-release, <=24hr	Arrhythmia, general
Distigmine		15876-67-2				
Disulfamide		671-88-5				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Disulfiram		97-77-8				
Ditazol		18471-20-0				
Dithiazanine		514-73-8				
dithranol	9(10H)-Anthracenone, 1,8-dihydroxy- [CAS]	1143-38-0			Formulation, dermal, topical	Psoriasis
Ditiocarb		148-18-5				
Dixanthogen		502-55-6				
Dixyrazine		2470-73-7				
DJ-927			WO	01027115	Anticancer, other	Cancer, general
DK-507k	(-)-7-[(7S)-7-Amino-5-azaspiro[2,4]heptan-5-yl]-6-fluoro-1-[(1R,2S)-2-fluoro-1-cyclopropyl]-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid hydrochloride monohydrate				Quinolone antibacterial	Infection, general
DL-Lactic Acid		598-82-3				
DMDC	Cytidine, 2'-deoxy-2'-methylene-, monohydrochloride [CAS]	113648-25-2	WO	8807049	Anticancer, antimetabolite	Cancer, general
DMXAA	5,6-dimethylxanthenone-4-acetic acid				Anticancer, other	Cancer, lung, general
DNA Stealth Nucleosides			US	6132776	Antiviral, anti-HIV	Infection, HIV/AIDS
Dobesilate		20123-80-2				
dobutamine	1,2-Benzenediol, 4-[2-[[3-(4-hydroxyphenyl)-1-methylpropyl]amino]ethyl]-, (+/-)- [CAS]	34368-04-2 49745-95-1	US	3987200	Cardiostimulant	
Docarpamine		74639-40-0				
docetaxel	(2R,3S)-N-Carboxy-3-phenylisoserine, N-tert-butyl ester, 13-ester with 5ß,20-epoxy-1,2Alpha,4,7ß,10ß,13Alpha-hexahydroxytax-11-en-9-one 4-acetate 2-benzoate- [CAS]	114977-28-5 148408-66-6	EP	253738	Anticancer, other	Cancer, breast
docosahexaenoic acid			EP	707487	Hypolipaemic/Antiatherosclerosis	Hyperlipidaemia, general
docosanol	1-Docosanol [CAS]	661-19-8	EP	469064	Antiviral, other	Infection, herpes simplex virus
docusate		128-49-4 577-11-7	US	4752617	Formulation, dermal, topical	Infection, herpes simplex virus prophylaxis

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
dofetilide	Methanesulfonamide, N-[4-[2-[methyl[2-[4-[(methylsulfonyl)amino]phenoxy]ethyl]amino]ethyl]phenyl]- [CAS]	115256-11-6	EP	245997	Antiarrhythmic	Fibrillation, atrial
dolasetron mesilate	1H-Indole-3-carboxylic acid, octahydro-3-oxo-2,6-methano-2H-quinolizin-8-yl ester, (2Alpha,6Alpha,8Alpha,9Alphaß)-, monomethanesulfonate- [CAS]	115956-13-3 115956-12-2	EP	266730	Antiemetic	Chemotherapy-induced nausea and vomiting
Domiodol		61869-07-6				
Domiphen		538-71-6				
Domitroban		112966-96-8				
domperidone	2H-Benzimidazol-2-one, 5-chloro-1-[1-[3-(2,3-dihydro-2-oxo-1H-benzimidazol-1-yl)propyl]-4-piperidinyl]-1,3-dihydro- [CAS]	57808-66-9	US	4066772	Antiemetic	
donepezil	1H-Inden-1-one, 2,3-dihydro-5,6-dimethoxy-2-((1-(phenylmethyl)-4-piperidinyl)methyl)-, [CAS]	120011-70-3 120014-06-4	EP	296560	Cognition enhancer	Alzheimer's disease
donitriptan	Piperazine, 1-(((3-(2-aminoethyl)-1H-indol-5-yl)oxy)acetyl)-4-(4-cyanophenyl)- [CAS]	170912-52-4			Antimigraine	Migraine
Dopamine		51-61-6				
Dopexamine		86197-47-9				
doramapimod	urea, N-[3-(1,1-dimethylethyl)-1-(4-methylphenyl)-1H-pyrazol-5-yl]-N'-[4-[2-(4-morpholinyl)ethoxy]-1-napthalenyl]-	285983-48-4			Antiarthritic, immunological	Arthritis, rheumatoid
doranidazole	(±)-1,2,4-Butanetriol, 3-((2-nitro-1H-imidazol-1-yl)methoxy)- [CAS]	137339-64-1	WO	9414778	Radio/chemosensitizer	Surgery adjunct
doripenem	(1R,5S,6S)-2-[(3S,5S)-5-(sulfamoylaminomethyl)pyrrolidin-3-yl]thio-6-[(1R)-1-hydroxyethyl]-1-methylcarbapen-2-em-3-carboxylic acid	148016-81-3	EP	528678	Beta-lactam antibiotic	Infection, urinary tract
dorzolamide	4H-Thieno(2,3-b)thiopyran-2-sulfonamide, 4-(ethylamino)-5,6-dihydro-6-methyl-,7,7-dioxide (4S-trans)- [CAS]	120279-96-1	EP	296879	Antiglaucoma	Glaucoma

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
dorzolamide + timolol	4H-Thieno(2,3-b)thiopyran-2-sulfonamide, 4-(ethylamino)-5,6-dihydro-6-methyl-7,7-dioxide (4S-trans) + ethyl 2-propanol, 1-[(1,1-dimethyl)amino]-3-[[4-(4-morpholinyl)-1,2,5-thiadiazol-3-yl]oxy]-, (S), (Z)-2-butenedioate (1:1) (salt) [CAS]	120279-96-1 26839-75-8 26921-17-5			Formulation, fixed-dose combinations	Glaucoma
dosmalfate	Aluminium, (μ7-(7-((6-O-(6-deoxy-2,3,4-tri-O-sulfo-Alpha-L-mannosylpyranosyl)-2,3,4-tri-O-sulfo-ß-D-glucopyranosyl)oxy)-5-hydroxy-2-(4-methoxy-3-(sulfooxy)phenyl-4H-1-benzopyran-4-onato(7-)))tetradeca-μ-hydroxyheneicosahydroxytetradeca- [CAS]	122312-55-4			Antiulcer	Ulcer, gastric
dosulepine	1-Propanamine, 3-dibenzo[b,e]thiepin-11(6H)-ylidene-N,N-dimethyl- [CAS]	113-53-1			Antidepressant	
Dotarizine		84625-59-2				
Dothiepin		113-53-1				
Doxacurium		106819-53-8				
Doxapram		309-29-5				
doxazosin	Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[(2,3-dihydro-1,4-benzodioxin-2-yl)carbonyl]- [CAS]	74191-85-8	GB	2007656	Antihypertensive, adrenergic	Hypertension, general
Doxefazepam		40762-15-0				
Doxenitoin		3254-93-1				
doxepin	1-Propanamine, 3-dibenz[b,e]oxepin-11(6H)-ylidene-N,N-dimethyl-	1668-19-5			Formulation, dermal, topical	Pruritus
doxercalciferol	9,10-secoergosta-5,7,10(19),22-tetraene-1,3-diol (1Alpha, 3ß, 5Z, 7E, 22E) [CAS]	54573-75-0	US	5104854	Hormone	Hyperparathyroidism
doxifluridine	Uridine, 5'-deoxy-5-fluoro- [CAS]	3094-09-5	US	4071680	Anticancer, antimetabolite	Cancer, colorectal
doxofylline	1H-Purine-2,6-dione, 7-(1,3-dioxolan-2-ylmethyl)-3,7-dihydro-1,3-dimethyl-[CAS]	69975-86-6	US	4187308	Antiasthma	Asthma

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
doxorubicin	5,12-Naphthacenedione, 10-[(3-amino-2,3,6-trideoxy-Alpha-L-lyxo-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-, (8S-cis)- [CAS]	23214-92-8	EP	191824	Formulation, optimized, liposomes	Cancer, general
doxycycline	2-Naphthacenecarboxamine, 4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-[4S-(4Alpha,4aAlpha,5Alpha,5aAlpha,6Alpha,12aAlpha)]- [CAS]	564-25-0 17086-28-1			Formulation, modified-release, immediate	Periodontitis
doxylamine	N,N-Dimethyl-2-[1-phenyl-1-(2-pyridinyl)ethoxy]ethanamine	469-21-6			Formulation, transmucosal, systemic	Rhinitis, allergic, general
DPC-817	ß-D-2',3'-didehydro-2',3'-dideoxy-5-fluorocytidine				Antiviral, anti-HIV	Infection, HIV/AIDS
DPI-3290			US	5681830	Analgesic, other	Pain, general
DQ-113	5-Amino-7-[(3S,4R)-(1-aminocyclopropyl)-3-fluoropyrrolidin-1-yl]-1-[(1R,2S)-2-fluoro-1-cyclopropyl]-1,4-dihydro-8-methyl-4-oxo-3-quinolinecarboxylic acid				Quinolone antibacterial	Infection, general
Drofenine		1679-76-1				
Droloxifene		82413-20-5				
Drometrizole		2440-22-4				
Dromostanolone		58-19-5				
dronabinol	6H-Dibenzo[b,d]pyran-1-ol, 6a,7,8,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-, (6aR-trans)- [CAS]	1972-08-3			Antiemetic	Chemotherapy-induced nausea and vomiting
dronedarone	2-n-Butyl 3-[4-(3-di-n-butylamino-propoxy)benzoyl]5-methylsulfonamidobenzofuran				Antiarrhythmic	Arrhythmia, general
Droperidol		548-73-2				
Droprenilamine		57653-27-7				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Dropropizine		17692-31-8				
Drospirenone		67392-87-4				
Drotaverine		14009-24-6				
Drotebanol		03/02/3176				
droxicam	2H,5H-1,3-Oxazino[5,6-c][1,2]benzothiazine-2,4(3H)-dione, 5-methyl-3-(2-pyridinyl)-, 6,6-dioxide [CAS]	90101-16-9	EP	99770	Anti-inflammatory	Inflammation, general
droxidopa	L-Tyrosine, ß,3-dihydroxy-, threo- [CAS]	23651-95-8	EP	128684	Antiparkinsonian	Parkinson's disease
Droxidopa		23651-95-8				
DU-125530	1,2-Benzisothiazol-3(2H)-one, 2-[4-[4-(7-chloro-2,3-dihydro-1,4-benzodioxin-5-yl)-1-piperazinyl]butyl]-, 1,1-dioxide [CAS]	161611-99-0	EP	633260	Anxiolytic	Anxiety, general
duloxetine	2-Thiophenepropanamine, N-methyl-Gamma-(1-naphthalenyloxy)-, hydrochloride, (S)- [CAS]	136434-34-9 116539-59-4	US	5362886	Antidepressant	Depression, general
duramycin			WO	9428726	Formulation, inhalable, solution	Cystic fibrosis
Durapatite		1306-06-5				
dutasteride	4-Azaandrost-1-ene-17-carboxamide, N-(2,5-bis(trifluoromethyl)phenyl)-3-oxo-, (5Alpha,17ß)- [CAS]	164656-23-9	US	5565467	Prostate disorders	Benign prostatic hyperplasia
DW-1141	N,N-diisopropyl-4-[4-(3-aminobenzo[d]isoxazol-6-yloxy)butoxy]-3-methoxybenzamide				Osteoporosis treatment	Osteoporosis
DW-286a	(R)-(-)-7-((4-aminomethyl-4-methyl-3-(Z)-methyloxyimino)pyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro[1,8]naphthyridine-3-carboxylic acid				Quinolone antibacterial	Infection, general
DW-471			US	5922871	Antiviral, other	Infection, hepatitis-B virus

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
DX-9065a	2-Naphthalenepropanoic acid, 7-(aminoiminomethyl)-Alpha-[4-[[1-(1-iminoethyl)-3-pyrrolidinyl]oxy]phenyl]-, monohydrochloride, pentahydrate, [S-(R*,R*)]- [CAS]	155204-81-2			Antithrombotic	Thrombosis, general
DY-9760e	1H-Indazole, 3-[2-[4-(3-chloro-2-methylphenyl)-1-piperazinyl]ethyl]-1-(1H-imidazol-4-ylmethyl)-5,6-dimethoxy- [CAS]	160522-00-9	US	5681954	Neuroprotective	Ischaemia, cerebral
Dyclonine		586-60-7				
Dydrogesterone		152-62-5				
Dymanthine		124-28-7				
Dyphylline		479-18-5				
E-1010	1-Azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid, 6-[(1R)-1-hydroxyethyl]-3-[[(3S,5S)-5-[(R)-hydroxy(3R)-3-pyrrolidinylmethyl]-3-pyrrolidinyl]thio]-4-methyl-7-oxo-, monohydrochloride, (4R,5S,6S)- [CAS]	186319-97-1			Beta-lactam antibiotic	Infection, general
E-2101	N-Ethyl-(1-[1-(2-fluorophenethyl)piperidin-4-yl]-1H-indol-6-yl)acetamide				Muscle relaxant	Muscle spasm, general
E2F antagonists			WO	9606943	Anticancer, other	Cancer, general
E-3620	Benzamide, 4-amino-5-chloro-N-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-2-[(1-methyl-2-butynyl)oxy]-, monohydrochloride, [3(S)-endo]- [CAS]	151213-86-4	EP	554794	Antacid/Antiflatulent	Dyspepsia
E-5564	Alpha-D-Glucopyranose, 3-O-decyl-2-deoxy-6-O-(2-deoxy-3-O-((3R)-3-methoxydecyl)-6-O-methyl-2-(((11Z)-1-oxo-11-octadecenyl)amino)-4-O-phosphono-ß-D-glucopyranosyl)-2-((1,3-dioxotetradecyl)amino)- 1-(dihydrogen phosphate), tetrasodium salt [CAS]	185954-98-7	EP	536969	Septic shock treatment	Sepsis

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
E-5842	Pyridine, 4-(4-fluorophenyl)-1,2,3,6-tetrahydro-1-[4-(1H-1,2,4-triazol-1-yl)butyl]-, 2-hydroxy-1,2,3-propanetricarboxylate (1:1) [CAS]	220120-14-9			Neuroleptic	Schizophrenia
E-6259	1-(4-Aminosulfonylphenyl)-5-(2,4-difluorophenyl)-4,5-dihydro-3-trifluoromethyl-1-H-pyrazole				Antiarthritic, other	Unspecified
EAA-90	[2-(8,9-Dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-yl)-ethyl]phosphonic acid				Analgesic, other	Pain, neuropathic
ε-Acetamidocaproic Acid		57-08-9				
ε-Aminocaproic Acid		60-32-2				
ebastine	1-Butanone, 1-[4-(1,1-dimethylethyl)phenyl]-4-[4-(diphenylmethoxy)-1-piperidinyl]- [CAS]	90729-43-4	EP	134124	Antiallergic, non-asthma	Rhinitis, allergic, seasonal
eberconazole	1H-Imidazole, 1-(2,4-dichloro-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)- [CAS]	128326-82-9 130104-32-4	ES	2012297	Antifungal	Infection, dermatological
ebrotidine	Benzenesulfonamide, N-[[2-[[[2-[(aminoiminomethyl)amino]-4-thiazolyl]methyl]thio]ethyl]amino]methylene]-4-bromo- [CAS]	100981-43-9	EP	159012	Antiulcer	Ulcer, duodenal
ebselen	1,2-Benzisoselenazol-3(2H)-one, 2-phenyl- [CAS]	60940-34-3	EP	44971	Neuroprotective	Haemorrhage, subarachnoid
Eburnamonine		474-00-0				
Ecabapide		104775-36-2				
ecabet	1-Phenanthrenecarboxylic acid, 1,2,3,4,4a,9,10,10a-octahydro-1,4a-dimethyl-7-(1-methylethyl)-6-sulfo-, [1R-(1Alpha,4aß,10aAlpha)]- [CAS]	33159-27-2 86408-72-2	DE	3239172	Antiulcer	Ulcer, gastric
ecadotril	Glycine, N-[2-[(acetylthio)methyl]-1-oxo-3-phenylpropyl]-,phenylmethyl ester, (S)- [CAS]	112573-73-6	EP	318377	Antihypertensive, other	Hypertension, general
Ecgonidine		484-93-5				
Ecgonine		481-37-8				
Echothiophate		513-10-0				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Econazole		27220-47-9				
ecopipam	5H-Benzo[d]naphth[2,1-b]azepin-12-ol, 11-chloro-6,6a,7,8,9,13b-hexahydro-7-methyl-, (6aS-trans)- [CAS]	112108-01-7	EP	230270	Anorectic/Antiobesity	Obesity
ecraprost	Prosta-8,13-dien-1-oic acid, 11,15-dihydroxy-9-(1-oxobutoxy)-, butyl ester, (11Alpha,13E,15S)- [CAS]	136892-64-3	EP	423697	Vasodilator, peripheral	Peripheral vascular disease
Ectylurea		95-04-5				
ED-71	9,10-Secocholesta-5,7,10(19)-triene-1,3,25-triol, 2-(3-hydroxypropoxy)-, (1Alpha,2ß,3ß,5Z,7E)- [CAS]	104121-92-8	EP	184206	Osteoporosis treatment	Osteoporosis
edaravone	3H-Pyrazol-3-one, 2,4-dihydro-5-methyl-2-phenyl- [CAS]	89-25-8	JP	62108814	Neuroprotective	Infarction, cerebral
Edatrexate		80576-83-6				
Edetate Calcium Disodium		62-33-9				
Edetate Disodium		139-33-3				
Edetate Sodium		64-02-8				
Edetate Trisodium		150-38-9				
edonentan	Butanamide,N-[[2'-[[4,5-dimethyl-3-isoxazoyl)amino]sulfonyl]-4-(2-oxazolyt)[1,1'-biphenyt]-2-yl]methyl]-N,3,3-trimethyl-, monohydrate	210891-04-6			Cardiostimulant	Heart failure
edotreotide	[N-[2-[4,7-Bis[(carboxy-kappaO)methyl]-10-(carboxymethyt)-1,4,7,10-tetraazacyclododec-1-yl-kappaN1,kappaN4,kappaN10]acetyl]-D-phenytalanyl-L-cysteinyl-L-tyrosyl-D-tryptophyl-L-lysyl-L-threonyl-L-cysteinyl-L-threoninol cyclic (2-7)-disulfidato(3-)]yttrium	204318-14-9	US	6183721	Anticancer, hormonal	Cancer, lung, small cell
edoxudine	Uridine, 2'-deoxy-5-ethyl- [CAS]	15176-29-1	GB	1170565	Antiviral, other	Infection, herpes virus, general
Edrecolomab		156586-89-9				
Edrophonium		116-38-1				
Efalith	Butanedioic acid, lithium salt [CAS]	16090-09-8			Antipruritic/inflamm, allergic	Eczema, seborrhoeic

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
efaproxiral	Propanoic acid, 2-[4-[2-[(3,5-dimethylphenyl)amino]-2-oxoethyl]phenoxy]-2-methyl- [CAS]	131179-95-8	US	5705521	Radio/chemosensitizer	Cancer, brain
efavirenz	2H-3,1-Benzoxazin-2-one, 6-chloro-4-(cyclopropylethynyl)-1,4-dihydro-4-(trifluoromethyl)-, (S)- [CAS]	154598-52-4	WO	9403440	Antiviral, anti-HIV	Infection, HIV/AIDS
efletirizine	[2-[4-[Bis(p-fluorophenyl)methyl]-1-piperazinyl]ethoxy]acetic acid	150756-35-7	GB	2311940	Antiallergic, non-asthma	Allergy, general
eflornithine	DL-Ornithine, 2-(difluoromethyl)- [CAS]	70052-12-9 67037-37-0	US	4413141	Protozoacide, dermal, topical	Infection, trypanosomiasis, African, Hirsutism
Efloxate		119-41-5				
eflucimibe	Benzeneacetamide, Alpha-(dodecylthio)-N-(4-hydroxy-2,3,5-trimethylphenyl)- (S)- [CAS]	202340-45-2			Hypolipaemic/Antiatherosclerosis	Hyperlipidaemia, general
efonidipine	3-pyridinecarboxylic acid, 5-(5,5-dimethyl-1,3,2-dioxaphosphorinan-2-yl)-1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-, 2-(phenyl(phenylmethyl)amino)ethyl ester, P-oxide [CAS]	111011-53-1 111011-63-3 111011-76-8	EP	230944	Antihypertensive, other	Hypertension, general
EGIS-7229	5-Chloro-4-[3-[N-[2-(3,4-dimethoxyphenyl)ethyl]-N-methylamino]propylamino]- 3(2H)-pyridazinone fumarate [CAS]	150800-12-7 190333-92-7	DE	4243381	Antiarrhythmic	Arrhythmia, general
eglumegad	Bicyclo[3.1.0]hexane-2,6-dicarboxylic acid, 2-amino-, (1S,2S,5R,6S)- [CAS]	176199-48-7 209216-09-1			Anxiolytic	Anxiety, general
egualen	1-Azulenesulfonic acid, 3-ethyl-7-(1-methylethyl)-,	97683-31-3 99287-30-6	EP	147915	Antiulcer	Ulcer, gastric
Eicosapentaenoic Acid		10417-94-4				
elarofiban	3-Pyridinepropanoic acid, ß-[((3R)-1-[1-oxo-3-(4-piperidinyl)propyl]-3-piperidinyl]carbonyl]amino]-, (ßS)- [CAS]	198958-88-2	WO	9741102	Antithrombotic	Thrombosis, general
Elcatonin		60731-46-6				
Eledoisin		69-25-0				
eletriptan	1H-Indole, 3-((1-methyl-2-pyrrolidinyl)methyl)-5-(2-(phenylsulfonyl)ethyl)- (R)- [CAS]	143322-58-1	US	5607951	Antimigraine	Migraine

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Elgodipine		119413-55-7				
Ellagic Acid		476-66-4				
Elliptinium		58337-35-2				
Eltoprazine		98224-03-4				
elvucitabine	ß-L-2',3'-Didehydro-2',3'-dideoxy-5-fluorocytidine	181785-84-2			Antiviral, other	Infection, hepatitis-B virus
elzasonan	(2Z)-4-(3,4-dichlorophenyl)-2-[2-(4-methylpiperazin-1-yl)benzylidene]thiomorpholin-3-one monohydrochloride- [CAS]	220322-05-4 361343-20-6			Antidepressant	Depression, general
Embelin		550-24-3				
Embramine		3565-72-8				
emedastine	1H-Benzimidazole, 1-(2-ethoxyethyl)-2-(hexahydro-4-methyl-1H-1,4-diazepin-1-yl)-, (E)-2-butenedioate (1:2) [CAS]	87233-61-2 87233-62-3	EP	79545	Antiallergic, non-asthma	Rhinitis, allergic, general
Emepronium		3614-30-0				
Emetine		483-18-1				
Emitefur		110690-43-2				
EMM-210525	17Alpha-Acetoxy-6Alpha-methyl-19-nor-1ß,2ß-dihydrocyclopropa[1,2']pregn-4-ene-3,20-dione+Estra-1,3,5(10)-triene-3,17-diol(17ß)				Formulation, fixed-dose combinations	Hormone replacement therapy
Emodin		518-82-1				
emorfazone	3(2H)-Pyridazinone, 4-ethoxy-2-methyl-5-(4-morpholinyl)- [CAS]	38957-41-4	JP	7224030	Anti-inflammatory	
EMR-62203			WO	9806722	Male sexual dysfunction	Impotence
emtricitabine	2(1H)-Pyrimidinone, 4-amino-5-fluoro-1-(2-(hydroxymethyl)-1,3-oxathiolan-5-yl)-, (2R-cis)- [CAS]	143491-57-0	WO	9214743	Antiviral, anti-HIV	Infection, HIV/AIDS
Emylcamate		78-28-4				
enalapril	L-Proline, 1-[N-[1-(ethoxycarbonyl)-3-phenylpropyl]-L-alanyl]-, (S)-, (Z)-2-butenedioate [CAS]	76095-16-4	US	4374829	Antihypertensive, renin system	
Enalaprilat		76420-72-9				
Enallylpropymal		1861-21-8				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Encainide		66778-36-7				
Enciprazine		68576-86-3				
Endralazine		39715-02-1				
enfenamic acid	Benzoic acid, 2-[(2-phenylethyl)amino]- [CAS]	23049-93-6	IN	103066	Anti-inflammatory	
enflurane	Ethane, 2-chloro-1-(difluoromethoxy)-1,1,2-trifluoro- [CAS]	13838-16-9	US	3469011	Anaesthetic, inhalation	Anaesthesia
Enilconazole		35554-44-0				
Eniluracil		59989-18-3				
ENMD-0995	S-3-amino-phthalidoglutarimide		US	5712291	Anticancer, other	Cancer, myeloma
Enocitabine		55726-47-1				
Enol-3-IPA	1H-Indole-3-propanoic acid, Alpha-oxo- [CAS]	392-12-1	EP	106813	Hypnotic/Sedative	Insomnia
enoxacin	1,8-Naphthyridine-3-carboxylic acid, 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)- [CAS]	74011-58-8	US	4359578	Quinolone antibacterial	Infection, general
enoxaparin	Heparin, [CAS]	9005-49-6 9041-08-1	EP	40144	Antithrombotic	Thrombosis, venous
enoximone	2H-Imidazol-2-one, 1,3-dihydro-4-methyl-5-[4-(methylthio)benzoyl]- [CAS]	77671-31-9	EP	59948	Cardiostimulant	Heart failure
Enoxolone		471-53-4				
enprostil	4,5-Heptadienoic acid, 7-[3-hydroxy-2-(3-hydroxy-4-phenoxy-1-butenyl)-5-oxocyclopentyl]-, methyl ester, [1Alpha,2ß(1E,3R*),3Alpha]- [CAS]	73121-56-9	GB	2025431	Prostaglandin	Ulcer, duodenal
enrasentan	1H-Indene-2-carboxylic acid, 1-(1,3-benzodioxol-5-yl)-2,3-dihydro-3-(2-(2-hydroxyethoxy)-4-methoxyphenyl)-5-propoxy-, (1S-(1Alpha,2ß,3Alpha))- [CAS]	167256-08-8	US	5817693	Antihypertensive, other	Hypertension, pulmonary
entacapone	2-Propenamide, 2-cyano-3-(4,5-dihydroxy-3-nitrophenyl)-N,N-diethyl- [CAS]	130929-57-6	EP	426468	Antiparkinsonian	Parkinson's disease
entecavir	6H-Purin-6-one, 2-amino-1,9-dihydro-9-((1S,3R,4S)-4-hydroxy-3-(hydroxymethyl)-2-methylenecyclopentyl]- [CAS]	142217-69-4	EP	481754	Antiviral, other	Infection, hepatitis-B virus

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Enviomycin		33103-22-9				
epalrestat	3-Thiazolidineacetic acid, 5-(2-methyl-3-phenyl-2-propenylidene)-4-oxo-2-thioxo-, (E,E)- [CAS]	82159-09-9	EP	47109	Symptomatic antidiabetic	Neuropathy, diabetic
Epavir	L-lysine-cis-5,8,11,14,17-eicosapentanoate with L-lysine-cis-4,7,10,13,16,19-doahexanoate				Antiviral, other	Infection, herpes simplex virus
EPC-K1	L-ascorbic acid 2-[3,4-dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-2H-1-benzopyran-6-yl-hydrogen phosphate]potassium- [CAS]	127061-56-7	EP	127471	Neuroprotective	Infarction, cerebral
eperisone	1-Propanone, 1-(4-ethylphenyl)-2-methyl-3-(1-piperidinyl)- [CAS]	64840-90-0	US	3995047	Muscle relaxant	Spastic paralysis
epervudine	Uridine, 2'-deoxy-5-(1-methylethyl)- [CAS]	60136-25-6	DE	2918260	Antiviral, other	Infection, herpes simplex virus
Ephedrine		299-42-3				
Epicillin		26774-90-3				
Epimestrol		7004-98-0				
epinastine	1H-Dibenz[c,f]imidazo[1,5-a]azepin-3-amine, 9,13b-dihydro- [CAS]	80012-43-7	DE	3008944	Antiasthma	Asthma
epinephrine	(R)-4-[1-hydroxy-2-(methylamino)-ethyl]-1,2-benzenediol	51-43-4			Formulation, inhalable, dry powder	Anaphylaxis
Epirizole		18694-40-1				
epirubicin	5,12-Naphthacenedione, 10-[(3-amino-2,3,6-trideoxy-Alpha-L-arabino-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-, (8S-cis)- [CAS]	56390-09-1 56420-45-2	GB	1457632	Anticancer, antibiotic	
Epitiostanol		2363-58-8				
eplerenone	Pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-17-hydroxy-3-oxo-,Gamma-lactone, methyl ester (7Alpha,11Alpha,17Alpha)- [CAS]	107724-20-9	EP	122232	Antihypertensive, diuretic	Hypertension, general

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
eplivanserin	1-Propanone, 1-(2-fluorophenyl)-3-(4-hydroxyphenyl)-, O-(2-(dimethylamino)ethyl)oxime, (Z)-, (E)-2-butenedioate (2:1) (salt) [CAS]	130580-02-8	EP	373998	Anxiolytic	Schizophrenia
epoprostenol	Prosta-5,13-dien-1-oic acid, 6,9-epoxy-11,15-dihydroxy-, (5Z,9Alpha,11Alpha,13E,15S)-[CAS]	35121-78-9 61849-14-7	DE	2720999	Prostaglandin	Hypertension, pulmonary
Epostane		80471-63-2				
Eprazinone		10402-90-1				
Epristeride		119169-78-7				
eprosartan	3-[2-Butyl-1-(4-carboxybenzyl)-1H-imidazol-5-yl]-2-(2-thienylmethyl)-2-(E)-propenoic acid	133040-01-4	EP	403159	Antihypertensive, renin system	Hypertension, general
Eprozinol		32665-36-4				
eptapirone	4-methyl-2-[4-(4-(pyrimidin-2-yl)-piperazino)-butyl]-2H,4H-1,2,4-triazin-3,5-dione	179756-85-5			Antidepressant	Depression, general
eptaplatin	Platinum, [(4R,5R)-2-(1-methylethyl)-1,3-dioxolane-4,5-dimethanamine-kappaN4,kappaN5][propanedioato(2-)-kappaO1,kappaO3]-, (SP-4-2)- [CAS]	146665-77-2	WO	9216539	Anticancer, alkylating	Cancer, lung, small cell
Eptastigmine		101246-68-8				
eptazocine	1,6-Methano-1H-4-benzazonin-10-ol, 2,3,4,5,6,7-hexahydro-1,4-dimethyl-, (1S)-[CAS]	72522-13-5	US	4082744	Analgesic, other	
Eptifibatide		188627-80-7				
Equilenin		517-09-9				
Equilin		474-86-2				
ERA-923	ERA 923 [CAS]	352233-89-7	EP	802183	Female contraceptive	Contraceptive, female
erdosteine	Acetic acid, [[2-oxo-2-[(tetrahydro-2-oxo-3-thienyl)amino]ethyl]thio]- [CAS]	84611-23-4	EP	61386	Respiratory	Respiratory disease, general
Ergocornine		564-36-3				
Ergocorninine		564-37-4				
Ergoloid Mesylates		8067-24-1				
Ergonovine		60-79-7				
Ergosterol		57-87-4				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
ergotamine	(5'Alpha)-12'-Hydroxy-2'methyl-(phenylmethyl)ergotaman-3',6', 18-trione	113-15-5			Formulation, inhalable, systemic	Migraine
Eritadenine		23918-98-1				
erlotinib	4-Quinazolinamine, N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-, monohydrochloride [CAS]	183319-69-9	WO	9630347	Anticancer, other	Cancer, lung, non-small cell
ertapenem	1-Azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid, 3-[[(3S,5S)-5-[[(3-carboxyphenyl)amino]carbonyl]-3-pyrrolidinyl]thio]-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-, [CAS]	153773-82-1 153832-46-3	WO	9315078	Beta-lactam antibiotic	Infection, GI tract
Erythrityl Tetranitrate		7297-25-8				
Erythrocentaurin		50276-98-7				
erythromycin acistrate	Erythromycin, 2'-acetate, octadecanoate (salt) [CAS]	96128-89-1	US	4599326	Macrolide antibiotic	Infection, general
Erythromycin Estolate		3521-62-8				
Erythromycin Glucoheptonate		23067-13-2				
Erythromycin Lactobionate		3847-29-8				
Erythromycin Propionate		134-36-1				
Erythromycin Stearate		643-22-1				
erythromycin stinoprate	Erythromycin, 2'-propanoate, compd. with N-acetyl-L-cysteine (1:1) [CAS]	84252-03-9	EP	57489	Macrolide antibiotic	Infection, respiratory tract, lower
erythromycin	Erythromycin [CAS]	114-07-8			Formulation, dermal, topical	Acne
Erythrophleine		36150-73-9				
Esaprazole		64204-55-3				
escitalopram	5-Isobenzofurancarbonitrile, 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-, (S)- [CAS]	128196-01-0	EP	347066	Antidepressant	Depression, general
Esculin		531-75-9				
Eseridine		25573-43-7				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
esmolol	Benzenepropanoic acid, 4-[2-hydroxy-3-[(1-methylethyl)amino]propoxy]-, methyl ester, (+/-)- [CAS]	81147-92-4	US	4387103	Antihypertensive, adrenergic	Tachycardia, supraventricular
esomeprazole	bis (5-methoxy-2-(((4-methoxy-3,5-dimethyl-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazolato)	161973-10-0	US	5877192	Antispasmodic	Gastro-oesophageal reflux
estazolam	4H-[1,2,4]Triazolo[4,3-a][1,4]benzodiazepine, 8-chloro-6-phenyl- [CAS]	29975-16-4	US	3987052	Hypnotic/Sedative	
estradiol	Androst-4-en-3-one, 17-hydroxy-, (17ß)- [CAS]	58-22-0	US	5460820	Formulation, transdermal, patch	Sexual dysfunction, female
estradiol	Estra-1,3,5(10)-triene-3,17-diol (17ß)- [CAS]	50-28-2	EP	430491	Formulation, transdermal, systemic	Menopausal symptoms, general
estramustine	Estra-1,3,5(10)-triene-3,17-diol (17ß)-, 3-[bis(2-chloroethyl)carbamate] 17- [CAS]	2998-57-4 4891-15-0 52205-73-9			Anticancer, alkylating	Cancer, prostate
Estriol		50-27-1				
estrogen			WO	9924041	Menopausal disorders	Menopausal symptoms, general
Estrone		53-16-7				
eszopiclone	1-Piperazinecarboxylic acid, 4-methyl- 6-(5-chloro-2-pyridinyl)-6,7-dihydro-7-oxo-5H-pyrrolo(3,4-b)pyrazin-5-yl ester (S)- [CAS]	138729-47-2	US	5786357	Hypnotic/Sedative	Insomnia
Etafedrine		7681-79-0				
Etafenone		90-54-0				
Etamiphyllin		314-35-2				
Etanercept		185243-69-0				
Etanidazole		22668-01-5				
Etaqualone		7432-25-9				
Eterobarb		27511-99-5				
Ethacridine		442-16-0				
Ethacrynic Acid		58-54-8				
Ethadione		520-77-4				
Ethambutol		74-55-5				
Ethamivan		304-84-7				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Ethamsylate		2624-44-4				
Ethanolamine		141-43-5				
Ethaverine		486-47-5				
Ethchlorvynol		113-18-8				
Ethenzamide		938-73-8				
Ethiazide		1824-58-4				
Ethinamate		126-52-3				
Ethinyl Estradiol		57-63-6				
ethinyl estradiol	19-Norpregna-1,3,5(10)-trien-20-yne-3,17-diol, 3-(2-propanesulfonate), (17Alpha)- [CAS]	28913-23-7	DE	1949095	Formulation, modified-release, >24hr	Cancer, prostate
Ethionamide		536-33-4				
Ethisterone		434-03-7				
Ethoheptazine		77-15-6				
Ethopropazine		522-00-9				
Ethosuximide		77-67-8				
Ethotoin		86-35-1				
Ethoxzolamide		452-35-7				
Ethybenztropine		524-83-4				
Ethyl Alcohol		64-17-5				
Ethyl Biscoumacetate		548-00-5				
Ethyl Chloride		75-00-3				
Ethyl Dibunate		5560-69-0				
Ethyl Ether		60-29-7				
ethyl icosapentate	5,8,11,14,17-Eicosapentaenoic acid, ethyl ester, (all-Z)- [CAS]	86227-47-6	JP	61043143	Antithrombotic	Peripheral vascular disease
ethyl loflazepate	1H-1,4-Benzodiazepine-3-carboxylic acid, 7-chloro-5-(2-fluorophenyl)-2,3-dihydro-2-oxo-, ethyl ester [CAS]	29177-84-2	US	3657223	Anxiolytic	Anxiety, general
Ethyl Loflazepate		29177-84-2				
Ethylamine		75-04-7				
Ethylene		74-85-1				
Ethylestrenol		965-90-2				
Ethylidene Dicoumarol		1821-16-5				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Ethylmethylthiambutene		441-61-2				
Ethylmorphine		76-58-4				
Ethylnorepinephrine		536-24-3				
Ethynodiol		1231-93-2				
ethynylcytidine	Uridine, 3'-C-ethynyl- [CAS]	180300-49-6	WO	9618636	Anticancer, antimetabolite	Cancer, general
Etidocaine		36637-18-0				
etidronate	Phosphonic acid, (1-hydroxyethylidene)bis-, [CAS]	2809-21-4 7414-83-7	US	4137309	Osteoporosis treatment	Osteoporosis
Etidronic Acid		2809-21-4				
Etifelmin		341-00-4				
etifoxine	4H-3,1-Benzoxazin-2-amine, 6-chloro-N-ethyl-4-methyl-4-phenyl- [CAS]	21715-46-8	US	3725404	Anxiolytic	
Etilefrin		709-55-7				
etilevodopa	L-Tyrosine, 3-hydroxy-, ethyl ester [CAS]	37178-37-3	US	5354885	Antiparkinsonian	Parkinson's disease
etiprednol	androsta-1,4-diene-17-carboxylic acid, 17-[(dichloroacetyl)oxy]-11-hydroxy-3-oxo-, ethyl ester, (11ß,17Alpha)-	199331-40-3			GI inflammatory/bowel disorders	Crohn's disease
Etiroxate		17365-01-4				
Etizolam		40054-69-1				
etodolac	Pyrano[3,4-b]indole-1-acetic acid, 1,8-diethyl-1,3,4,9-tetrahydro- [CAS]	41340-25-4	US	3939178	Antiarthritic, other	Arthritis, osteo
Etodroxizine		17692-34-1				
etofenamate	Benzoic acid, 2-[[3-(trifluoromethyl)phenyl]amino]-, 2-(2-hydroxyethoxy)ethyl ester [CAS]	30544-47-9	GB	1285400	Anti-inflammatory, topical	Inflammation, general
etofibrate	3-Pyridinecarboxylic acid, 2-[2-(4-chlorophenoxy)-2-methyl-1-oxopropoxy]ethyl ester [CAS]	31637-97-5	US	3723446	Hypolipaemic/Antiatherosclerosis	
Etofylline		519-37-9				
etofylline clofibrate	Propanoic acid, 2-(4-chlorophenoxy)-2-methyl-, 2-(1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo-7H-purin-7-yl)ethyl ester [CAS]	54504-70-0	DE	2308826	Hypolipaemic/Antiatherosclerosis	
Etofylline Nicotinate		13425-39-3				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Etoglucid		1954-28-5				
Etomidate		33125-97-2				
Etomidoline		21590-92-1				
Etonitazene		911-65-9				
etonogestrel	18,19-Dinorpregn-4-en-20-yn-3-one, 13-ethyl-17-hydroxy-11-methylene, (17Alpha)- [CAS]	54048-10-1			Formulation, implant	Contraceptive, female
Etoperidone		52942-31-1				
etoposide	Furo[3',4':6,7]naphtho[2,3-d]-1,3-dioxol-6(5aH)-one, 9-[(4,6-O-ethylidene-ß-D-glucopyranosyl)oxy]-5,8,8a,9-tetrahydro-5-(4-hydroxy-3,5-dimethoxyphenyl)-, [5R-[5Alpha,5aß,8aAlpha,9ß(R*)]]- [CAS]	33419-42-0	GB	1205966	Anticancer, other	Cancer, testicular
etoposide phosphate	Furo[3',4':6,7]naphtho[2,3-d]-1,3-dioxol-6(5aH)-one, 5-[3,5-dimethoxy-4-(phosphonooxy)phenyl]-9-[(4,6-0-ethylidene-ß-D-glucopyranosyl)oxy]-5,8,8a,9-tetrahydro-, [5R-[5Alpha,5aß,8aAlpha,9ß(R*)]]- [CAS]	117091-64-2	EP	302473	Anticancer, other	Cancer, testicular
etoricoxib	2,3-Bipyridine, 5-chloro-6'-methyl-3-(4-(methylsulfonyl)phenyl) [CAS]	202409-33-4	WO	9803484	Antiarthritic, other	Arthritis, osteo
Etoxadrol		28189-85-7				
Etozolin		73-09-6				
etretinate	2,4,6,8-Nonatetraenoic acid, 9-(4-methoxy-2,3,6-trimethylphenyl)-3,7-dimethyl-, ethyl ester, (all-E)- [CAS]	54350-48-0	US	4215215	Antipsoriasis	
Etryptamine		2235-90-7				
Etymemazine		523-54-6				
Eucatropine		100-91-4				
Eugenol		97-53-0				
EUK-134	Manganese, chloro[[2,2'-[1,2-ethanediylbis[(nitrilo-kappaN)methylidyne]]bis(6-methoxyphenolato-kappaO]][]-, (SP-5-13)- [CAS]	81065-76-1	US	6046188	Cardiovascular	Unspecified

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
EUK-189			US	6046188	Radio/chemoprotective	Chemotherapy-induced injury, general
Evan's Blue		314-13-6				
everolimus	Rapamycin, 42-O-(2-hydroxyethyl)- [CAS]	159351-69-6	WO	9409010	Immunosuppressant	Transplant rejection, general
exalamide	Benzamide, 2-(hexyloxy)- [CAS]	53370-90-4	GB	726786	Antifungal	Infection, fungal, general
Exametazime		105613-48-7				
exatecan	10H,13H-Benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinoline-10,13-dione, 1-amino-9-ethyl-5-fluoro-1,2,3,9,12,15-hexahydro-9-hydroxy-4-methyl-, (1S,9S)-, [CAS]	171335-80-1			Anticancer, other	Cancer, pancreatic
exemestane	Androsta-1,4-diene-3,17-dione, 6-methylene- [CAS]	107868-30-4	DE	3622841	Anticancer, hormonal	Cancer, breast
Exifone		52479-85-3				
exisulind	1H-Indene-3-acetic acid 5-fluoro-2-methyl-1-((4-(methylsulfonyl)phenyl)methylene)-, (Z)- [CAS]	59973-80-7			Anticancer, other	Polyp
Exosurf®		99732-49-7				
ezetimibe	2-Azetidinone, 1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxyphenyl)-, (3R,4S)- [CAS]	163222-33-1	US	5846966	Hypolipaemic/Antiatherosclerosis	Hypercholesterolaemia
Factor IX		9001-28-9				
Factor VIII		9001-27-8				
Factor XIII		9013-56-3				
fadolmidine	1H-Inden-5-ol, 2,3-dihydro-3-(1H-imidazol-4-ylmethyl)-, monohydrochloride [CAS]	189353-32-0	WO	9712874	Analgesic, other	Pain, general
Fadrozole		102676-47-1				
falecalcitriol	9,10-Secocholesta-5,7,10(19)-triene-1,3,25-triol, 26,26,26,27,27,27-hexafluoro-, (1Alpha,3ß,5Z,7E)- [CAS]	83805-11-2	JP	03099022	Osteoporosis treatment	Hyperparathyroidism
famciclovir	1,3-Propanediol, 2-[2-(2-amino-9H-purin-9-yl)ethyl]-, diacetate (ester)- [CAS]	104227-87-4	JP	61085388	Antiviral, other	Infection, gynaecological

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
famotidine	Propanimidamide, 3-[[[2-[(aminoiminomethyl)amino]-4-thiazolyl]methyl]thio]-N-(aminosulfonyl)- [CAS]	76824-35-6	US	4283408	Antiulcer	Ulcer, duodenal
fampridine	4-pyridinamine	504-24-5			Neuroprotective	Spinal cord injury
fandofloxacin	3-Quinolinecarboxylic acid, 6-fluoro-1-(5-fluoro-2-pyridinyl)-1,4-dihydro-7-(4-methyl-1-piperazinyl)-4-oxo, [CAS]	164150-85-0 164150-99-6	US	5496947	Quinolone antibacterial	Infection, urinary tract
Fantofarone		114432-13-2				
faropenem daloxate	(5R,6S)-6-[1(R)-Hydroxyethyl]-2-[2(R)-tetrahydrofuryl]-2-penem-3-carboxylic acid-5-methyl-2-oxo-1,3-dioxol-4-ylmethyl ester				Beta-lactam antibiotic	Infection, general
faropenem	4-Thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid, 6-(1-hydroxyethyl)-7-oxo-3-(tetrahydro-2-furanyl)-, [5R-[3(R*),5Alpha,6Alpha(R*)]]-[CAS]	122547-49-3	EP	410727	Beta-lactam antibiotic	Infection, ocular
fasidotril	L-Alanine, N-[(2S)-3-(acetylthio)-2-(1,3-benzodioxol-5-ylmethyl)-1-oxopropyl]-, phenylmethyl ester [CAS]	135038-57-2	EP	419327	Antihypertensive, renin system	Hypertension, general
fasudil	1H-1,4-Diazepine, hexahydro-1-(5-isoquinolinylsulfonyl)- [CAS]	103745-39-7 105628-07-7	EP	187371	Neuroprotective	Vasospasm, general
Fazadinium Bromide		49564-56-9				
febarbamate	2,4,6(1H,3H,5H)-Pyrimidinetrione, 1-[2-[(aminocarbonyl)oxy]-3-butoxypropyl]-5-ethyl-5-phenyl- [CAS]	13246-02-1	US	3075983	Psychostimulant	
Febuprol		3102-00-9				
febuxostat	5-Thiazolecarboxylic acid, 2-[3-cyano-4-(2-methylpropoxy)phenyl]-4-methyl- [CAS]	144060-53-7	WO	9209279	Antigout	Hyperuricaemia
Fedotozine		123618-00-8				
felbamate	1,3-Propanediol, 2-phenyl-, dicarbamate [CAS]	25451-15-4	US	4868327	Antiepileptic	Epilepsy, general
felbinac	[1,1'-Biphenyl]-4-acetic acid [CAS]	5728-52-9	EP	127840	Anti-inflammatory, topical	
felodipine	3,5-Pyridinedicarboxylic acid, 4-(2,3-dichlorophenyl)-1,4-dihydro-2,6-dimethyl-, ethyl methyl ester [CAS]	72509-76-3	US	4264611	Antihypertensive, other	Hypertension, general
Felypressin		56-59-7				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Femoxetine		59859-58-4				
Fenbenicillin		1926-48-3				
fenbufen	[1,1'-Biphenyl]-4-butanoic acid, Gamma-oxo- [CAS]	36330-85-5	US	3784701	Anti-inflammatory	
Fenbutrazate		4378-36-3				
Fencamfamine		1209-98-9				
Fencamine		28947-50-4				
Fenclozic Acid		17969-20-9				
Fendiline		13042-18-7				
Fendosal		53597-27-6				
Fenethylline		3736081				
Fenfluramine		458-24-2				
Fenipentol		583-03-9				
fenofibrate	Propanoic acid, 2-[4-(4-chlorobenzoyl)phenoxy]-2-methyl-, 1-methylethyl ester [CAS]	26129-32-8 49562-28-9			Formulation, modified-release, <=24hr	Hyperlipidaemia, general
fenoldopam	1H-3-Benzazepine-7,8-diol, 6-chloro-2,3,4,5-tetrahydro-1-(4-hydroxyphenyl)- [CAS]	67227-56-9 67227-57-0	EP	22330	Antihypertensive, other	Hypertension, general
Fenoprofen		31879-05-7				
Fenoterol		13392-18-2				
fenoverine	10H-Phenothiazine, 10-[[4-(1,3-benzodioxol-5-ylmethyl)-1-piperazinyl]acetyl]-[CAS]	37561-27-6	FR	2092639	Antispasmodic	
Fenoxazoline		4846-91-7				
Fenoxedil		54063-40-0				
Fenozolone		15302-16-6				
Fenpentadiol		15687-18-0				
Fenpiprane		3540-95-2				
Fenpiverinium Bromide		125-60-0				
Fenproporex		15686-61-0				
Fenquizone		20287-37-0				
fenretinide	Retinamide, N-(4-hydroxyphenyl)- [CAS]	65646-68-6	BE	847942	Anticancer, other	Cancer, breast

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Fenspiride		5053066				
fentanyl	Propanamide, N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]- [CAS]	437-38-7			Formulation, transmucosal, systemic	Anaesthesia, adjunct
Fentiazac		18046-21-4				
Fenticlor		97-24-5				
fenticonazole	1H-Imidazole, 1-[2-(2,4-dichlorophenyl)-2-[[4-(phenylthio)phenyl]methoxy]ethyl]- [CAS]	72479-26-6 73151-29-8	US	4221803	Antifungal	Infection, gynaecological
Fentonium Bromide		5868064				
fepradinol	Benzenemethanol, Alpha-[[(2-hydroxy-1,1-dimethylethyl)amino]methyl]-, (+/-)- [CAS]	36981-91-6 67704-50-1 63075-47-8			Anti-inflammatory, topical	
Feprazone		30748-29-9				
Ferric Sodium Edetate		15708-41-5				
ferrioxamine B			WO	9426263	Septic shock treatment	Respiratory distress syndrome, adult
Ferrocholinate		1336-80-7				
Ferrous Gluconate		299-29-6				
ferumoxytol	Polyglucose sorbitol carboxymethyl ether-coated non-stoichiometric magnetite				Imaging agent	Diagnosis, cancer
fesoterodine	2-((1R)-3-(bis(1-methylethyl)amino)-1-phenylpropyl)-4-(hydroxymethyl)Phenyl ester, (2E)-2-butenedioate (1:1) (Salt) - [CAS]	286930-03-8			Urological	Incontinence
fexofenadine	Benzeneacetic acid, 4-[1-hydroxy-4-[4(hydroxydiphenylmethyl)-1-piperidinyl]butyl]-Alpha,Alpha-dimethyl-, [CAS]	153439-40-8 83799-24-0 138452-21-8	US	5375693	Antiallergic, non-asthma	Rhinitis, allergic, seasonal
Fibrostat			CA	2132416	Vulnerary	Wound healing
fidarestat	Spiro(4H-1-benzopyran-4,4'-imidazolidine)-2-carboxamide, 6-fluoro-2,3-dihydro-2',5'-dioxo-, (2S-cis)-, [CAS]	136087-85-9	EP	418834	Symptomatic antidiabetic	Neuropathy, diabetic

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
fiduxosin	8-Phenyl-3-[4-[(3aR,9bR)-1,3a,4,9b-tetrahydro-9-methoxy[1]benzopyrano[3,4-c]pyrrol-2(3H)-yl]butyl]pyrazino[2',3':4,5]thieno[3,2-d]pyrimidine-2,4(1H,3H)-dione	208993-54-8			Prostate disorders	Benign prostatic hyperplasia
finasteride	4-Azaandrost-1-ene-17-carboxamide, N-(1,1-dimethylethyl)-3-oxo-, (5Alpha,17ß)- [CAS]	98319-26-7	EP	155096	Prostate disorders	Benign prostatic hyperplasia
finrozole	Benzonitrile, 4-(3-(4-fluorophenyl)-2-hydroxy-1-(1H-1,2,4-triazol-1-yl)-propyl)- [CAS]	160146-16-7	EP	476944	Urological	Urinary retention
Fipexide		34161-24-5				
FK-960	N-(4-Acetyl-1-piperazinyl)-4-fluorobenzamide monohydrate- [CAS]	133920-70-4	WO	9101979	Cognition enhancer	Alzheimer's disease
Flavopiridol		146426-40-6				
flavoxate	4H-1-Benzopyran-8-carboxylic acid, 3-methyl-4-oxo-2-phenyl-, 2-(1-piperidinyl)ethyl ester [CAS]	15301-69-6 3717-88-2	US	2921070	Urological	
flecainide	Benzamide,N-(2-piperidinylmethyl)-2,5-bis(2,2,2-trifluoroethoxy)-,[CAS]	54143-55-4 54143-56-5			Formulation, modified-release, <=24hr	Fibrillation, atrial
fleroxacin	3-Quinolinecarboxylic acid, 6,8-difluoro-1-(2-fluoroethyl)-1,4-dihydro-7-(4-methyl-1-piperazinyl)-4-oxo- [CAS]	79660-53-0 79660-72-3	US	4398029	Quinolone antibacterial	Infection, general
Flesinoxan		98206-10-1				
flibanserin	2H-Benzimidazol-2-one, 1,3-dihydro-1-(2-(4-(3-(trifluoromethyl)phenyl)-1-piperazinyl)ethyl)- [CAS]	167933-07-5			Reproductive/gonadal, general	Sexual dysfunction, female
floctafenine	Benzoic acid, 2-[[8-(trifluoromethyl)-4-quinolinyl]amino]-, 2,3-dihydroxypropyl ester [CAS]	23779-99-9	US	3644368	Analgesic, NSAID	
flomoxef	5-Oxa-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[[[(difluoromethyl)thio]acetyl]amino]-3-[[[1-(2-hydroxyethyl)-1H-tetrazol-5-yl]thio]methyl]-7-methoxy-8-oxo-, (6R-cis)- [CAS]	92823-03-5 99665-00-6	EP	128536	Cephalosporin, injectable	Infection, general

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Flopropione		2295-58-1				
Florantyrone		519-95-9				
Flosequinan		76568-02-0				
Floxacillin		5250-39-5				
Floxuridine		50-91-9				
Fluacizine		30223-48-4				
Fluanisone		1480-19-9				
fluasterone	Androst-5-en-17-one, 16-fluoro-, (16Alpha)- [CAS]	112859-71-9	EP	246650	Cardiovascular	Keratosis
fluazacort	5'H-Pregna-1,4-dieno[17,16-d]oxazole-3,20-dione, 21-(acetyloxy)-9-fluoro-11-hydroxy-2'-methyl-, (11ß,16ß)- [CAS]	19888-56-3	US	3461119	Antipruritic/inflamm, non-allergic	
Flucloronide		3693-39-8				
flucloxacillin		1847-24-1 34214-51-2			Formulation, other	Infection, general
fluconazole	1H-1,2,4-Triazole-1-ethanol, Alpha-(2,4-difluorophenyl)-Alpha-(1H-1,2,4-triazol-1-ylmethyl)- [CAS]	86386-73-4	EP	96569	Antifungal	Infection, dermatological
Flucytosine		2022-85-7				
fludarabine	9H-Purin-6-amine, 2-fluoro-9-(5-O-phosphono-ß-D-arabinofuranosyl)- [CAS]	75607-67-9 21679-14-1	US	4357324	Anticancer, antimetabolite	Cancer, leukaemia, chronic lymphocytic
Fludeoxyglucose F_{18}		105851-17-0				
Fludiazepam		3900-31-0				
Fludrocortisone		127-31-1				
Flufenamic Acid		530-78-9				
Fluindione		957-56-2				
flumazenil	4H-Imidazo[1,5-a][1,4]benzodiazepine-3-carboxylic acid, 8-fluoro-5,6-dihydro-5-methyl-6-oxo-, ethyl ester [CAS]	78755-81-4	EP	27214	Neurological	
Flumecinol		56430-99-0				
Flumequine		42835-25-6				
Flumethasone		2135-17-3				
Flumethiazide		148-56-1				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
flunarizine	Piperazine, 1-[bis(4-fluorophenyl)methyl]-4-(3-phenyl-2-propenyl)-,(E)- [CAS]	30484-77-6 52468-60-7 27848-84-6	GB	1268710	Antimigraine	
flunisolide	Pregna-1,4-diene-3,20-dione, 6-fluoro-11,21-dihydroxy-16,17-[(1-methylethylidene)bis(oxy)]-, (6Alpha,11ß,16Alpha)- [CAS]	3385-03-3	US	3124571	Antiasthma	Rhinitis, allergic, general
flunitrazepam	2H-1,4-Benzodiazepin-2-one, 5-(2-fluorophenyl)-1,3-dihydro-1-methyl-7-nitro- [CAS]	1622-62-4	US	3116203	Hypnotic/Sedative	
Flunoxaprofen		66934-18-7				
Fluocinolone Acetonide		67-73-2				
Fluocinonide		356-12-7				
Fluocortin Butyl		41767-29-7				
Fluocortolone		152-97-6				
Fluorescein		2321-07-5				
Fluoresone		2924-67-6				
Fluorometholone		426-13-1				
Fluorosalan		4776061				
fluorouracil	2,4(1H,3H)-Pyrimidinedione, 5-fluoro- [CAS]	51-21-8			Formulation, transdermal, enhanced	Keratosis
fluoxetine	Benzenepropanamine, N-methyl-Gamma-[4-(trifluoromethyl)phenoxy]-, (+/-)- [CAS]	54910-89-3 56296-78-7	US	4314081	Antidepressant	Depression, general
Fluoxymesterone		76-43-7				
Flupentixol		2709-56-0				
Fluperolone		2119-75-7				
Fluphenazine		69-23-8				
flupirtine	Carbamic acid, [2-amino-6-[[(4-fluorophenyl)methyl]amino]-3-pyridinyl]-, ethyl ester [CAS]	33400-45-2 56995-20-1 75507-68-5	US	4481205	Analgesic, other	Pain, post-operative
Fluprednidene Acetate		1255-35-2				
Fluprednisolone		53-34-9				
Fluproquazone		40507-23-1				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Flurandrenolide		1524-88-5				
Flurazepam		17617-23-1				
flurbiprofen	[1,1'-Biphenyl]-4-acetic acid, 2-fluoro-Alpha-methyl- [CAS]	5104-49-4	US	3793457	Anti-inflammatory	
flurithromycin	Erythromycin, 8-fluoro-mono(ethyl butanedioate) (ester)- [CAS]	82730-23-2	EP	56291	Macrolide antibiotic	Infection, respiratory tract, lower
Flurogestone		2529-45-5				
Flurothyl		333-36-8				
Fluroxene		406-90-6				
Fluspirilene		1841-19-6				
flutamide	Propanamide, 2-methyl-N-[4-nitro-3-(trifluoromethyl)phenyl]- [CAS]	13311-84-7	US	4329364	Anticancer, hormonal	
flutazolam	Oxazolo[3,2-d][1,4]benzodiazepin-6(5H)-one, 10-chloro-11b-(2-fluorophenyl)-2,3,7,11b-tetrahydro-7-(2-hydroxyethyl)- [CAS]	27060-91-9	US	3905956	Anxiolytic	
fluticasone	Androsta-1,4-diene-17-carbothioic acid, 6,9-difluoro-11,17-dihydroxy-16-methyl-3-oxo-, S-(fluoromethyl) ester, (6Alpha,11ß,16Alpha,17Alpha)- [CAS]	80474-14-2 90566-53-3			Formulation, inhalable, solution	Asthma
flutoprazepam	2H-1,4-Benzodiazepin-2-one, 7-chloro-1-(cyclopropylmethyl)-5-(2-fluorophenyl)-1,3-dihydro- [CAS]	25967-29-7	GB	1253368	Anxiolytic	Psychosis, general
flutrimazole	1H-Imidazole, 1-[(2-fluorophenyl)(4-fluorophenyl)phenylmethyl]- [CAS]	119006-77-8	EP	352352	Antifungal	Infection, dermatological
Flutropium Bromide		63516-07-4				
fluvastatin	6-Heptenoic acid, 7-[3-(4-fluorophenyl)-1-(1-methylethyl)-1H-indol-2-yl]-3,5-dihydroxy-, monosodium salt, [R*,S*-(E)]-(±)- [CAS]	93957-55-2 93957-54-1	EP	114027	Hypolipaemic/Antiatherosclerosis	Hypercholesterolaemia
fluvoxamine	1-Pentanone, 5-methoxy-1-[4-(trifluoromethyl)phenyl]-O-(2-aminoethyl)oxime, (E)- [CAS]	54739-18-3 61718-82-9	GB	1535226	Antidepressant	Depression, general, Obsessive-compulsive disorder
Folic Acid		59-30-3				
Folinic Acid		58-05-9				
Fomepizole		7554-65-6				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
fominoben	Benzamide, N-[3-chloro-2-[[methyl[2-(4-morpholinyl)-2-oxoethyl]amino]methyl]phenyl]- [CAS]	18053-31-1 24600-36-0	US	3661903	Respiratory stimulant	Eczema, general
Fomivirsen		144245-52-3				
Fomocaine		17692-39-6				
Fonazine		7456-24-8				
fondaparinux	Alpha-D-Glucopyranoside, methyl O-2-deoxy-6-O-sulfo-2-(sulfoamino)-Alpha-D-glucopyranosyl-(1-4)-O-ß-D-glucopyranuronosyl-(1-4)-O-2-deoxy-3,6-di-O-sulfo-2-(sulfoamino)-Alpha-D-glucopyranosyl-(1-4)-O-2-O-sulfo-Alpha-L-idopyranuronosyl-(1-4)-2-deoxy-2-(sulfoamino)-,6-(hydrogen sulfate) [CAS]	104993-28-4 114870-03-0			Anticoagulant	Thrombosis, venous
Formebolone		2454117				
formestane	Androst-4-ene-3,17-dione, 4-hydroxy- [CAS]	566-48-3	EP	346953	Anticancer, hormonal	Cancer, breast
Formocortal		2825-60-7				
formoterol	Formamide, N-[2-hydroxy-5-[1-hydroxy-2-[[2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl]-, (R*,R*)-(+/-)- [CAS]	43229-80-7 73573-87-2	GB	1415256	Antiasthma	Asthma
fosamprenavir	Carbamic acid, ((1S,2R)-3-(((4-aminophenyl)sulfonyl)(2-methylpropyl)amino)-1-(phenylmethyl)-2-(phosphonooxy)propyl)- C-((3S)-tetrahydro-3-furanyl ester, [CAS]	226700-81-8			Antiviral, anti-HIV	Infection, HIV/AIDS
foscarnet	Phosphinecarboxylic acid, dihydroxy-, oxide, trisodium salt [CAS]	34156-56-4 4428-95-9 63585-09-1	US	4839445	Antiviral, other	Infection, cytomegalovirus
Fosfestrol		522-40-7				
fosfluconazole	2,4-difluoro-Alpha,Alpha-bis(1H-1,2,4-triazol-1-ylmethyl)benzyl alcohol, dihydrogen phosphate (ester)	194798-83-9			Antifungal	Infection, fungal, general
fosfomycin	Phosphonic acid, (3-methyloxiranyl)-, (2R-cis)- [CAS]	23155-02-4 26016-98-8	GB	1223923	Antibiotic, other	Infection, general

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
fosfomycin trometamol	Phosphonic acid, (3-methyloxiranyl)-, (2R-cis)-, compd. with 2-amino-2-(hydroxymethyl)-1,3-propanediol (1:1)- [CAS]	78964-85-9	EP	27597	Antibiotic, other	Infection, urinary tract
Fosfosal		6064-83-1				
fosinopril	L-Proline, 4-cyclohexyl-1-[[[2-methyl-1-(1-oxopropoxy)propoxy](4-phenylbutyl)phosphinyl]acetyl]-, (2Alpha,4ß)- [CAS]	88889-14-9 98048-97-6	EP	63896	Antihypertensive, renin system	Hypertension, general
fosphenytoin	2,4-Imidazolidinedione, 5,5-diphenyl-3-[(phosphonooxy)methyl]- [CAS]	92134-98-0 93390-81-9	US	4260769	Antiepileptic	Epilepsy, generalized, tonic-clonic
fotemustine	Phosphonic acid, [1-[[[(2-chloroethyl)nitrosoamino]carbonyl]amino]ethyl]-, diethyl ester [CAS]	92118-27-9	EP	117959	Anticancer, alkylating	Cancer, melanoma
Fropenem		106560-14-9				
frovatriptan	1H-Carbazole-6-carboxamide, 2,3,4,9-tetrahydro-3-(methylamino)-, (R)- [CAS]	158747-02-5	WO	9922730	Antimigraine	Migraine
Fructose		57-48-7				
Fructose-1,6-diphosphate		488-69-7				
FTC	2(1H)-Pyrimidinone, 4-amino-5-fluoro-1-(2-(hydroxymethyl)-1,3-oxathiolan-5-yl)- (4R)				Antiviral, anti-HIV	Infection, HIV/AIDS
FTY-720	1,3-Propanediol, 2-amino-2-(2-(4-octylphenyl)ethyl)-,hydrochloride [CAS]	162359-56-0	WO	9408943	Immunosuppressant	Transplant rejection, general
fudosteine	Alanine, 3-((3-hydroxypropyl)thio)- [CAS]	13189-98-5	US	5047428	Antitussive	Cough
fulvestrant	Estra-1,3,5(10)-triene-3,17-diol, 7-[9-[(4,4,5,5,5-pentafluoropentyl)sulfinyl]nonyl]-, (7Alpha,17ß)- [CAS]	129453-61-8	EP	346014	Anticancer, hormonal	Cancer, breast
fumagilline	2,4,6,8-Decatetraenedioic acid, mono[5-methoxy-4-[2-methyl-3-(3-methyl-2-butenyl)oxiranyl]-1-oxaspiro[2.5]oct-6-yl] ester, [3R-[3Alpha,4Alpha(2R*,3R*),5ß,6ß(all-E)]]- [CAS]	23110-15-8			Protozoacide	Infection, GI tract

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Fumagillin		23110-15-8				
Furaltadone		139-91-3				
Furazabol		1239-29-8				
Furazolidone		67-45-8				
Furazolium Chloride		5118-17-2				
Furonazide		3460-67-1				
furosemide	Benzoic acid, 5-(aminosulfonyl)-4-chloro-2-[(2-furanylmethyl)amino]- [CAS]	54-31-9			Formulation, modified-release, other	Hypertension, general
Fursultiamine		804-30-8				
Furtrethonium		7618-86-2				
Fusidic Acid		06/03/6990				
G1, YM BioSciences	1-(5-bromofur-2-yl)-2-bromo-2-nitroethene				Antifungal	Infection, gynaecological
G25			WO	9804252	Antimalarial	Infection, malaria
GABA-A Alpha5 inverse agonist,Mer			WO	0206285	Cognition enhancer	Alzheimer's disease
gabapentin	Cyclohexaneacetic acid, 1-(aminomethyl)- [CAS]	60142-96-3	US	4152326	Antiepileptic	Epilepsy, general
gabexate	Benzoic acid, 4-[[6-[(aminoiminomethyl)amino]-1-oxohexyl]oxy]-, ethyl ester, monomethanesulfonate [CAS]	39492-01-8 56974-61-9	US	3751447	GI inflammatory/bowel disorders	Pancreatitis
gaboxadol	Isoxazolo[5,4-c]pyridin-3(2H)-one, 4,5,6,7-tetrahydro- [CAS]	64603-91-4	CA	1125288	Hypnotic/Sedative	Sleep disorder, general
Gadobenate Dimeglumine		127000-20-8				
Gadobutrol		138071-82-6				
Gadodiamide		131410-48-5				
Gadopentetic Acid		80529-93-7				
Gadoteridol		120066-54-8				
Gadoversetamide		131069-91-5				
Gadoxetic Acid		135326-11-3				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
galantamine	(4aS,6R,8aS)-6-Hydroxy-3-methoxy-11-methyl-5,6,9,10,11,12-hexahydro-4aH-benzofuro[3a,3,2-e,f][2]benzazepine				Formulation, modified-release, other	Alzheimer's disease
Galanthamine		357-70-0				
galarubicin	ß-Alanine, 2-[4-[(2,6-dideoxy-2-fluoro-Alpha-L-talopyranosyl)oxy]-1,2,3,4,6,11-hexahydro-2,5,12-trihydroxy-7-methoxy-6,11-dioxo-2-naphthacenyl]-2-oxoethyl ester, [CAS]	140637-82-7 140637-86-1	EP	424899	Anticancer, antibiotic	Cancer, breast
Gallamine Triethiodide		65-29-2				
Gallic Acid		149-91-7				
gallium maltolate	4H-Pyran-4-one, 3-hydroxy-2-methyl-, gallium complex				Anticancer, other	Cancer, myeloma
gallium nitrate	Nitric acid, gallium salt [CAS]	13494-90-1	US	4529593	Osteoporosis treatment	Hypercalcaemia of malignancy
gallopamil	Benzeneacetonitrile, Alpha-[3-[[2-(3,4-dimethoxyphenyl)ethyl]methylamino]propyl]-3,4,5-trimethoxy-Alpha-(1-methylethyl)- [CAS]	16662-47-8	GB	1367677	Antianginal	Angina, general
γ-Aminobutyric Acid		56-12-2				
Ganaxolone		38398-32-2				
ganciclovir	6H-Purin-6-one, 2-amino-1,9-dihydro-9-[[2-hydroxy-1-(hydroxymethyl)ethoxy]methyl]- [CAS]	107910-75-8 82410-32-0	EP	49072	Antiviral, other	Infection, cytomegalovirus
ganirelix	[N-Ac-D-Nal,D-pCl-Phe,D-Pal,D-hArg(Et)2,hArg(Et)2,D-Ala]GnRH- [CAS]	124904-93-4	EP	312052	Releasing hormones	Infertility, female
ganstigmine	Carbamic acid, (2-ethylphenyl)-, (3aS,8aS)-1,2,3,3a,8,8a-hexahydro-1,3a,8-trimethylpyrroto[2,3-b]indol-5-yl ester,	223585-99-7	EP	1023297	Cognition enhancer	Alzheimer's disease

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
gantofiban	1-Piperazineacetic acid, 4-[[(5R)-3-[4-[imino[(methoxycarbonyl)amino]methyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]-, ethylester [CAS]	183547-57-1	EP	741133	Antithrombotic	Thrombosis, general
garenoxacin	3-Quinolinecarboxylic acid, 1-cyclopropyl-8-(difluoromethoxy)-7-((1R)-2,3-dihydro-1-methyl-1H-isoindol-5-yl)-1,4-dihydro-4-oxo-monomethanesulfonate [CAS]	223652-82-2			Quinolone antibacterial	Infection, respiratory tract, lower
garnocestim	5-73-macrophage inflammatory protein 2Alpha (human gene gro2)- [CAS]	246861-96-1			Radio/chemoprotective	Chemotherapy-induced injury, bone marrow, neutropenia
gatifloxacin	3-Quinolinecarboxylic acid, 1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-, (+/-)- [CAS]	112811-59-3	EP	230295	Quinolone antibacterial	Infection, respiratory tract, general
Gefarnate		51-77-4				
gefitinib	4-Quinazolinamine, N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-(4-morpholinyl)propoxy) [CAS]	184475-35-2	WO	9633980	Anticancer, other	Cancer, lung, non-small cell
gemcabene	6,6'-oxybis(2,2-dimethylhexanoate)	209789-08-2			Hypolipaemic/Antiatherosclerosis	Hyperlipidaemia, general
gemcitabine	Cytidine, 2'-deoxy-2', 2'-difluoro-, [CAS]	122111-03-9 95058-81-4	GB	2136425	Anticancer, antimetabolite	Cancer, pancreatic
gemeprost	Prosta-2,13-dien-1-oic acid, 11,15-dihydroxy-16,16-dimethyl-9-oxo-,methyl ester, (2E,11Alpha,13E,15R)- [CAS]	64318-79-2	GB	1540427	Prostaglandin	
gemfibrozil	Pentanoic acid, 5-(2,5-dimethylphenoxy)-2,2-dimethyl- [CAS]	25812-30-0	US	3674836	Hypolipaemic/Antiatherosclerosis	Hyperlipidaemia, general
gemifloxacin	1,8-Naphthyridine-3-carboxylic acid, 7-(3-(aminomethyl)-4-(methoxyimino)-1-pyrrolidinyl)-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo- [CAS]	175463-14-6	US	5869670	Quinolone antibacterial	Infection, respiratory tract, general
gentamicin	Gentamicin [CAS]	1403-66-3			Formulation, implant	Infection, general
Gentian Violet		548-62-9				
Gentiopicrin		20831-76-9				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Gentisic Acid		490-79-9				
Gepefrine		18840-47-6				
gepirone	2,6-Piperidinedione, 4,4-dimethyl-1-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]- [CAS]				Formulation, modified-release, other	Depression, general
gestodene	18,19-Dinorpregna-4,15-dien-20-yn-3-one, 13-ethyl-17-hydroxy-, (17Alpha)- [CAS]	109852-02-0 60282-87-3	GB	1569135	Formulation, fixed-dose combinations	Contraceptive, female
gestodene + ethinylest	18,19-Dinorpregna-4,15-dien-20-yn-3-one, 13-ethyl-17-hydroxy-, (17Alpha) mixt with 19-Norpregna-1,3,5(10)-trien-20-yne-13,17-diol (17Alpha)				Formulation, modified-release, >24hr	Contraceptive, female
Gestonorone Caproate		1253-28-7				
Gestrinone		16320-04-0				
γ-Hydroxybutyrate		591-81-1				
gimatecan	(4S)-11-[(E)-[(1,1-dimethylethoxy)imino]methyl]-4-ethyl-4-hydroxy-1-12-dihydro-14H-pyrano[3',4':6,7]indolizino[1,2-b]quinoline-3,14(4H)-dione	292618-32-7			Anticancer, other	Cancer, brain
Giractide		24870-04-0				
Gitoxin		4562-36-1				
GL-406349	N,N'-Bis[2-[N-[2-(N2,N5-dimethyl-DL-lysylamino)-ethyl]carbamoyl]1H-indol-6-yl]-1H-indole-2,5-dicarboxamide				Antifungal	Infection, fungal, general
Glafenine		3820-67-5				
glatiramer	L-Glutamic acid, polymer with L-alanine, L-lysine and L-tyrosine, [CAS]	147245-92-9 28704-27-0	WO	5800808	Multiple sclerosis treatment	Multiple sclerosis, relapsing-remitting
Glibornuride		26944-48-9				
gliclazide	Benzenesulfonamide, N-[[(hexahydrocyclopenta[c]pyrrol-2(1H)-yl)amino]carbonyl]-4-methyl- [CAS]	21187-98-4	GB	1153982	Antidiabetic	Diabetes, Type II

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
glimepiride	1H-Pyrrole-1-carboxamide, 3-ethyl-2,5-dihydro-4-methyl-N-[2-[4-[[[[(4-methylcyclohexyl)amino]carbonyl]amino]sulfonyl]phenyl]ethyl]-2-oxo- [CAS]	93479-97-1	WO	9303724	Antidiabetic	Diabetes, Type II
γ-Linolenic Acid		506-26-3				
glipizide	Pyrazinecarboxamide, N-[2-[4-[[[(cyclohexylamino)carbonyl]amino]sulfonyl]phenyl]ethyl]-5-methyl- [CAS]	29094-61-9	US	3669966	Antidiabetic	
gliquidone	Benzenesulfonamide, N-[(cyclohexylamino)carbonyl]-4-[2-(3,4-dihydro-7-methoxy-4,4-dimethyl-1,3-dioxo-2(1H)-isoquinolinyl)ethyl]- [CAS]	33342-05-1	GB	1277847	Antidiabetic	Diabetes, general
glisolamide	3-Isoxazolecarboxamide, N-[2-[4-[[[(cyclohexylamino)carbonyl]amino]sulfonyl]phenyl]ethyl]-5-methyl- [CAS]	24477-37-0			Antidiabetic	Diabetes, general
Glisoxepid		25046-79-1				
Glucametacin		52443-21-7				
Glucoheptonic Acid		87-74-1				
Gluconic Acid		526-95-4				
glucosamine	D-Glucose, 2-amino-2-deoxy-, [CAS]	29031-19-4 3416-24-8	DE	1953689	Antiarthritic, other	Arthritis, osteo
Glucosulfone		554-18-7				
glufosfamide	ß-D-Glucopyranose, 1-(N,N'-bis(2-chloroethyl)phosphorodiamidate)- [CAS]	132682-98-5	DE	3835772	Anticancer, alkylating	Cancer, general
Glutamic Acid		56-86-0				
Glutaraldehyde		111-30-8				
Glutethimide		77-21-4				
Glyburide		10238-21-8				
Glybuthiazol(e)		535-65-9				
Glybuzole		1492-02-0				
Glycerol		56-81-5				
Glycocyamine		352-97-6				
Glycol Salicylate		87-28-5				
Glyconiazide		3691-74-5				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Glycopyrrolate		596-51-0				
Glyhexamide		451-71-8				
Glymidine		339-44-6				
Glypinamide		1228-19-9				
GMDP	N-acetylglucosaminyl-N-acetylmuramyl dipeptide				Anti-infective, other	Infection, general
Gold Sodium Thiomalate		12244-57-4				
Gold Sodium Thiosulfate		10233-88-2				
goserelin	Luteinizing hormone-releasing factor (pig), 6-[O-(1,1-dimethylethyl)-D-serine]-10-deglycinamide-, 2-(aminocarbonyl)hydrazide [CAS]	65807-02-5	US	4100274	Releasing hormones	Cancer, prostate
GPI-1485	L-Proline, 1-(3,3-dimethyl-1,2-dioxopentyl)-, 3-(3-pyridinyl)propyl ester [CAS]	186452-09-5			Antiparkinsonian	Parkinson's disease
GPI-5693	2-(Phosphonomethyl)pentanedioic acid		US	5672592	Analgesic, other	Pain, neuropathic
Graftskin						
granisetron	1H-Indazole-3-carboxamide, 1-methyl-N-(9-methyl-9-azabicyclo[3.3.1]non-3-yl)-, endo- [CAS]	107007-99-8 109889-09-0	EP	200444	Antiemetic	Chemotherapy-induced nausea and vomiting
Grepafloxacin		119914-60-2				
griseofulvin	Spiro[benzofuran-2(3H),1'-[2]cyclohexane]-3,4'-dione, 7-chloro-2',4,6-trimeth-oxy-6'methyl-, (1'S-trans)- [CAS]	126-07-8			Formulation, dermal, topical	Infection, dermatological
Guaiacol		90-05-1				
Guaiapate		852-42-6				
Guaiazulene		489-84-9				
Guaifenesin		93-14-1				
guaimesal	4H-1,3-Benzodioxin-4-one, 2-(2-methoxyphenoxy)-2-methyl- [CAS]	81674-79-5	GB	2098201	Anti-inflammatory	
Guamecycline		16545-11-2				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Guanabenz		5051-62-7				
Guanadrel		40580-59-4				
Guanethidine		55-65-2				
Guanfacine		29110-47-2				
Guanoxabenz		24047-25-4				
Guanoxan		2165-19-7				
gugulipid	Pregna-4,17(20)-diene-3,16-dione [CAS]	95975-55-6	EP	447706	Hypolipaemic/Antiatherosclerosis	
Gusperimus		104317-84-2				
GW-280430A	(Z)-2-Chlorofumaric acid 1-[3-[-[6,7-dimethoxy-2(S)-methyl-1(R)-(3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinolinium-2-yl]propyl]				Muscle relaxant	Anaesthesia, adjunct
GW-320659	[2S,3S,5R]-2-[3,5-difluorophenyl]-3,5-dimethyl-2-morpholinol				Anorectic/Antiobesity	Obesity
GYKI-16084	(+)-R-2-{3-[N-(2-Benzo[1,4]dioxanylmethyl)amino]-1-propyl}-3(2H)-pyridazinone hydrochloride		US	6194411	Prostate disorders	Benign prostatic hyperplasia
Hachimycin		1394-02-1				
Halazepam		23092-17-3				
Halcinonide		3093-35-4				
halobetasol	Pregna-1,4-diene-3,20-dione, 21-chloro-6,9-difluoro-11-hydroxy-16-methyl-17-(1-oxopropoxy)-, (6Alpha,11ß,16ß)- [CAS]	66852-54-8	US	4619921	Antipsoriasis	Psoriasis
halofantrine	9-Phenanthrenemethanol, 1,3-dichloro-Alpha-[2-(dibutylamino)ethyl]-6-(trifluoromethyl)- [CAS]	36167-63-2 69756-53-2	EP	138374	Antimalarial	Infection, malaria
halometasone	Pregna-1,4-diene-3,20-dione, 2-chloro-6,9-difluoro-11,17,21-trihydroxy-16-methyl-, (6Alpha,11ß,16Alpha)- [CAS]	50629-82-8	US	4076737	Antipruritic/inflamm, allergic	
Haloperidol		52-86-8				
Halopredone		57781-14-3				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Haloprogin		777-11-7				
Halopropane		679-84-5				
Halothane		151-67-7				
Haloxazolam		59128-97-1				
harkoseride	2(R)-Acetamido-N-benzyl-3-methoxypropionamide		WO	9733861	Antiepileptic	Epilepsy, general
HE-2000	16Alpha-Bromo-3ß-hydroxy-5Alpha-androstane-17-one				Antiviral, anti-HIV	Infection, HIV/AIDS
Healos			WO	9714376	Musculoskeletal	Regeneration, bone
Hematoporphyrin		14459-29-1				
Hepronicate		7237-81-2				
Heptabarbital		509-86-4				
Heptaminol		372-66-7				
Hetacillin		3511-16-8				
Hetastarch		9004-62-0				
Hexachlorophene		70-30-4				
Hexadimethrine Bromide		28728-55-4				
Hexafluorenium Bromide		317-52-2				
Hexamethonium		60-26-4				
Hexamidine		3811-75-4				
Hexapropymate		358-52-1				
Hexedine		5980-31-4				
Hexestrol		84-16-2				
Hexestrol Bis(β-diethylaminoethyl ether)		2691-45-4				
Hexethal		144-00-3				
Hexetidine		141-94-6				
Hexobarbital		56-29-1				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Hexobendine		54-03-5				
Hexocyclium Methyl Sulfate		115-63-9				
Hexoprenaline		3215-70-1				
Hextend	Hextend [CAS]	235746-51-7	US	5407428	Plasma substitute	Surgery adjunct
Hexylcaine		532-76-3				
HF-0299	11b-hydroxy androstenedione				Osteoporosis treatment	Osteoporosis
HGP-2	Benzeneacetic acid, 4-[2-hydroxy-3-[(1-methylethyl)amino]propoxy]-, 2-tricyclo[3.3.1.13,7]dec-1-ylethyl ester, (2Z)-2-butenedioate (1:1) (salt) [CAS]	121009-31-2			Antiglaucoma	Glaucoma
HGP-6^	8-Azoniabicyclo[3.2.1]octane, 3-(3-ethoxy-1,3-dioxo-2-phenylpropoxy)-8,8-dimethyl-, (3-endo)-, methyl sulfate [CAS]	113932-41-5			Antiepileptic	Epilepsy, general
hidrosmin	Hydrosmin- [CAS]	120250-44-4			Vasoprotective, systemic	
histamine	histamine	51-45-6	EP	0493468	Anticancer, immunological	Cancer, melanoma
Histapyrrodine		493-80-1				
histrelin	Luteinizing hormone-releasing factor (pig), 6-[1-(phenylmethyl)-D-histidine]-9-(N-ethyl-L-prolinamide)-10-deglycinamide- [CAS]	76712-82-8	EP	217659	Releasing hormones	Precocious puberty
HM-101	HM 101 [CAS]	217311-70-1			Osteoporosis treatment	Osteoporosis
HMN-214	(E)-4-[2-[2-(p-methoxybenzenesulfonamide)-phenyl]ethenyl]pyridine-1-oxide				Anticancer, other	Cancer, general
Homatropine		87-00-3				
Homocamfin		535-86-4				
Homochlorcyclizine		848-53-3				
Hopantenic Acid		18679-90-8				
HP-228	Glycinamide, N-acetyl-L-norleucyl-L-glutaminyl-L-histidyl-D-phenylalanyl-L-arginyl-D-tryptophyl- [CAS]	172617-89-9	EP	759770	Analgesic, other	Pain, post-operative

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Huperzine A		102518-79-6				
hyaluronan	Hyaluronic acid [CAS]	9004-61-9			Formulation, other	Restenosis
Hycanthone		3105-97-3				
Hydnocarpic Acid		459-67-6				
Hydralazine		86-54-4				
Hydrastine		118-08-1				
Hydrastinine		6592-85-4				
Hydrochlorothiazide		58-93-5				
hydrocodone	Morphinan-6-one, 4,5-epoxy-3-hydroxy-17-methyl-,(5Alpha)- [CAS]	466-99-9 125-29-1			Formulation, modified-release, other	Pain, general
Hydrocortamate		76-47-1				
hydrocortisone	Pregn-4-ene-3,20-dione, 21-(acetyloxy)-11-hydroxy-17-(1-oxopropoxy)-, (11ß)-[CAS]	74050-20-7 50-23-7	DE	2826257	Dermatological	Unspecified
hydrocortisone butyrate propio	Pregn-4-ene-3,20-dione, 11-hydroxy-17-(1-oxobutoxy)-21-(1-oxopropoxy)-, (11ß)-[CAS]	72590-77-3	DE	2910899	Antipruritic/inflamm, allergic	
Hydroflumethiazide		135-09-1				
hydromorphone	Morphinan-6-one,4,5-epoxy-3-hydroxy-17-methyl-,(5Alpha)-, mixt with acetamide, N-(4-hydroxyphenyl)-, mixt with morphinan-6-one,17-(cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxy-, (5Alpha)-	103-90-2 16590-41-3 466-99-9			Formulation, fixed-dose combinations	Pain, general
Hydroquinidine		1435-55-8				
Hydroquinine		522-66-7				
Hydroquinone		123-31-9				
Hydroxocobalamin		13422-51-0				
Hydroxyamphetamine		1518-86-1				
Hydroxychloroquine		118-42-3				
Hydroxydione		53-10-1				
Hydroxypethidine		468-56-4				
Hydroxyphenamate		50-19-1				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Hydroxypropyl Cellulose		9004-64-2				
Hydroxystilbamidine		495-99-8				
Hydroxytetracaine		490-98-2				
Hydroxyzine		68-88-2				
Hylan G-F 20						
Hymecromone		90-33-5				
hyoscyamine	benzeneacetic acid, Alpha(hydroxymethyl)-, 8-methyl-8-azabicyclo [3.2.1.]oct-3-yl ester, [3(S)-endo],	101-31-5			Formulation, oral, orally-disintegrating	Ulcer, GI, general
hypericin	Phenanthro[1,10,9,8-opqra]perylene-7,14-dione, 1,3,4,6,8,13-hexahydroxy-10,11-dimethyl- [CAS]	548-04-9			Anticancer, other	Cancer, brain
IACFT		180468-34-2				
ibandronic acid	Phosphonic acid, [1-hydroxy-3-(methylpentylamino)propylidene] bis- [CAS]	114084-78-5	EP	252504	Osteoporosis treatment	Hypercalcaemia of malignancy
ibopamine	Propanoic acid, 2-methyl-, 4-[2-(methylamino)ethyl]-1,2-phenylene ester- [CAS]	66195-31-1	GB	1551661	Cardiostimulant	Heart failure
ibopamine	Propanoic acid, 2-methyl-, 4-[2-(methylamino)ethyl]-1,2-phenylene ester- [CAS]	66195-31-1			Formulation, mucosal, topical	Surgery adjunct
Ibritumomab Tiuxetan		206181-63-7				
ibrolipim	Phosphonic acid, [[4-[[(4-bromo-2-cyanophenyl)amino]carbonyl]phenyl]methyl.)-, diethyl ester [CAS]	133208-93-2	EP	402033	Hypolipaemic/Antiatherosclerosis	Hypertriglyceridaemia
ibudilast	1-Propanone, 2-methyl-1-[2-(1-methylethyl)pyrazolo[1,5-a]pyridin-3-yl]- [CAS]	50847-11-5	EP	215438	Antiasthma	Asthma
Ibufenac		1553-60-2				
ibuprofen piconol	Benzeneacetic acid, Alpha-methyl-4-(2-methylpropyl)-, 2-pyridinylmethyl ester [CAS]	64622-45-3	DE	2658610	Antipruritic/inflamm, non-allergic	Eczema, contact

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
ibuprofen	Benzeneacetic acid, Alpha-methyl-4-(2-methylpropyl)- [CAS]	15687-27-1			Formulation, modified-release, other	Inflammation, general
Ibuproxam		53648-05-8				
ibutilide	Methanesulfonamide, N-[4-[4-(ethylheptylamino)-1-hydroxybutyl]phenyl]-, (+/-)-, [CAS]	122647-31-8 122647-32-9	JP	60239458	Antiarrhythmic	Fibrillation, atrial
ICA-17043			US	6288122	Antisickling	Anaemia, sickle cell
icodextrin	Dextrin- [CAS]	9004-53-9			Urological	Renal failure
idarubicin	5,12-Naphthacenedione, 9-acetyl-7-[(3-amino-2,3,6-trideoxy-Alpha-L-lyxo-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,9,11-trihydroxy-, (7S-cis)- [CAS]	58957-92-9 86189-66-4	US	4471052	Anticancer, antibiotic	Cancer, leukaemia, acute lymphocytic
Idazoxan		79944-58-4				
IdB-1016	2-(2,3-dihydro-2-(4-hydroxy-3-methoxyphenyl)-3-(hydroxymethyl)-1,4-benzodioxin-6-yl)-2,3-dihydro-3,5,7-trihydroxy-4H-1-benzopyran-4-one phosphatidylcholine complex	134499-06-2	EP	209038	Anticancer, hormonal	Cancer, ovarian
idebenone	2,5-Cyclohexadiene-1,4-dione, 2-(10-hydroxydecyl)-5,6-dimethoxy-3-methyl- [CAS]	58186-27-9	EP	58057	Neuroprotective	Ischaemia, cerebral
IDN-5109	4-Hexenoic acid, 3-[[(1,1-dimethylethoxy)carbonyl]amino]-2-hydroxy-5-methyl-, (3aS,4R,7R,8aS,9S,10aR,12aS,12bR,13S,13aS)-7,12a-bis(acetyloxy)-13-(benzoyloxy)-3a,4,7,8,8a,9,10,10a,12,12a,12b,13-dodecahydro-9-hydroxy-5,8a,14,14-tetramethyl-2,8-dioxo-6,13a-methano-13aH-oxeto [2",3",5',6'] benzo[1,2:4,5] cyclodeca [1,2-d] dioxyl-4-yl ester, 2R,3S) [CAS]	186348-05-0	US	5264591	Anticancer, other	Cancer, colorectal
Idoxifene		116057-75-1				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
idraparinux	Alpha-D-Glucopyranoside, methyl O-2,3,4-tri-O-methyl-6-O-sulfo-Alpha-D-glucopyranosyl-(1-4)-O-2,3-di-O-methyl-ß-D-glucopyranuronosyl-(1-4)-O-2,3,6-tri-O-sulfo-Alpha-D-glucopyranosyl-(1-4)-O-2,3-di-O-methyl-Alpha-L-idopyranuronosyl-(1-4)-, tris(hydrogen sulfate) nonasodium salt [CAS]	149920-56-9	AU	698456	Antithrombotic	Thrombosis, venous
idrocilamide	2-Propenamide, N-(2-hydroxyethyl)-3-phenyl- [CAS]	6961-46-2	US	3659014	Anti-inflammatory, topical	
ifenprodil	(7)-2-(4-benzyl piperidino)-1-p-hydroxyphenylpropanol tartrate	23210-58-4 23210-56-2	US	3509164	Neuroprotective	
ifosfamide	2H-1,3,2-Oxazaphosphorin-2-amine, N,3-bis(2-chloroethyl)tetrahydro-,2-oxide [CAS]	3778-73-2	US	3732340	Anticancer, alkylating	Cancer, lung, general
iguratimod	N-[3-(Formylamino)-4-oxo-6-phenoxy-4H-chromen-7-yl] methanesulfonamide	123663-49-0	DE	3834204	Antiarthritic, other	Arthritis, rheumatoid
ilaprazole	1H-Benzimidazole, 2-(((4-methoxy-3-methyl-2-pyridinyl) methyl)sulfinyl)-5-(1H-pyrrol-1-yl)- [CAS]	172152-36-2	US	5703097	Antiulcer	Ulcer, GI, general
ilomastat	Butanediamide, N4-hydroxy-N1-(1-(1H-indol-3-ylmethyl)-2-(methylamino)-2-oxoethyl)-2-(2-methylpropyl)-, (S-(R*, S*))- [CAS]	142880-36-2	US	5892112	COPD treatment	Emphysema, smoking-related
iloperidone	Ethanone, 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]- [CAS]	133454-47-4	US	5776963	Neuroleptic	Schizophrenia
iloprost trometamol	Pentanoic acid, 5-[hexahydro-5-hydroxy-4-(3-hydroxy-4-methyl-1-octen-6-ynyl)-2(1H)-pentalenylidene]- [CAS]	78919-13-8	DE	3417638	Prostaglandin	Peripheral vascular disease
ILX23-7553	1Alpha,25-Hydroxy-16-yne vitamin D3				Anticancer, other	Cancer, general

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
imatinib	4-((Methyl-1-piperazinyl)methyl)-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]-phenyl]benzamide methanesulfonate	152459-95-5	US	5521184	Anticancer, other	Cancer, leukaemia, chronic myelogenous
imidapril	4-Imidazolidinecarboxylic acid, 3-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1-methyl-2-oxo-, [4S-[3[R*(R*)],4R*]]- [CAS]	89371-37-9 89396-94-1	EP	95163	Antihypertensive, renin system, Musculoskeletal	Hypertension, general, Cachexia
imidazole salicylate	Benzoic acid, 2-hydroxy-, compd. with 1H-imidazole (1:1) [CAS]	36364-49-5	US	4329340	Anti-inflammatory	Pain, general
imipenem	1-Azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid, 6-(1-hydroxyethyl)-3-[[2-[(iminomethyl)amino]ethyl]thio]-7-oxo-, [5R-[5Alpha,6Alpha(R*)]]- [CAS]	64221-86-9 74431-23-5 81129-83-1	GB	1570990	Beta-lactam antibiotic	Infection, general
Imipramine		50-49-7				
Imipramine N-Oxide		6829-98-7				
imiquimod	1H-Imidazo[4,5-c]quinolin-4-amine, 1-(2-methylpropyl)- [CAS]	99011-02-6	EP	145340	Antiviral, other	Infection, human papilloma virus
Imolamine		318-23-0				
imptitapide	Benzeneacetamide, Alpha-cyclopentyl-4-((2,4-dimethyl-9H-pyrido(2,3-b)indol-9-yl)methyl)-N-((1R)-2-hydroxy-1-phenylethyl)- (AlphaS)- [CAS]	177469-96-4	EP	705831	Hypolipaemic/Antiatherosclerosis	Atherosclerosis
Improsulfan		13425-98-4				
Inaperisone		99323-21-4				
incadronate	Phosphonic acid, [(cycloheptylamino)methylene]bis-, [CAS]	138330-18-4			Musculoskeletal	Hypercalcaemia of malignancy
Incadronic Acid		124351-85-5				
Indalpine		63758-79-2				
Indanazoline		40507-78-6				
indapamide	4-chloro-N-(2-methylindolin-1-yl)-3-sulfamoylbenzamide	26807-65-8	GB	1203691	Antihypertensive, diuretic	Hypertension, general
Indecainide		74517-78-5				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
indeloxazine	Morpholine, 2-[(1H-inden-7-yloxy)methyl]- [CAS]	60929-23-9 65043-22-3	JP	52083773	Cognition enhancer	Alzheimer's disease
Indeloxazine		65043-22-3				
indenolol	2-Propanol, 1-[1H-inden-4(or 7)-yloxy]-3-[(1-methylethyl)amino]- [CAS]	30190-87-5 60607-68-3 68906-88-7	GB	1290343	Antihypertensive, adrenergic	
indinavir	D-erythro-Pentonamide, 2,3,5-trideoxy-N-(2,3-dihydro-2-hydroxy-1H-inden-1-yl)-5-(2-(((1,1-dimethylethyl)amino)carbonyl)-4-(3-pyridinylmethyl)-1-piperazinyl)-2-(phenylmethyl), [1S-[1Alpha(R*),2Alpha]]-, [CAS]	150378-17-9 157810-81-6	EP	0541168	Antiviral, anti-HIV	Infection, HIV/AIDS
indiplon	Acetamide, N-methyl-N-(3-(3-(2-thienylcarbonyl)pyrazolo(1,5-a) pyrimidin-7-yl)phenyl)- [CAS]	325715-02-4	US	6399621	Hypnotic/Sedative	Insomnia
indisetron	1H-Indazole-3-carboxamide, N-(3,9-dimethyl-3,9-diazabicyclo(3.3.1)non-7-yl)-, diendo- [CAS]	160472-97-9			Antiemetic	Nausea and vomiting, general
indisulam	1,4-Benzenedisulfonamide, N-(3-chloro-1H-indol-7-yl)- [CAS]	165668-41-7			Anticancer, other	Cancer, lung, non-small cell
Indobufen		63610-08-2				
Indocyanine Green		3599-32-4				
indometacin	1H-Indole-3-acetic acid, 1-(4-chlorobenzoyl)-5-methoxy-2-methyl- [CAS]	53-86-1			Formulation, modified-release, other	Inflammation, general
Indoprofen		31842-01-0				
indoramin	Benzamide, N-[1-[2-(1H-indol-3-yl)ethyl]-4-piperidinyl]- [CAS]	26844-12-2 38821-52-2	GB	1218570	Antihypertensive, adrenergic	
Inducterm			US	5993810	Labour inducer	Labour, induction
Infliximab		170277-31-3				
Inosine Pranobex		36703-88-5				
Inositol		87-89-8				
Inositol Niacinate		6556112				
Iobenguane		80663-95-2				
Iobenzamic Acid		3115057				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference	Example of Therapeutic Use	Example of Indication
Iobitridol		136949-58-1			
Iocarmic Acid		10397-75-8			
Iocetamic Acid		16034-77-8			
Iodamide		440-58-4			
Iodine	Iodine [CAS]	7553-56-2		Formulation, oral, other	Fibrocystic breast disorder
Iodipamide		606-17-7			
Iodixanol		92339-11-2			
Iodoalphionic Acid		577-91-3			
Iodochlorhydroxyquin	5-Chloro-7-Iodo-8-quinolinol	130-26-7		Cognition enhancer	Alzheimer's disease
Iodoform		75-47-8			
Iodopyracet		300-37-8			
Iodopyrrole		87-58-1			
Iodoquinol		83-73-8			
Iofetamine ^{123}I		75917-92-9			
Ioglycamic Acid		2618-25-9			
Iohexol		66108-95-0			
Iomeglamic Acid		25827-76-3			
Iomeprol		78649-41-9			
Iopamidol		60166-93-0			
Iopanoic Acid		96-83-3			
Iopentol		89797-00-2			
Iophendylate		99-79-6			
Iophenoxic Acid		96-84-4			
Iopromide		73334-07-3			
Iopronic Acid		41473-08-9			
Iopydol		5579-92-0			
Iopydone		5579-93-1			
Iothalamic Acid		2276-90-6			
Iotrolan		79770-24-4			
Ioversol		87771-40-2			
Ioxaglic Acid		59017-64-0			

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Ioxilan		107793-72-6				
IP-751	(3R,4R)-(delta6)-THC-DMH-11-oic acid		WO	9401429	Analgesic, other	Pain, neuropathic
Ipidacrine		62732-44-9				
IPL-576092	Stigmastan-15-one, 22,29-epoxy-3,4,6,7,29-pentahydroxy-, (3Alpha,4ß,5Alpha,6Alpha,7ß,14ß,22S)- [CAS]	137571-30-3	US	6046185	Antiasthma	Asthma
Ipodate		5587-89-3				
ipratropium bromide		66985-17-9 22254-24-6			Formulation, inhalable, solution	Chronic obstructive pulmonary disease
ipratropium	(endo,syn)-(±)-3-(3-Hydroxy-1-oxo-2-phenylpropoxy)-8-methyl-8-(1-methylethyl)-8-azoniabicyclo[3.2.1]octane				Formulation, inhalable, topical	Asthma
iprazochrome	Hydrazinecarboxamide, 2-[1,2,3,6-tetrahydro-3-hydroxy-1-(1-methylethyl)-6-oxo-5H-indol-5-ylidene]- [CAS]	7248-21-7			Haemostatic	
ipriflavone	4H-1-Benzopyran-4-one, 7-(1-methylethoxy)-3-phenyl- [CAS]	35212-22-7	EP	214647	Osteoporosis treatment	Osteoporosis
Iprindole		5560-72-5				
Iproclozide		3544-35-2				
Iproniazid		54-92-2				
Ipsapirone		95847-70-4				
irbesartan	2-n-butyl-4-spirocyclopentane-1-[((2'-tetrazol-5-yl)biphenyl-4-yl)methyl]-2-imidazolin-5-one	138402-11-6	WO	9114679	Antihypertensive, renin system	Hypertension, general
IRFI-042	Butanedioic acid, mono[2-[2-(acetylthio)ethyl]-2,3-dihydro-4,6,7-trimethyl-5-benzofuranyl] ester, (+/-)- [CAS]	134867-62-2	US	5114966	Cardiovascular	Atherosclerosis
IRFI-165	N-Cyclopentyl-1-methylimidazo[1,2-a]quinoxalin-4-amine	191349-26-5	EP	865442	Antidepressant	Depression, general
Iridomyrmecin		485-43-8				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
irindalone	-Imidazolidinone, 1-[2-[4-[3-(4-fluorophenyl)-2,3-dihydro-1H-inden-1-yl]-1-piperazinyl]ethyl]-, (1R-trans)- [CAS]	104113-57-7 96478-43-2	EP	183349	Antidepressant	Depression, general
Irinotecan		97682-44-5				
irofulven	Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-2',4',6'-trimethyl-, (R)- [CAS]	125392-76-9	US	5563176	Anticancer, other	Cancer, prostate
Iron Sorbitex		1338-16-5				
irsogladine	1,3,5-Triazine-2,4-diamine, 6-(2,5-dichlorophenyl)- [CAS]	57381-26-7 57381-28-9 57381-33-6	US	4657907	Antihypertensive, diuretic	Hypertension, general
IS-741	Cyclohexanecarboxamide, N-[2-[(ethylsulfonyl)amino]-5-(trifluoromethyl)-3-pyridinyl)- [CAS]	141283-87-6	EP	465913	GI inflammatory/bowel disorders	Pancreatitis
isaglitazone	2,4-Thiazolidinedione, 5-[[6-[(2-fluorophenyl)methoxy]-2-naphthalenyl]methyl]-[CAS]	161600-01-7	US	5594016	Antidiabetic	Diabetes, Type II
ISAtx-247			NZ	502362	Immunosuppressant	Transplant rejection, general
Isbogrel		89667-40-3				
isepamicin	D-Streptamine, O-6-amino-6-deoxy-Alpha-D-glucopyranosyl-(1-4)-O-[3-deoxy-4-C-methyl-3-(methylamino)-ß-L-arabinopyranosyl-(1-6)]-N1-(3-amino-2-hydroxy-1-oxopropyl)-2-deoxy-, (S)- [CAS]	58152-01-5 58152-03-7	US	4029882	Aminoglycoside antibiotic	Infection, dermatological
Isoaminile		77-51-0				
Isobutyl p-Aminobenzoate		94-14-4				
Isocarboxazid		59-63-2				
isoconazole	1-[2-(2-6-dichlorobenzyloxy)-2-(2-,4-dichlorophenyl)ethyl]	24168-96-5 27523-40-6	GB	1244530	Antifungal	Infection, fungal, general
Isoetharine		530-08-5				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
isofloxythepin	1-Piperazineethanol, 4-[3-fluoro-10,11-dihydro-8-(1-methylethyl)dibenzo[b,f]thiepin-10-yl]- [CAS]	106819-39-0 106819-41-4 70931-18-9	GB	2010843	Neuroleptic	
isoflurane	Ethane, 2-chloro-2-(difluoromethoxy)-1,1,1-trifluoro- [CAS]	26675-46-7	US	3535388	Anaesthetic, inhalation	Anaesthesia
Isoflurophate		55-91-4				
Isoladol		530-34-7				
Isomethadone		466-40-0				
Isometheptene		503-01-5				
Isoniazid		54-85-3				
Isonixin		57021-61-1				
Isopromethazine		303-14-0				
Isopropamide Iodide		71-81-8				
Isopropyl Alcohol		67-63-0				
isopropyl unoprostone	5-Heptenoic acid, 7-(3,5-dihydroxy-2-(3-oxodecyl)cyclopentyl)-, 1-methylethylester, (1R-(1Alpha(Z), 2ß,3Alpha,5Alpha))- [CAS]	120373-24-2	EP	289349	Prostaglandin	Glaucoma
Isoproterenol		7683-59-2				
Isosorbide		652-67-5				
isosorbide dinitrate	D-Glucitol, 1,4:3,6-dianhydro-, dinitrate [CAS]	87-33-2			Formulation, modified-release, other	Angina, general
isosorbide mononitrate	D-Glucitol, 1,4:3,6-dianhydro-, 5-nitrate [CAS]	16051-77-7			Formulation, modified-release, other	Angina, general
Isothipendyl		482-15-5				
isotretinoin	Retinoic acid, 13-cis- [CAS]	4759-48-2	US	4843096	Antiacne	Acne
Isovaleryl Diethylamide		533-32-4				
Isoxepac		55453-87-7				
Isoxicam		34552-84-6				
Isoxsuprine		395-28-8				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
isradipine	3,5-Pyridinedicarboxylic acid, 4-(4-benzofurazanyl)-1,4-dihydro-2,6-dimethyl-, methyl 1-methylethyl ester [CAS]	75695-93-1	GB	2037766	Antihypertensive, other	Hypertension, general
israpafant	6H-Thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepine, 4-(2-chlorophenyl)-6,9-dimethyl-2-[2-[4-(2-methylpropyl)phenyl]ethyl]-[CAS]	117279-73-9	EP	268242	Antiasthma	Asthma
ISV-403			US	5447926	Formulation, mucosal, topical	Conjunctivitis
Itasetron		123258-84-4				
ITF-282	ITF 282 [CAS]	93615-44-2	GB	2115821	Antianaemic	Anaemia, general
itopride	Benzamide, N-[[4-[2-(dimethylamino)ethoxy]phenyl]methyl]-3,4-dimethoxy-, monohydrochloride [CAS]	122892-31-3	EP	306827	Gastroprokinetic	Gastritis
itraconazole	3H-1,2,4-Triazol-3-one, 4-[4-[4-[4-[[2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(1-methylpropyl)- [CAS]	84625-61-6	EP	6711	Antifungal	Infection, fungal, general
Itramin		13445-63-1				
itriglumide	1-Naphthalenepropanoic acid, ß-[2-[[2-(8-azaspiro[4.5]dec-8-ylcarbonyl)-4,6-dimethylphenyl]amino]-2-oxoethyl]-, (ßR)-[CAS]	201605-51-8	WO	9800404	Anxiolytic	Anxiety, general
iturelix	D-Alaninamide N-acetyl-3-(2-naphthalenyl)-D-alanyl-4-chloro-D-phenylalanyl-3-(3-pyridinyl)-D-alanyl-L-seryl-N6-(3-pyridinylcarbonyl)-L-lysyl-N6-(3-pyridinylcarbonyl)-D-lysyl-L-leucyl-N6-(1-methylethyl)-L-lysyl-L-prolyl- [CAS]	112568-12-4	WO	8901944	Fertility enhancer	Infertility, female
ivabradine	7,8-dimethoxy-3-(3-[[(1S)(4,5-dimethoxybenzocyclobutan-1-yl)methyl]methylamino]propyl)-1,3,4,5-tetrahydro-2H-benzazepin-2-one				Antianginal	Angina, general

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
ixabepilone	17-Oxa-4-azabicyclo(14.1.0)heptadecane-5,9-dione, 7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl, (1R,3S,7S,10R,11S,12S,16R) [CAS]	219989-84-1			Anticancer, other	Cancer, breast
J-104132	5H-Cyclopenta[b]pyridine-6-carboxylic acid, 5-(1,3-benzodioxol-5-yl)-2-butyl-7-[2[(2S)-2-carboxypropyl]-4-methoxyphenyl]-6,7-dihydro-, (5S,6R,7R)- [CAS]	198279-45-7	WO	9737665	Antihypertensive, other	Heart failure
J-107088	5H-Indolo(2,3-a)pyrrolo(3,4-c)carbazole-5,7(6H)-dione, 12-ß-D-glucopyranosyl-12,13-dihydro-2,10-dihydroxy-6-((2-hydroxy-1-(hydroxymethyl)ethyl)amino- [CAS]	174402-32-5			Anticancer, other	Cancer, bladder
J-113397	1-[(3R,4R)-1-Cyclooctylmethyl-3-hydroxymethyl-4-piperidyl]-3-ethyl-1,3-dihydro-2H-benzimidazole-2-one				Analgesic, other	Pain, general
Janex-1	Phenol, 4-[(6,7-dimethoxy-4-quinazolinyl)amino]-[CAS]	202475-60-3			Anticancer, other	Cancer, leukaemia, general
josamycin	Leucomycin V, 3-acetate 4B-(3-methylbutanoate) [CAS]	16846-24-5	JP	41021759	Macrolide antibiotic	Infection, general
JTV-519	1,4-Benzothiazepine, 2,3,4,5-tetrahydro-7-methoxy-4-[1-oxo-3-[4-(phenylmethyl)-1-piperidinyl]propyl]- [CAS]	145903-06-6	WO	9212148	Cardiovascular	Infarction, myocardial
K-777			US	6287840	Protozoacide	Infection, trypanosomiasis, American
Kainic Acid		487-79-6				
Kalimate	Kalimate- [CAS]	92354-70-6			Urological	
Kallidin		342-10-9				
KB-130015	Acetic acid (2,6-diiodo-4-((2-methyl-3-benzofuranyl)methyl)phenoxy)- [CAS]	147030-48-6			Antiarrhythmic	Arrhythmia, general

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
KCB-328	Methanesulfonamide, N-[3-amino-4-[2-[[2-(3,4-dimethoxyphenyl)ethyl]methylamino]ethoxy]phenyl]-, monohydrochloride [CAS]	177596-55-3	WO	9604231	Antiarrhythmic	Arrhythmia, general
Kebuzone		853-34-9				
ketamine	2-(2-Chlorophenyl)-2-(methylamino)-cyclohexanone hydrochloride	6740-88-1			Formulation, transmucosal, nasal	Pain, post-operative
ketanserin	2,4(1H,3H)-Quinazolinedione, 3-[2-[4-(4-fluorobenzoyl)-1-piperidinyl]ethyl]-[CAS]	74050-98-9 83846-83-7	EP	13612	Antihypertensive, other	Hypertension, general
ketazolam	4H-[1,3]Oxazino[3,2-d][1,4]benzodiazepine-4,7(6H)-dione, 11-chloro-8,12b-dihydro-2,8-dimethyl-12b-phenyl- [CAS]	27223-35-4	GB	1222294	Anxiolytic	
Kethoxal		27762-78-3				
Ketobemidone		469-79-4				
ketoconazole	Piperazine, 1-acetyl-4-[4-[[2-(2,4-dichlorophenyl)-2-(1H-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-, cis- [CAS]	65277-42-1	US	4335125	Antifungal	Infection, fungal, general
ketoprofen	mono(3-benzoyl-Alpha-methylbenzeneacetate) [CAS]	173011-11-5	EP	502502	Formulation, transdermal, systemic	Pain, general
ketorolac	1H-Pyrrolizine-1-carboxylic acid, 5-benzoyl-2,3-dihydro-, (+/-)- [CAS]	74103-06-3 74103-07-4	EP	53021	Analgesic, NSAID	
Ketorolac Tromethamine						
ketotifen	10-H-Benzo[4,5]cyclohepta[1,2-b]thiophen-10-one, 4,9-dihydro-4-(1-methyl-4-piperidinylidene)-, (E)-2-butenedioate (1:1)- [CAS]	34580-13-7 34580-14-8	GB	1355539	Antiasthma	Asthma
Khellin		82-02-0				
kinetin		9001-29-0			Dermatological	Photodamage

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
KNI-272	4-Thiazolidinecarboxamide, N-(1,1-dimethylethyl)-3-[2-hydroxy-3-[[2-[[(5-isoquinolinyloxy)acetyl]amino]-3-(methylthio)-1-oxopropyl]amino]-1-oxo-4-phenylbutyl]-, [4R-[3[2S*,3S*(R*)],4R*]]-[CAS]	147318-81-8	US	5644028	Antiviral, anti-HIV	Infection, HIV/AIDS
KP-103	(R,R)-2-(2,4-Difluorophenyl)-3-(4-methylenepiperidin-1-yl)-1-(1,2,4-triazol-1-yl)-2-butanol				Antifungal	Infection, general
KP-157			US	6110961	Antidepressant	Depression, general
KP-544			WO	9919305	Cognition enhancer	Unspecified
KRN-5500	L-glycero-ß-L-manno-Heptopyranosylamine, 4-deoxy-4-[[[[(2E,4E)-1-oxo-2,4-tetradecadienyl]amino]acetyl]amino]-N-1H-purin-6-yl- [CAS]	151276-95-8	WO	9015811	Anticancer, antibiotic	Cancer, colorectal
KT-136	Alpha-D-Glucopyranoside, ß-D-fructofuranosyl, mixt. with 1-ethenyl-2-pyrrolidinone homopolymer compd. with iodine [CAS]	121602-88-8			Formulation, dermal, topical	Ulcer, decubitus
KUL-7211	(-)-2-[(2S)-1,2,3,4-tetrahydro-2-[[(2R)-2-hydroxy-2-(4-hydroxphenyl)ethyl]amino]naphthalen-7-yloxy]-N,N-dimethylacetamide hydrochloride monohydrate				Urological	Urinary calculus
KW-2170	6H-Pyrazolo[4,5,1-de]acridin-6-one,5-[(3-aminopropyl)amino]-7,10-dihydroxy-2-[[(2-hydroxyethyl)amino]methyl]-, dihydrochloride [CAS]	207862-44-0			Anticancer, alkylating	Cancer, lung, non-small cell
KW-6002	1H-Purine-2,6-dione, 8-(2-(3,4-dimethoxyphenyl)ethenyl)-1,3-diethyl-3,7-dihydro-7-methyl- (E)- [CAS]	155270-99-8			Antiparkinsonian	Parkinson's disease
KW-7158	3,3,3-Trifluoro-2-hydroxy-2-methyl-N-(10-oxo-4,10-dihydrothieno[3,2-C][1] benzothiepin-9-yl)propanamide 5,5 dioxide				Urological	Incontinence

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
L-365260	Urea, N-(2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-N'-(3-methylphenyl)-, (R)- [CAS]	118101-09-0	EP	284256	Anticancer, other	Cancer, general
L-5-hydroxytryptophan	L-Tryptophan, 5-hydroxy- [CAS]	4350-09-8			Metabolic and enzyme disorders	Unspecified
L-745337	Methanesulfonamide, N-[6-[(2,4-difluorophenyl)thio]-2,3-dihydro-1-oxo-1H-inden-5-yl]- [CAS]	158205-05-1	WO	9413635	Analgesic, NSAID	Pain, general
L-758298	Phosphonic acid, [3-[[(2R,3S)-2-.(.(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-2,5-dihydro-5-oxo-1H-1,2,4-triazol-1-yl]- [CAS]	172673-20-0	WO	9523798	Antiemetic	Chemotherapy-induced nausea and vomiting
L-826141			WO	9722585	Antiasthma	Unspecified
labetalol	5-[1-hydroxy-2-[(1-methyl-3-phenylpropyl)amino]ethyl]salicylamide HCl	32780-64-6 36894-69-6	US	4012444	Antihypertensive, adrenergic	
lacidipine	3,5-Pyridinedicarboxylic acid, 4-[2-[3-(1,1-dimethylethoxy)-3-oxo-1-propenyl]phenyl]-1,4-dihydro-2,6-dimethyl-, diethyl ester, (E)- [CAS]	103890-78-4	GB	2164336	Antihypertensive, other	Hypertension, general
Lactic Acid						
lactitol	D-Glucitol, 4-O-ß-D-galactopyranosyl- [CAS]	585-86-4			Hepatoprotective	Infection, neurological
Lactulose		4618-18-2				
lafutidine	Acetamide, 2-[(2-furanylmethyl)sulfinyl]-N-[4-[[4-(1-piperidinylmethyl)-2-pyridinyl]oxy]-2-butenyl]-, (Z)- [CAS]	118288-08-7 169899-19-8	EP	282077	Antiulcer	Ulcer, gastric
Lamifiban		144412-49-7				
lamivudine	2(1H)-Pyrimidinone, 4-amino-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]-, (2R-cis)- [CAS]	134678-17-4	EP	513917	Antiviral, anti-HIV	Infection, HIV/AIDS
lamotrigine	1,2,4-Triazine-3,5-diamine, 6-(2,3-dichlorophenyl)- [CAS]	84057-84-1	EP	21121	Antiepileptic	Epilepsy, partial (focal, local)

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
landiolol	Benzenepropanoic acid, 4-[2-hydroxy-3-[[2-[(4-morpholinylcarbonyl)amino]ethyl]amino]propoxy]-, (2,2-dimethyl-1,3-dioxolan-4-yl)methyl ester, [S-(R*,R*)]- HCL	133242-30-5	EP	397031	Antiarrhythmic	Tachycardia, general
lanicemine	(S)-Alpha-phenyl-2-pyridine ethanamine dihydrochloride	153322-05-5			Neurological	Unspecified
laniquidar	Methyl 6,11-dihydro-11-[1-[2-[4-(-2-quinolylmethoxy)phenyl]ethyl]-4-piperidinylidene]-5H-imidazo[2,1-b][3]benzazepine-3-carboxylate	197509-46-9	WO	9734897	Radio/chemosensitizer	Cancer, general
lanoconazole	1H-Imidazole-1-acetonitrile, Alpha-[4-(2-chlorophenyl)-1,3-dithiolan-2-ylidene]-, (E)-(±)- [CAS]	101530-10-3	US	4738976	Antifungal	Infection, fungal, general
Lanoteplase		171870-23-8				
Lanreotide		108736-35-2				
lansoprazole	1H-Benzimidazole, 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-[CAS]	103577-45-3	EP	174726	Antiulcer	Ulcer, duodenal
lanthanum carbonate	Carbonic acid, lanthanum(3+) salt (3:2)[CAS]	587-26-8	US	5968976	Urological	Hyperphosphataemia
lapatinib	4-Quinazolinamine, N-[3-chloro-4-[(3-fluorobenzyl)methoxy phenyl]-6-[5-[[[2-[methylsulfonyl]ethyl]amino]methyl]furan-2-yl]	388082-78-8			Anticancer, other	Cancer, breast
laquinimod		248281-84-7			Multiple sclerosis treatment	Multiple sclerosis, general
lasofoxifene	2-Naphthalenol, 5,6,7,8-tetrahydro-6-phenyl-5-(4-(2-(1-pyrrolidinyl)ethoxy)phenyl-(5R-cis)-, (S-(R*, R*))-2,3-dihydroxybutanedioate [CAS]	190791-29-8	WO	9716434	Menopausal disorders	Hormone replacement therapy

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
latamoxef	5-Oxa-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[[carboxy(4-hydroxyphenyl)acetyl]amino]-7-methoxy-3-[[(1-methyl-1H-tetrazol-5-yl)thio]methyl]-8-oxo- [CAS]	64952-97-2 64953-12-4	GB	1547351	Beta-lactam antibiotic	Infection, general
latanoprost	5-Heptenoic acid, 7-(3,5-dihydroxy-2-(3-hydroxy-5-phenylpentyl)cyclopentyl)-, 1-methylethyl ester, (1R-(1Alpha(Z),2ß(R*),3Alpha,5Alpha))- [CAS]	130209-82-4	WO	9002553	Prostaglandin	Glaucoma
Lauroguadine		135-43-3				
Laurolinium Acetate		146-37-2				
Lawsone		83-72-7				
LAX-111	1-(Z,Z,Z,Z,Z-eicosa-5,8,11,14,17-pentaenoyloxy)-3-(Z,Z,Z,Z,Z-eicosa-5,8,11,14,17-pentaenoyloxy)-propane				Neuroleptic	Schizophrenia
Lazabemide		103878-84-8				
LB-30057	Benzenecarboximidic acid, 4-[(2S)-3-(cyclopentylmethylamino)-2-[(2-naphthalenylsulfonyl)amino]-3-oxopropyl]-, hydrazide [CAS]		WO	9749673	Antithrombotic	Thrombosis, venous
L-Cystine						
Lefetamine		7262-75-1				
leflunomide	4-Isoxazolecarboxamide, 5-methyl-N-[4-(trifluoromethyl)phenyl]- [CAS]	75706-12-6	EP	13376	Antiarthritic, immunological	Arthritis, rheumatoid
leflunomide	4-Isoxazolecarboxamide, 5-methyl-N-[4-(trifluoromethyl)phenyl]- [CAS]	104981-93-3 75706-12-6	US	5610173	Anticancer, other	Cancer, ovarian
Leiopyrrole		5633-16-9				
lenampicillin	4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 6-[(aminophenylacetyl)amino]-3,3-dimethyl-7-oxo-, (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl ester, [2S-[2Alpha,5Alpha,6ß(S*)]]- [CAS]	80734-02-7 86273-18-9	EP	61206	Penicillin, oral	Infection, general
lentinan	Lentinan [CAS]	37339-90-5			Anticancer, immunological	Cancer, stomach

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Lepirudin						
lercanidipine	3,5-Pyridinedicarboxylic acid, 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyt)-, 2-[(3,3-diphenylpropyl)methylamino]-1,1-dimethylethyl methyl ester-, hydrochloride [CAS]	100427-26-7 132866-11-6	US	4705797	Antihypertensive, other	Hypertension, general
lerisetron	1H-Benzimidazole, 1-(phenylmethyl)-2-(1-piperazinyl)- [CAS]	143257-98-1	US	5256665	Antiemetic	Nausea and vomiting, general
Lesopitron		132449-46-8				
leteprinim	Benzoic acid, 4-((3-(1,6-dihydro-6-oxo-9H-purin-9-yl)-1-oxopropyl)amino)-, monopotassium salt [CAS]	138117-50-7	US	6338963	Antiparkinsonian	Parkinson's disease
letosteine	4-Thiazolidinecarboxylic acid, 2-[2-[(2-ethoxy-2-oxoethyl)thio]ethyl]- [CAS]	53943-88-7	US	4032534	COPD treatment	Bronchitis, chronic
letrozole	Benzonitrile, 4,4'-(1H-1,2,4-triazol-1-ylmethylene)bis- [CAS]	112809-51-5	EP	236940	Anticancer, hormonal	Cancer, breast
Leucocyanidin		480-17-1				
Leuprolide		53714-56-0				
leuprolide acetate	Luteinizing hormone-releasing factor (pig), 6-D-leucine-9-(N-ethyl-L-prolinamide)-10-deglycinamide-, monoacetate (salt) [CAS]	53714-56-0 74381-53-6			Formulation, implant	Cancer, prostate
leuprorelin	Luteinizing hormone-releasing factor (pig), 6-D-leucine-9-(N-ethyl-L-prolinamide)-10-deglycinamide- [CAS]	53714-56-0			Formulation, implant	Cancer, prostate
Levallorphan		152-02-3				
levamisole	Imidazo[2,1-b]thiazole, 2,3,5,6-tetrahydro-6-phenyl-, (S)- [CAS]	14769-73-4 16595-80-5	US	4584305	Anthelmintic	Infection, helminth, general
Levcromakalim		94535-50-9				
levetiracetam	1-Pyrrolidineacetamide, Alpha-ethyl-2-oxo-, (S)- [CAS]	102767-28-2	EP	162036	Antiepileptic	Epilepsy, general
levobetaxolol	2-Propanol, 1-(4-(2-(cyclopropylmethoxy)ethyl)phenoxy)-3-((1-methylethyl)amino) hydrochloride [CAS]	116209-55-3			Formulation, mucosal, topical	Glaucoma

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
levobunolol	1(2H)-Naphthalenone, 5-[3-[(1,1-dimethylethyl)amino]-2-hydroxypropoxy]-3,4-dihydro-, (S)- [CAS]	27912-14-7 47141-42-4	US	3641152	Formulation, mucosal, topical	Glaucoma
levobupivacaine	2-Piperidinecarboxamide, 1-butyl-N-(2,6-dimethylphenyl)-, (S)- [CAS]	27262-47-1	WO	9510276	Anaesthetic, injectable	Anaesthesia
levocabastine	4-Piperidinecarboxylic acid, 1-[4-cyano-4-(4-fluorophenyl)cyclohexyl]-3-methyl-4-phenyl-, [3S-[1(cis),3Alpha,4ß]]- [CAS]	79449-98-2 79516-68-0 79547-78-7	US	4369184	Antiallergic, non-asthma	Rhinitis, allergic, general
levocetirizine	Acetic acid, (2-(4-((4-chlorophenyl)phenylmethyl)-1-piperazinyl)ethoxy)-, (R)- [CAS]	130018-77-8	WO	9406429	Antiallergic, non-asthma	Allergy, general
Levodopa		59-92-7				
levodropropizine	1,2-Propanediol, 3-(4-phenyl-1-piperazinyl)-, (S)- [CAS]	99291-25-5	EP	147847	Antitussive	Cough
levofloxacin	7H-Pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid, 9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-, (S)- [CAS]	100986-85-4 138199-71-0	EP	206283	Quinolone antibacterial	Infection, respiratory tract, lower
Levomethadyl Acetate		1477-40-3				
levomoprolol	2-Propanol, 1-(2-methoxyphenoxy)-3-[(1-methylethyl)amino]-, (S)- [CAS]	27058-84-0 5741-22-0 77164-20-6	EP	15418	Antihypertensive, adrenergic	
levonorgestrel	18,19-Dinorpregn-4-en-20-yn-3-one, 13-ethyl-17-hydroxy-, (17Alpha)- [CAS]	797-63-7			Formulation, implant	Contraceptive, female
Levophacetoperane		24558-01-8				
Levopropoxyphene		2338-37-6				
Levorphanol		77-07-6				
levosimendan	Propanedinitrile, [[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]hydrazono]-, (R)- [CAS]	131741-08-7 141505-33-1	EP	383449	Cardiostimulant	Heart failure
levosulpiride	Benzamide, 5-(aminosulfonyl)-N-[(1-ethyl-2-pyrrolidinyl)methyl]-2-methoxy-, (S)- [CAS]	23672-07-3	GB	2014990	Antiemetic	Dyspepsia

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Levothyroxine						
levovirin	1-ß-L-ribofuranosyl-1,2,4-triazole-3-carboxamide				Antiviral, other	Infection, hepatitis-C virus
lexipafant	L-Leucine, N-methyl-N-[[4-[(2-methyl-1H-imidazo[4,5-c]pyridin-1-yl)methyl]phenyl]sulfonyl]-, ethyl ester- [CAS]	139133-26-9	WO	9203423	Neurological	Dementia, AIDS-related
LF-15-0195			WO	9624579	Immunosuppressant	Lupus erythematosus, general
LF-16-0687	2-Pyrrolidinecarboxamide, N-[3-[[4-(aminoiminomethyl)benzoyl]amino]propyl]-1-[[2,4-dichloro-3-[[(2,4-dimethyl-8-quinolinyl)oxy]methyl]phenyl]sulfonyl]-, (2S)- [CAS]	209733-45-9	FR	2756562	Neuroprotective	Head trauma
LGD-1550	2,4,6-Octatrienoic acid, 7-(3,5-bis(1,1-dimethylethyl)phenyl)-3-methyl-(2E,4E,6E)- [CAS]	178600-20-9			Anticancer, other	Cancer, cervical
LH		9002-67-9				
LH-RH		9034-40-6				
liarozole	1H-Benzimidazole, 5-[(3-chlorophenyl)-1H-imidazol-1-ylmethyl]- [CAS]	115575-11-6			Formulation, other	Psoriasis
licofelone	1H-Pyrrolizine-5-acetic acid, 6-(4-chlorophenyl)-2,3-dihydro-2,2-dimethyl-7-phenyl- [CAS]	156897-06-2			Antiarthritic, other	Arthritis, osteo
Licostinel		153504-81-5				
lidadronate	Phosphonic acid, [1-amino-3-(dimethylamino)propylidene]bis- [CAS]	63132-38-7	WO	9702827	Urological	Unspecified
Lidamidine		66871-56-5				
lidocaine	Acetamide, 2-(diethylamino)-N-(2,6-dimethylphenyl)- [CAS]	137-58-6			Formulation, transdermal, patch	Pain, post-herpetic
Lidofenin		59160-29-1				
Lidoflazine		3416-26-0				
limaprost	Prosta-2,13-dien-1-oic acid, 11,15-dihydroxy-17,20-dimethyl-9-oxo-,(2E,11Alpha,13E,15S,17S)-, [CAS]	74397-12-9	GB	2041368	Prostaglandin	Buerger's syndrome

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Lincomycin		154-21-2				
Lindane		58-89-9				
linezolid	Acetamide, N-((3-(3-fluoro-4-(4-morpholinyl)phenyl)-2-oxo-5-oxazolidinyl)methyl)-, (S)- [CAS]	165800-03-3	WO	9507271	Antibiotic, other	Infection, dermatological
Linoleic Acid		60-33-3				
Linolenic Acid		463-40-1				
Liothyronine		6893023				
Lipase		9001-62-1				
Lipo-dexamethasone palmitate	Pregna-1,4-diene-3,20-dione, 9-fluoro-11,17-dihydroxy-16-methyl-21-[(1-oxohexadecyl)oxy]-, (11ß,16Alpha)- [CAS]	14899-36-6			Formulation, optimized, microemulsion	Arthritis, rheumatoid
lipo-flurbiprofen	[1,1'-Biphenyl]-4-acetic acid, 2-fluoro-Alpha-methyl-, 1-(acetyloxy)ethyl ester [CAS]	91503-79-6	JP	60208910	Formulation, optimized, microemulsion	Pain, cancer
Lipogel HA			EP	525655	Formulation, optimized, liposomes	Unspecified
LiquiVent	perfluorooctylbromide	423-55-2	US	5437272	Lung Surfactant	Respiratory distress syndrome, adult
liranaftate	Carbamothioic acid, (6-methoxy-2-pyridinyl)methyl-, O-(5,6,7,8-tetrahydro-2-naphthalenyl) ester [CAS]	88678-31-3	GB	2124617	Antifungal	Infection, dermatological
lisinopril	L-Proline, 1-[N2-(1-carboxy-3-phenylpropyl)-L-lysyl]-, (S)- [CAS]	76547-98-3 83915-83-7	EP	12401	Antihypertensive, renin system	Hypertension, general
Lisofylline		100324-81-0				
lisuride	Urea, N'-[(8Alpha)-9,10-didehydro-6-methylergolin-8-yl]-N,N-diethyl-, [CAS]	19875-60-6 305-13-5 18016-80-3			Antiprolactin	Acromegaly
Lithium Citrate		919-16-4				
lithium	Carbonic acid, dilithium salt [CAS]	554-13-2			Formulation, modified-release, <=24hr	Depression, bipolar
lixivaptan	Benzamide, N-[3-chloro-4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)phenyl]-5-fluoro-2-methyl- [CAS]	168079-32-1	US	5736540	Cardiovascular	Heart failure
LJP-1082			US	6207160	Immunosuppressant	Thrombosis, venous

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
LLUAlpha	S-2,7,8-Trimethyl-6-(ß-carboxyethyl)-6-hydroxychroman				Antihypertensive, other	Hypertension, general
LMP-160			US	5643893	Antiasthma	Asthma
LMP-420			US	5643893	Antiarthritic, other	Arthritis, rheumatoid
lobaplatin	Platinum, (1,2-cyclobutanedimethanamine-N,N')[2-hydroxypropanoato(2-)-O1,O2]-, [SP-4-3-(S),(trans)]- [CAS]	135558-11-1	DE	4115559	Anticancer, alkylating	Cancer, lung, small cell
Lobeline		90-69-7				
Lobenzarit		63329-53-3				
lodoxamide	2,2'-((2-chloro-5-cyano-1,3-phenylene)diimino)bis(2-oxoacetate):2-amino-2-(hydroxymethyl)-1,3-propanediol (1:2)	63610-09-3 53882-12-5	US	4439445	Antiasthma	Asthma
Lofentanil		61380-40-3				
lofepramine	Ethanone, 1-(4-chlorophenyl)-2-[[3-(10,11-dihydro-5H-dibenz[b,f]azepin-5-yl)propyl]methylamino]- [CAS]	23047-25-8 26786-32-3	GB	1177525	Antidepressant	
lofexidine	1H-Imidazole, 2-[1-(2,6-dichlorophenoxy)ethyl]-4,5-dihydro- [CAS]	31036-80-3	GB	1181356	Antihypertensive, adrenergic	Hypertension, general
Loflucarban		790-69-2				
lomefloxacin	3-Quinolinecarboxylic acid, 1-ethyl-6,8-difluoro-1,4-dihydro-7-(3-methyl-1-piperazinyl)-4-oxo- [CAS]	98079-51-7 98079-52-8	EP	140116	Quinolone antibacterial	Infection, respiratory tract, lower
lomerizine	Piperazine, 1-[bis(4-fluorophenyl)methyl]-4-[(2,3,4-trimethoxyphenyl)methyl]-, [CAS]	101477-54-7 101477-55-8	EP	159566	Antimigraine	Migraine
lomifylline	7-(5-oxohexyl)theophylline	10226-54-7	DE	2207860	Neurological	
lomustine	Urea, N-(2-chloroethyl)-N'-cyclohexyl-N-nitroso- [CAS]	13010-47-4	JP	48075526	Anticancer, alkylating	
lonafarnib	1-Piperidinecarboxamide, 4-[2-[4-[(11R)-3,10-dibromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl]-1-piperidinyl]-2-oxoethyl]- [CAS]	193275-84-2	US	5874442	Anticancer, other	Cancer, lung, non-small cell

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Lonapalene		91431-42-4				
Lonazolac		53808-88-1				
lonidamine	1H-Indazole-3-carboxylic acid, 1-[(2,4-dichlorophenyl)methyl]- [CAS]	50264-69-2	DE	2310031	Radio/chemosensitizer	Cancer, breast
loperamide	4-(p-chlorophenyl)-4-hydroxy-N,N-dimethyl-Alpha,Alpha-diphenyl-1-piperidine butyramide HCl	34552-83-5 53179-11-6	US	3714159	Antidiarrhoeal	Diarrhoea, general
loperamide oxide	1-Piperidinebutanamide, 4-(4-chlorophenyl)-4-hydroxy-N,N-dimethyl-Alpha,Alpha-diphenyl-, 1-oxide, trans- [CAS]	106900-12-3	EP	219898	Antidiarrhoeal	Diarrhoea, general
loprazolam	1H-imidazo[1,2-a][1,4]benzodiazepin-1-one, 6-(2-chlorophenyl)-2,4-dihydro-2-[(4-methyl-1-piperazinyl)methylene]-8-nitro- [CAS]	61197-73-7 61197-93-1 70111-54-5	GB	1496426	Hypnotic/Sedative	
Loprinone		106730-54-5				
loracarbef	1-Azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[(aminophenylacetyl)amino]-3-chloro-8-oxo-, [6R-[6Alpha,7ß(R*)]]- [CAS]	76470-66-1 121961-22-6	EP	14475	Cephalosporin, oral	Infection, respiratory tract, lower
Lorajmine		47562-08-3				
loratadine	1-Piperidinecarboxylic acid, 4-(8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)-, ethyl ester- [CAS]	79794-75-5	EP	42544	Antiallergic, non-asthma	Rhinitis, allergic, general
lorazepam	2H-1,4-Benzodiazepin-2-one, 7-chloro-5-(2-chlorophenyl)-1,3-dihydro-3-hydroxy-	846-49-1			Formulation, oral, orally-disintegrating	Epilepsy, general
lorcainide	Benzeneacetamide, N-(4-chlorophenyl)-N-[1-(1-methylethyl)-4-piperidinyl]-[CAS]	58934-46-6 59729-31-6	DE	2642856	Antiarrhythmic	
lormetazepam	2H-1,4-Benzodiazepin-2-one, 7-chloro-5-(2-chlorophenyl)-1,3-dihydro-3-hydroxy-1-methyl- [CAS]	848-75-9	US	3296249	Hypnotic/Sedative	Insomnia

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
lornoxicam	2H-Thieno[2,3-e]-1,2-thiazine-3-carboxamide, 6-chloro-4-hydroxy-2-methyl-N-2-pyridinyl-, 1,1-dioxide- [CAS]	70374-39-9	EP	313935	Analgesic, NSAID	Pain, post-operative
losartan	1H-Imidazole-5-methanol, 2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, [CAS]	124750-99-8 114798-26-4	EP	253310	Antihypertensive, renin system	Hypertension, general
loteprednol	Androsta-1,4-diene-17-carboxylic acid, 17-[(ethoxycarbonyl)oxy]-11-hydroxy-3-oxo-, chloromethyl ester, (11ß,17Alpha)- [CAS]	82034-46-6	GB	2079755	Anti-inflammatory, topical	Uveitis
Lotrafiban		171049-14-2				
Lovastatin		75330-75-5				
Loxapine		10/02/1977				
loxiglumide	Pentanoic acid, 4-[(3,4-dichlorobenzoyl)amino]-5-[(3-methoxypropyl)pentylamino]-5-oxo-, (±)- [CAS]	107097-80-3	WO	8703869	GI inflammatory/bowel disorders	Pancreatitis
loxoprofen	Benzeneacetic acid, Alpha-methyl-4-[(2-oxocyclopentyl)methyl]- [CAS]	68767-14-6 80382-23-6 87828-36-2	EP	55588	Antiarthritic, other	Arthritis, rheumatoid
Lu-35-138	1-[3[[2-[5-chloro-1-(4-fluorophenyl)-3-1H-indolyl]ethyl]methylamino]propyl]-2-imidazolidinone hydrochloride		WO	9516684	Neuroleptic	Psychosis, general
Lubeluzole		144665-07-6				
lubiprostone	(-)-7-[(2R,4aR,5R,7aR)-2-(1,1-difluoropentyl)-2-hydroxy-6-oxooctahydrocyclopenta[b]pyran-5-yl]heptanoic acid	136790-76-6			Laxative	Constipation
lucanthone	Thioxanthen-9-one, 1-((2-(diethylamino)ethyl)amino-4-methyl- [CAS]	479-50-5			Radio/chemosensitizer	Cancer, brain
Lucanthone		548-57-2				
Lumefantrine		82186-77-4				
lumiracoxib	Benzeneacetic acid, 2-((2-chloro-6-fluorophenyl)amino)-5-methyl- [CAS]	220991-20-8			Analgesic, NSAID	Pain, general

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
lurtotecan	11H-1,4-Dioxino[2,3-g]pyrano[3',4':6,7]indolizino[1,2-b]quinoline-9,12[8H,14H]-dione, 8-ethyl-2,3-dihydro-8-hydroxy-15-[[4-methyl-1-piperazinyl]methyl]-, [CAS]	155773-58-3			Formulation, optimized, liposomes	Cancer, ovarian
lutetium texaphyrin	Lutetium, bis(acetato-O)[9,10-diethyl-20,21-bis-[2-[2-(2-methoxyethoxy)ethoxy]ethoxy]-4,15-dimethyl-8,11-imino-3,6:16,13-dinitrilo-1,18-benzodiazacycloeicosine-5,14-dipropanolato-N1,N18,N23,N24,N25]-, (PB 7-11-233'2'4)- [CAS]	156436-90-7	WO	9906411	Radio/chemosensitizer	Atherosclerosis
LV-216	Zinc[2-(2,6-dichloroanilino)phenyl]acetate				Anti-inflammatory	Arthritis, rheumatoid
LX-104	Hexadecanamide, N-[4-[[2-[2-[2-[[O-(N-acetyl-Alpha-neuraminosyl)-(2-3)-O-ß-D-galactopyranosyl-(1-4)-O-[6-deoxy-Alpha-L-galactopyranosyl-(1-3)]-ß-D-glucopyranosyl]oxy]ethoxy]ethoxy]ethoxy]methyl]phenyl]-2-tetradecyl- [CAS]	158792-45-1			Cognition enhancer	Dementia, senile, general
LY-156735	ß-methyl-6-chloromelatonin		EP	655243	Hypnotic/Sedative	Sleep disorder, general
LY-293111	Benzoic acid, 2-[3-[3-[(5-ethyl-4'-fluoro-2-hydroxy[1,1'-biphenyl]-4-yl)oxy]propoxy]-2-propylphenoxy]- [CAS]	161172-51-6			Anticancer, other	Cancer, melanoma
LY-293558	3-Isoquinolinecarboxylic acid, decahydro-6-[2-(1H-tetrazol-5-yl)ethyl]-, [3S-(3Alpha.,4aAlpha ,6ß ,8aAlpha.)]- [CAS]	154652-83-2			Analgesic, other	Pain, neuropathic
LY-355703	1,4-Dioxa-8,11-diazacyclohexadec-13-ene-2,5,9,12-tetrone, 10-[(3-chloro-4-methoxyphenyl)methyl]-6,6-dimethyl-3-(2-methylpropyl)-16-[(1S)-1-[(2S,3R)-3-phenyloxiranyl]ethyl]-, (3S,10R,13E,16S)- [CAS]	18256-67-7	WO	9707798	Anticancer, other	Cancer, lung, non-small cell
Lyapolate		25053-27-4				
Lymecycline		992-21-2				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Lynestrenol		52-76-6				
Lypressin		50-57-7				
Lysine Acetylsalicylate		62952-06-1				
lysine salicylate	L-Lysine, 2-hydroxybenzoate [CAS]	59535-08-9	WO	9624331	Analgesic, NSAID	
lysophospholipids			WO	9843093	Diagnostic	Diagnosis, cancer
M-40403	Dichloro[(4aR,13aR,17aR,21aR)-1,2,3,4,4a,5,6,12,13,13a,14,15,16,17,17a,18,19,20,21,21a-eicosahydro-1,7-nitrilo-7H-dibenzo[b,h] [1,4,7,10]tetraazacyclo-heptadecine-kappaN5,kappaN13,kappaN18,kappaN21,kappaN22]manganese		US	6180620	Anticancer, other	Unspecified
mabuprofen	Benzeneacetamide, N-(2-hydroxyethyl)-Alpha-methyl-4-(2-methylpropyl)-, (+/-)- [CAS]	82821-47-4	DE	3121595	Anti-inflammatory	
Mabuterol		56341-08-3				
Macrophage Colony-Stimulating Factor		81627-83-0				
MADU		840-50-6				
mafenide	Benzenesulfonamide, 4-(aminomethyl)-monoacetate [CAS]	13009-99-9 138-39-6			Vulnerary	Burns
mafosfamide	Ethanesulfonic acid, 2-[[2-[bis(2-chloroethyl)amino]tetrahydro-2H-1,3,2-oxazaphosphorin-4-yl]thio]-, P-oxide, cis-(±)- [CAS]	88859-04-5 98845-64-8	EP	393575	Anticancer, alkylating	Cancer, renal
magaldrate	Aluminum magnesium hydroxide sulfate (Al5Mg10(OH)31(SO4)2), hydrate [CAS]	74978-16-8	US	2923660	Antacid/Antiflatulent	
Magenta I		632-99-5				
Magnesium Acetylsalicylate		132-49-0				
Magnesium Carbonate Hydroxide		39409-82-0				
magnesium chloride	Magnesium chloride (MgCl2) [CAS]	7786-30-3			Formulation, oral, enteric-coated	Nutrition

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Magnesium Citrate		3344-18-1				
magnesium gluconate	D-Gluconic acid, magnesium salt (2:1) [CAS]	3632-91-5			Formulation, other	Hypertension, general
Magnesium Lactate		18917-93-6				
Magnesium Salicylate		18917-89-0				
Malathion		121-75-5				
Malotilate		59937-28-9				
Mandelic Acid		90-64-2				
Mandelic Acid Isoamyl Ester		5421045				
Mangafodipir		118248-94-5 (free acid); 155319-91-8 (hexahydrogen)				
manidipine	3,5-Pyridinedicarboxylic acid, 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-, 2-[4-(diphenylmethyl)-1-piperazinyl]ethyl methyl ester [CAS]	89226-50-6 89226-75-5	EP	94159	Antihypertensive, other	Hypertension, general
Mannomustine		551-74-6				
mannose-6-phosphate	mannose-6-phosphate				Vulnerary	Wound healing
Maprotiline		10262-69-8				
maribavir	1H-Benzimidazol-2-amine, 5,6-dichloro-N-(1-methylethyl)-1-ß-L-ribofuranosyl- [CAS]	176161-24-3			Antiviral, other	Infection, cytomegalovirus
marimastat	N-[2,2-Dimethyl-1(S)-(N-methylcarbamoyl)propyl]-N,3(S)-dihydroxy-2(R)-isobutylsuccinamide	154039-60-8	WO	9402447	Anticancer, other	Cancer, pancreatic
maxacalcitol	1,3-Cyclohexanediol, 4-methylene-5-(2-(octahydro-1-(1-(3-hydroxy-3-methylbutoxy)ethyl)-7a-methyl-4H-inden-4-ylidene)ethylidene)-, (1S-(1Alpha(R*),3aß,4E(1S*,3R*,5Z),7aAlpha))- [CAS]	103909-75-7	US	4891364	Hormone	Hyperparathyroidism

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
mazindol	3H-Imidazo[2,1-a]isoindol-5-ol, 5-(4-chlorophenyl)-2,5-dihydro- [CAS]	22232-71-9	US	3763178	Anorectic/Antiobesity	Obesity
Mazipredone		13085-08-0				
MC-5723			US	6043259	Cardiovascular	Unspecified
MCC-478	(2-amino-6-(4-methoxyphenylthio)-9-[2-(phosphonomethoxy)ethyl]purine bis(2,2,2-trifluoroethyl) ester)				Antiviral, other	Infection, hepatitis-B virus
MCI-154	3(2H)-Pyridazinone, 4,5-dihydro-6-[4-(4-pyridinylamino)phenyl]-, monohydrochloride [CAS]	98326-32-0 98326-33-1	EP	145019	Cardiostimulant	Heart failure
m-Cresyl Acetate		122-46-3				
MDAM	Gamma-Methylene-10-deazaaminopterin				Anticancer, antimetabolite	Cancer, general
MDI-101			US	4885311	Antiacne	Acne
MDI-403		403849-94-5	US	4677120	Antiacne	Acne
MDL-100907	4-Piperidinemethanol, Alpha-(2,3-dimethoxyphenyl)-1-(2-(4-fluorophenyl)ethyl)-, (R)- [CAS]	139290-65-6			Hypnotic/Sedative	Sleep disorder, general
mebendazole	methyl-5-benzoylbenzimidazole-2-carbamate	31431-39-7	GB	1307306	Anthelmintic	
mebeverine	Benzoic acid, 3,4-dimethoxy-, 4-[ethyl[2-(4-methoxyphenyl)-1-methylethyl]amino]butyl ester [CAS]	3625-06-7			Antispasmodic	Irritable bowel syndrome
Mebhydroline		524-81-2				
Mebrofenin		78266-06-5				
Mebutamate		64-55-1				
mecamylamine	Bicyclo(2.2.1)heptan-2-amine, N,2,3,3-tetramethyl- [CAS]	60-40-2			Neurological	Unspecified
Mechlorethamine		51-75-2				
Mechlorethamine Oxide		302-70-5				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
mecillinam	4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 6-[[(hexahydro-1H-azepin-1-yl)methylene]amino]-3,3-dimethyl-7-oxo-, [2S-(2Alpha,5Alpha,6.beta.)]- [CAS]	32887-01-7 32887-03-9	GB	1293590	Penicillin, injectable	Infection, general
Meclizine		569-65-3				
Meclocycline		2013-58-3				
meclofenamate	Benzoic acid, 2-[(2,6-dichloro-3-methylphenyl)amino]-, monosodium salt [CAS]	6385-02-0 644-62-2			Antiarthritic, other	Arthritis, osteo
Meclofenamic Acid		644-62-2				
Meclofenoxate		51-68-3				
Mecloqualone		340-57-8				
Mecysteine		18598-63-5				
Medazepam		12/06/2898				
medifoxamine	Ethanamine, N,N-dimethyl-2,2-diphenoxy- [CAS]	32359-34-5	FR	M5498	Antidepressant	
Medrogestone		977-79-7				
Medronic Acid		1984-15-2				
medroxyprogesterone	Pregn-4-ene-3,20-dione, 17-(acetyloxy)-6-methyl-,(6Alpha)	71-58-9 520-85-4			Formulation, fixed-dose combinations	Contraceptive, female
Medrysone		2668-66-8				
Mefenamic Acid		61-68-7				
Mefenorex		17243-57-1				
Mefexamide		1227-61-8				
mefloquine	4-Quinolinemethanol, Alpha-2-piperidinyl-2,8-bis(trifluoromethyl)-, (R*,S*)-(±)-[CAS]	51773-92-3 53230-10-7 69191-18-0	GB	1594282	Antimalarial	
Mefruside		7195-27-9				
Megestrol		595-33-5				
Meglumine		22154-43-4 131-49-7				
meglutol	2-hydroxy-2-methyl-1,3-propandicarboxylic acid	503-49-1	US	3629449	Hypolipaemic/Antiatherosclerosis	Hyperlipidaemia, general

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
melagatran	Glycine, N-[(1R)-2-[(2S)-2-[[[[4-(aminoiminomethyl)phenyl]methyl]amino]carbonyl]-1-azetidinyl]-1-cyclohexyl-2-oxoethyl]- [CAS]	159776-70-2	WO	9616671	Antithrombotic	Thrombosis, general
melanocortin-4 agonist	N-[(3R)-1,2,3,4-Tetrahydroisoquinolinium-3-ylcarbonyl]-(1R)-1-(4-chlorobenzyl)-2-[4-cyclohexyl-4-(1H-1,2,4-triazol-1-ylmethyl)piperidin-1-yl]-2-oxoethylamine(1)				Anorectic/Antiobesity	Obesity
Melarsoprol		494-79-1				
Melengestrol		5633-18-1				
melevodopa	Alanine, 3-(3,4-dihydroxyphenyl)-methylester [CAS]	7101-51-1	EP	252290	Antiparkinsonian	Parkinson's disease
Melinamide		14417-88-0				
Melitracen		5118-29-6				
meloxicam	2H-1,2-Benzothiazine-3-carboxamide, 4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-, 1,1-dioxide- [CAS]	71125-38-7	US	4233299	Antiarthritic, other	Arthritis, rheumatoid
melperone	1-Butanone, 1-(4-fluorophenyl)-4-(4-methyl-1-piperidinyl)- [CAS]	1622-79-3 3575-80-2	BE	651144	Neuroleptic	
Melphalan		148-82-3				
meluadrine	Benzenemethanol, 2-chloro-Alpha-(((1,1-dimethylethyl)amino)methyl)-4-hydroxy-, (R)-, (R*,R*))-2,3-dihydroxybutanedioate (1:1) (salt) [CAS]	134865-37-5	EP	420120	Labour inhibitor	Labour, preterm
memantine	Tricyclo[3.3.1.13,7]decan-1-amine, 3,5-dimethyl [CAS]	41100-52-1 19982-08-2	EP	392059	Cognition enhancer	Dementia, AIDS-related
MEN-10700	Acetamide, 2-[[[(5R,6S)-6-[(1R)-1-hydroxyethyl]-2-methyl-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-en-3-yl]methyl]methylamino]- [CAS]	195874-55-6	WO	9406803	Beta-lactam antibiotic	Infection, general

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
MEN-10755	5,12-Naphthacenedione, 7-[[4-O-(3-amino-2,3,6-trideoxy-Alpha-L-lyxo-hexopyranosyl)-2,6-dideoxy-Alpha-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,9,11-trihydroxy-9-(hydroxyacetyl)-, hydrochloride, (7S,9S)- [CAS]	169317-77-5	WO	9509173	Anticancer, antibiotic	Cancer, breast
Menadiol		481-85-6				
Menadione		58-27-5				
Menadoxime		573-01-3				
Menbutone		3562-99-0				
Menogaril		71628-96-1				
MENT	7Alpha-Methyl-19-nortestosterone				Formulation, transdermal, systemic	Contraceptive, male
menthol	Cyclohexanol, 5-methyl-2-(1-methlethyl)-[CAS]	1490-04-6 89-78-1			Formulation, dermal, topical	Pruritus
Menthyl Valerate		89-47-4				
Meobentine		46464-11-3				
Meparfynol		77-75-8				
mepartricin	Partricin, methyl ester [CAS]	11121-32-7	US	3780173	Antifungal	Infection, Candida, general
Mepazine		60-89-9				
Mepenzolate Bromide		76-90-4				
Meperidine		57-42-1				
Mephenesin		59-47-2				
Mephenoxalone		70-07-5				
Mephentermine		100-92-5				
Mephenytoin		50-12-4				
Mephobarbital		115-38-8				
Mepindolol		23694-81-7				
Mepitiostane		21362-69-6				
mepivacaine	N-(2,6-Dimethylphenyl)-1-methyl-2-piperidinecarboxamide	96-88-8			Formulation, modified-release, >24hr	Pain, post-operative
Mepixanox		17854-59-0				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Meprednisone		1247-42-3				
Meprobamate		57-53-4				
meproscillarin	Bufa-4,20,22-trienolide, 3-[(6-deoxy-4-O-methyl-Alpha-L-mannopyranosyl)oxy]-14-hydroxy-, (3ß)- [CAS]	33396-37-1	DE	1910207	Cardiostimulant	Heart failure
meptazinol	Phenol, 3-(3-ethylhexahydro-1-methyl-1H-azepin-3-yl)- [CAS]	54340-58-8 59263-76-2	GB	1285025	Analgesic, other	Pain, general
mequitazine	10H-Phenothiazine, 10-(1-azabicyclo[2.2.2]oct-3-ylmethyl)- [CAS]	29216-28-2	GB	1250534	Antiallergic, non-asthma	
Meralein		4386-35-0				
Meralluride		8069-64-5				
Merbromin		129-16-8				
Mercaptomerin		21259-76-7				
Mercumallylic Acid		86-36-2				
Mercuric Chloride, Ammoniated		10124-48-8				
Mercuric Oleate		1191-80-6				
Mercuric Oxycyanide		1335-31-5				
merimepodib	Carbamic acid, ((3-((((3-methoxy-4-(5-oxazolyl)phenyl)amino)carbonyl)amino)phenyl)methyl)- (3S)-tetrahydro-3-furanyl ester [CAS]	198821-22-6	US	5807876	Antiviral, other	Infection, hepatitis-C virus
meropenem	1-Azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid, 3-[[5-[(dimethylamino)carbonyl]-3-pyrrolidinyl]thio]-6-(1-hydroxyethyl)-4-methyl-7-oxo-, [4R-[3(3S*,5S*),4Alpha,5ß,6ß(R*)]]- [CAS]	96036-03-2	EP	126587	Beta-lactam antibiotic	Infection, respiratory tract, lower
Mersalyl		492-18-2				
Mesalamine		89-57-6				
mesalazine	Benzoic acid, 5-amino-2-hydroxy- [CAS]	89-57-6	WO	5541170	Formulation, oral, other	Colitis, ulcerative
Mesna		19767-45-4				
Mesoridazine		5588-33-0				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Mestanolone		521-11-9				
Mesterolone		1424-00-6				
Mestranol		72-33-3				
Mesulfen		135-58-0				
Metaclazepam		84031-17-4				
Metampicillin		6489-97-0				
Metapramine		21730-16-5				
Metaproterenol		586-06-1				
Metaraminol		54-49-9				
Metazocine		3734-52-9				
metergoline	Carbamic acid, [[(8ß)-1,6-dimethylergolin-8-yl]methyl]-, phenylmethyl ester [CAS]	17692-51-2 21631-37-8 2706-42-5	GB	1401935	Antiprolactin	Amenorrhoea
metformin	Imidodicarbonimidic diamide, N,N-dimethyl- [CAS]	657-24-9			Formulation, modified-release, <=24hr	Diabetes, Type II
Methacholine		62-51-1				
Methacycline		914-00-1				
Methadone		76-99-3				
Methafurylene		531-06-6				
Methamphetamine		537-46-2				
Methandriol		521-10-8				
Methandrostenolone		72-63-9				
Methantheline		53-46-3				
Methapyrilene		91-80-5				
Methaqualone		72-44-6				
Metharbital		50-11-3				
Methazolamide		554-57-4				
Methdilazine		1982-37-2				
Methenamine		100-97-0				
Methenolone		153-00-4				
Methestrol		130-73-4				
Methetoin		5696-06-0				
Methicillin		132-92-3				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Methimazole		60-56-0				
Methiodal		126-31-8				
Methionic Acid		503-40-2				
Methionine		63-68-3				
Methisazone		1910-68-5				
Methitural		467-43-6				
Methixene		02/02/4969				
Methocarbamol		532-03-6				
Methohexital		22151-68-4				
methotrexate	L-Glutamic acid, N-[4-[[(2,4-diamino-6-pteridinyl)methyl]methylamino]benzoyl]-[CAS]	59-05-2	US	2512572	Anticancer, antimetabolite	Cancer, general
Methotrimeprazine		60-99-1				
Methoxamine		390-28-3				
Methoxsalen		298-81-7				
Methoxyflurane		76-38-0				
Methoxyphenamine		93-30-1				
Methoxypromazine		61-01-8				
Methscopolamine		155-41-9				
Methsuximide		77-41-8				
Methyclothiazide		135-07-9				
Methyl Blue		28983-56-4				
Methyl Nicotinate		93-60-7				
Methyl Propyl Ether		557-17-5				
Methyl Salicylate		119-36-8				
Methyl tert-Butyl Ether		1634-04-4				
Methylbenzethonium Chloride		25155-18-4				
Methylcobalamin		13422-55-4				
methyldopa	L-Tyrosine, 3-hydroxy-Alpha-methyl-[CAS]	555-30-6			Formulation, modified-release, <=24hr	Hypertension, general
Methylene Blue		61-73-4				
Methylergonovine		113-42-8				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Methylhexaneamine		105-41-9				
methylphenidate	2-Piperidineacetic acid, Alpha-phenyl-, methyl ester [CAS]	113-45-1 298-59-9			Formulation, modified-release, multi	Attention deficit disorder
Methylprednisolone		83-43-2				
methylprednisolone aceponate	Pregna-1,4-diene-3,20-dione, 21-(acetyloxy)-11-hydroxy-6-methyl-17-(1-oxopropoxy)-, (6Alpha,11ß)- [CAS]	86401-95-8	EP	72547	Antipruritic/inflamm, allergic	Pruritus
methylprednisolone suleptanate	Pregna-1,4-diene-3,20-dione, 11,17-dihydroxy-6-methyl-21-[[8-[methyl(2-sulfoethyl)amino]-1,8-dioxooctyl]oxy]-, monosodium salt, (6Alpha,11ß)- [CAS]	90350-40-6	JP	59137500	Antiasthma	Asthma
Methylthiouracil		56-04-2				
Methyltrienolone		965-93-5				
Methyprylon		125-64-4				
Methysergide		361-37-5				
Metiazinic Acid		13993-65-2				
metipranolol	Phenol, 4-[2-hydroxy-3-[(1-methylethyl)amino]propoxy]-2,3,6-trimethyl-, 1-acetate [CAS]	22664-55-7	GB	1206148	Antihypertensive, adrenergic	
metoclopramide	Benzamide, 4-amino-5-chloro-N-[2-(diethylamino)ethyl]-2-methoxy- [CAS]	364-62-5			Formulation, modified-release, <=24hr	Gastro-oesophageal reflux
Metocurine Iodide		7601-55-0				
Metofenazate		388-51-2				
metolazone	6-Quinazolinesulfonamide, 7-chloro-1,2,3,4-tetrahydro-2-methyl-3-(2-methylphenyl)-4-oxo- [CAS]	17560-51-9	US	4517179	Antihypertensive, diuretic	
Metopimazine		14008-44-7				
Metopon		143-52-2				
metoprolol	2-Propanol, 1-[4-(2-methoxyethyl)phenoxy]-3-[(1-methylethyl)amino]-, (+/-)- [CAS]	51384-51-1 56392-17-7 37350-58-6			Formulation, modified-release, other	Hypertension, general
Metralindole		54188-38-4				
Metrizamide		31112-62-6				
Metrizoic Acid		1949-45-7				
Metron S		13946-02-6				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Metyrapone		54-36-4				
Metyrosine		672-87-7				
Mexazolam		31868-18-5				
Mexenone		1641-17-4				
Mexiletine		31828-71-4				
mezlocillin	4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 3,3-dimethyl-6-[[[[[3-(methylsulfonyl)-2-oxo-1-imidazolidinyl]carbonyl]amino]phenylacetyl]amino]-7-oxo-, [2S-[2Alpha,5Alpha,6ß(S*)]]- [CAS]	42057-22-7 51481-65-3 72539-76-5	GB	1301961	Penicillin, injectable	Infection, general
MFH-244	Benzenecarboximidic acid, 3,4,5-trihydroxy-, ethyl ester, hydrochloride	95933-76-9	US	4623659	Cardiovascular	Reperfusion injury
mianserin	Dibenzo[c,f]pyrazino[1,2-a]azepine, 1,2,3,4,10,14b-hexahydro-2-methyl- [CAS]	21535-47-7 24219-97-4	GB	1173783	Antidepressant	Depression, general
Mibefradil		116644-53-2				
Miboplatin		103775-75-3				
Micafungin		235114-32-6				
miconazole	1H-Imidazole,1-(2,4-dichlorophenyl)-2[2,4-dichlorophenyl)methoxy]ethyl]	22916-47-8			Formulation, modified-release, other	Infection, Candida, general
Micronomicin		52093-21-7				
midaxifylline	1H-Purine-2,6-dione, 8-(1-aminocyclopentyl)-3,7-dihydro-1,3-dipropyl- [CAS]	151159-23-8	US	5378844	Cardiovascular	Unspecified
midazolam	4H-Imidazo[1,5-a][1,4]benzodiazepine, 8-chloro-6-(2-fluorophenyl)-1-methyl-[CAS]	59467-70-8 59467-94-6	US	4280957	Anaesthetic, injectable	
midecamycin	Leucomycin V, 3,4B-dipropanoate [CAS]	35457-80-8	US	3761588	Macrolide antibiotic	Infection, general
midecamycin acetate	Leucomycin V, 3B,9-diacetate 3,4B-dipropanoate [CAS]	55881-07-7	JP	49124087	Macrolide antibiotic	Infection, general
midesteine	2-Thiophenecarbothioic acid, S-[1-methyl-2-oxo-2-[(tetrahydro-2-oxo-3-thienyl)amino]ethyl] ester [CAS]	94149-41-4	EP	120534	COPD treatment	Emphysema, general

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
midodrine	Acetamide, 2-amino-N-[2-(2,5-dimethoxyphenyl)-2-hydroxyethyl]- [CAS]	42318-56-0 42794-76-3	EP	164571	Urological	Incontinence
midostaurin	Benzamide, N-(2,3,10,11,12,13-hexahydro-10-methoxy-9-methyl-1-oxo-9,13-epoxy-1H,9H-diindolo[1,2,3-gh:3',2',1'-lm]pyrrolo[3,4-j][1,7]benzodiazonin-11-yl)-N-methyl-, (9Alpha,10ß,11ß,13Alpha)- [CAS]	120685-11-2	EP	296110	Anticancer, other	Cancer, leukaemia, acute myelogenous
mifepristone	Estra-4,9-dien-3-one, 11-[4-(dimethylamino)phenyl]-17-hydroxy-17-(1-propynyl)-, (11ß,17ß)- [CAS]	84371-65-3	EP	57115	Abortifacient	Abortion
miglitol	3,4,5-Piperidinetriol, 1-(2-hydroxyethyl)-2-(hydroxymethyl)-, [2R-(2Alpha,3ß,4Alpha,5ß)]- [CAS]	72432-03-2	EP	55431	Antidiabetic	Diabetes, Type I
miglustat	3,4,5-Piperidinetriol, 1-butyl-2-(hydroxymethyl)-(2R-(2Alpha, 3ß, 4Alpha, 5ß)) [CAS]	72599-27-0	DE	2758025	Metabolic and enzyme disorders	Gaucher's disease
mildronate	Hydrazinium, 2-(2-carboxyethyl)-1,1,1-trimethyl-, inner salt- [CAS]	76144-81-5	WO	8001068	Cardiostimulant	Heart failure
milnacipran	Cyclopropanecarboxamide, 2-(aminomethyl)-N,N-diethyl-1-phenyl-, cis-(±)-[CAS]	101152-94-7 92623-85-3	US	4478836	Antidepressant	Depression, general
Miloxacin		37065-29-5				
milrinone	[3,4'-Bipyridine]-5-carbonitrile, 1,6-dihydro-2-methyl-6-oxo- [CAS]	78415-72-2	US	4313951	Cardiostimulant	Heart failure
miltefosine	Ethanaminium, 2-[[(hexadecyloxy)hydroxyphosphinyl]oxy]-N,N,N-trimethyl-, hydroxide, inner salt [CAS]	53949-20-5 58066-85-6	EP	225608	Anticancer, other	Cancer, skin, general
minaprine	4-Morpholineethanamine, N-(4-methyl-6-phenyl-3-pyridazinyl)- [CAS]	25905-77-5 25953-17-7	GB	1345880	Antidepressant	Depression, general

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
minocycline	2-Naphthacenecarboxamide, 4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-, [4S-(4Alpha,4aAlpha,5a.alpha.,12aAlpha)]-[CAS]	10118-90-8			Formulation, optimized, microparticles	Infection, oral
minodronic acid	Phosphonic acid, (1-hydroxy-2-imidazo(1,2-a)pyridin-3-ylethylidene)bis-, [CAS]	180064-38-4	EP	354806	Anticancer, other	Cancer, myeloma
minoxidil	2,4-Pyrimidinediamine, 6-(1-piperidinyl)-, 3-oxide [CAS]	38304-91-5	US	4139619	Vasodilator, peripheral	Hypertension, general
Miokamycin		55881-07-7				
mirtazapine	Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine, 1,2,3,4,10,14b-hexahydro-2-methyl-[CAS]	85650-52-8 61337-67-5	GB	1543171	Antidepressant	Depression, general
misoprostol	Prost-13-en-1-oic acid, 11,16-dihydroxy-16-methyl-9-oxo-, methyl ester, (11Alpha,13E)-(±)- [CAS]	59122-46-2 59122-48-4	US	4301146	Prostaglandin	Ulcer, gastric
mitemcinal	Erythromycin, 8,9-didehydro-N-demethyl-9-deoxo-6,11-dideoxy-6,9-epoxy-12-O-methyl-N-(1-methylethyl)-11-oxo-, (2E)-2-butenedioate (2:1) [CAS]	154802-96-7	WO	9324509	Gastroprokinetic	Gastro-oesophageal reflux
mitiglinide	Calcium (2S)-2-benzyl-3-(cis-hexahydro-2-isoindolinylcarbonyl)propionate, dihydrate-[CAS]	145525-41-3	EP	507534	Antidiabetic	Diabetes, Type II
Mitobronitol		488-41-5				
Mitoguazone		459-86-9				
mitolactol	Galactitol, 1,6-dibromo-1,6-dideoxy- [CAS]	10318-26-0	US	3993781	Anticancer, alkylating	Cancer, cervical

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
mitomycin	Azirino[2',3':3,4]pyrrolo[1,2-a]indole-4,7-dione, 6-amino-8-[[(aminocarbonyl)oxy]methyl]-1,1a,2,8,8a,8b-hexahydro-8a-methoxy-5-methyl-, [1aS-(1aAlpha,8ß,8aAlpha,8bAlpha)]- [CAS]	50-07-7			Formulation, parenteral, other	Cancer, stomach
Mitotane		53-19-0				
mitoxantrone	9,10-Anthracenedione, 1,4-dihydroxy-5,8-bis[[2-[(2-hydroxyethyl)amino]ethyl]amino]- [CAS]	65271-80-9 70476-82-3	US	4197249	Anticancer, other	Cancer, breast
mitoxantrone	9,10-Anthracenedione, 1,4-dihydroxy-5,8-bis[[2-[(2-hydroxyethyl)amino]ethyl]amino]- [CAS]	65271-80-9 70476-82-9			Formulation, optimized, liposomes	Cancer, general
MIV-210	(3'-Fluoro-2'-3'-dideoxy guanosine)				Antiviral, other	Infection, hepatitis-B virus
mivacurium	Isoquinolinium, 2,2'-[(1,8-dioxo-4-octene-1,8-diyl)bis(oxy-3,1-propanediyl)]bis[1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-[(3,4,5-trimethoxyphenyl)methyl]-, dichloride, [R-[R*,R*-(E)]]]- [CAS]	106861-44-3	EP	181055	Muscle relaxant	Anaesthesia, adjunct
Mivazerol		125472-02-8				
mizolastine	4(1H)-Pyrimidinone, 2-[[1-[1-[(4-fluorophenyl)methyl]-1H-benzimidazol-2-yl]-4-piperidinyl]methylamino]- [CAS]	108612-45-9	EP	217700	Antiallergic, non-asthma	Rhinitis, allergic, general
Mizoribine		50924-49-7				
MKC-733	(R)-N-(3-quinuclidinyl)-7-oxo-4,7-dihydrothieno[3,2-b]pyridine-6-carboxamide hydrochloride	194093-42-0	JP	09216888	Gastroprokinetic	Gastro-oesophageal reflux
MLN-519	6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione, 1-[(1S)-1-hydroxy-2-methylpropyl]-4-propyl-, (1R,4R,5S)- [CAS]	211866-70-5	WO	9915183	Neuroprotective	Ischaemia, cerebral
MLN-576	4-Methoxy-benzo[a]phenazine-11-carboxylic acid (2-(dimethylamino)-1-(R)-methylethyl)-amide				Anticancer, other	Cancer, general

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
moclobemide	Benzamide, 4-chloro-N-[2-(4-morpholinyl)ethyl]- [CAS]	71320-77-9	EP	326023	Antidepressant	Depression, general
modafinil	Acetamide, 2-[(diphenylmethyl)sulfinyl]- [CAS]	68693-11-8	DE	2809625	Psychostimulant	Narcolepsy
moexipril	3-Isoquinolinecarboxylic acid, 2-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-6,7-dimethoxy- (3S-(2(R*(R*)),3R*))- [CAS]	103775-10-6 103775-14-0	US	4344949	Antihypertensive, renin system	Hypertension, general
Mofarotene		125533-88-2				
Mofebutazone		2210-63-1				
Mofegiline		119386-96-8				
mofezolac	5-Isoxazoleacetic acid, 3,4-bis(4-methoxyphenyl)- [CAS]	78967-07-4	EP	26928	Analgesic, NSAID	Pain, post-operative
MOL-6131	N-[4-(aminomethyl)benzyl]-8(S)-[1-[4-[2-(4-aminophenyl)-acetamido]butyryl]piperidin-4-yl]-2-(naphthalen-1-ylmethyl)-1,3-dioxo-2,3,5,8-tetrahydro-1H-[1,2,4]triazolo[1,2-a]-pyridazine-5(R)-carboxamide				Antiasthma	Asthma
Molindone		7416-34-4				
molsidomine	Sydnone imine, N-(ethoxycarbonyl)-3-(4-morpholinyl)- [CAS]	25717-80-0	US	3769283	Vasodilator, coronary	
mometasone	Pregna-1,4-diene-3,20-dione, 9,21-dichloro-11,17-dihydroxy-16-methyl-, (11ß,16Alpha)- [CAS]	105102-22-5 83919-23-7	EP	57401	Antipruritic/inflamm, allergic	Psoriasis
Monatepil		103377-41-9				
Monobenzone		103-16-2				
monolaurin	Dodecanoic acid, monoester with 1,2,3-propanetriol [CAS]	27215-38-9	US	4885282	Dermatological	Ichthyosis
montelukast	Cyclopropaneacetic acid, 1-[[[1-[3-[2-(7-Chloro-2-quinolinyl)ethenyl]phenyl]-3-[2-(1-hydroxy-1-methylethyl)phenyl]propyl]thio]methyl]-, [CAS]	151767-02-1 158966-92-8			Antiasthma	Asthma
Monteplase		122007-85-6				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Moperone		1050-79-9				
Mopidamol		13665-88-8				
Moprolol		5741-22-0				
moracizine	Carbamic acid, [10-[3-(4-morpholinyl)-1-oxopropyl]-10H-phenothiazin-2-yl]-, ethyl ester [CAS]	29560-58-5 31883-05-3	US	3864487	Antiarrhythmic	Tachycardia, ventricular
Morazone		6536-18-1				
Moricizine		31883-05-3				
Moroxydine		3731-59-7				
Morphazinamide		952-54-5				
morphine	Morphinan-3,6-diol, 7,8-didehydro-4,5-epoxy-17-methyl- (5Alpha,6Alpha)-, [CAS]	57-27-2 6055-06-7 64-31-3			Formulation, parenteral, other	Pain, cancer
morphine-6-glucuronide	morphine-6-glucuronide				Formulation, inhalable, systemic	Pain, general
mosapramine	Spiro[imidazo[1,2-a]pyridine-3(2H),4'-piperidin]-2-one, 1'-[3-(3-chloro-10,11-dihydro-5H-dibenz[b,f]azepin-5-yl)propyl]hexahydro-, (+/-)- [CAS]	89419-40-9 98043-60-8	US	4337260	Neuroleptic	
mosapride	Benzamide, 4-amino-5-chloro-2-ethoxy-N-((4-((4-fluorophenyl)methyl)-2-morpholinyl)methyl)- [CAS]	112885-41-3 112885-42-4	EP	243959	GI inflammatory/bowel disorders	Gastritis
motexafin gadolinium	Gadolinium, bis(acetetato-kappaO)(9,10-diethyl-20,21-bis(2-(2-(2-methoxy)ethoxy)ethoxy)-4,15-dimethyl-8,11-imino-3,16:16,13-dinitrilo-1,18-benzodiazacycloeicosine-5,14-dipropanalato-kappaN1, kappaN18, kappaN23, kappaN24, kappaN25), (PB-7-11-233'2'4) [CAS]	246252-06-2			Radio/chemosensitizer	Cancer, brain
Motretinide		56281-36-8				
Moveltipril		85856-54-8				
Moxalactam		64952-97-2				
Moxastine		3572-74-5				
Moxaverine		10539-19-2				
Moxestrol		34816-55-2				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
moxifloxacin	3-Quinolinecarboxylic acid, 1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(octahydro-6H-pyrrolo(3,4-b)pyridin-6-yl)-4-oxo-, hydrochloride (4aS-cis)- [CAS]	186826-86-8 151096-09-2	DE	19546249	Quinolone antibacterial	Infection, respiratory tract, general
moxisylyte	Phenol, 4-[2-(dimethylamino)ethoxy]-2-methyl-5-(1-methylethyl)-, acetate (ester), [CAS]	964-52-3 54-32-0			Male sexual dysfunction	Impotence
moxonidine	5-Pyrimidinamine, 4-chloro-N-(4,5-dihydro-1H-imidazol-2-yl)-6-methoxy-2-methyl- [CAS]	75438-57-2	DE	2849537	Antihypertensive, other	Hypertension, general
M-PGA	(-)-(S)-2-Methyl-2-(1-oxo-2,3-dihydro-1H-isoindol-2-yl)pentanedioic acid		US	5712291	Anticancer, other	Cancer, general
MPI-5010	Platinum diamminedichloro-, (SP-4-2) + (R)-4-[1-hydroxy-2-(methylamino)-ethyl]-1,2-benzenediol		US	6224883	Formulation, parenteral, other	Cancer, head and neck
MPI-5020	2,4(1H,3H)-Pyrimidinedione, 5-fluoro- [CAS]	51-21-8	US	5750146	Formulation, parenteral, other	Cancer, breast
MPL		198076-81-2			Immunostimulant, other	Vaccine adjunct
MRS-1754			US	6060481	Antiasthma	Asthma
MS-209	1-Piperazineethanol, 4-(diphenylacetyl)-Alpha-[(5-quinolinyloxy)methyl]-, (2E)-2-butenedioate(2:3) (salt) [CAS]	158681-49-3			Radio/chemosensitizer	Cancer, breast
MS-275	N-(2-Aminophenyl)-4-[N-(pyridin-3-yl-methoxycarbonyl)aminomethyl]benzamide				Anticancer, antimetabolite	Cancer, lung, general
MS-325		201688-00-8				
MS-377			EP	839805	Neuroleptic	Schizophrenia
Mupirocin		12650-69-0				
Muscarine		300-54-9				
Muzolimine		55294-15-0				
MX-1013			US	6153591	Hepatoprotective	Unspecified

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
mycophenolate mofetil	4-Hexenoic acid, 6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-, 2-(4-morpholinyl)ethyl ester, (E)- [CAS]	116680-01-4 128794-94-5	WO	9119498	Immunosuppressant	Transplant rejection, general
mycophenolic acid	4-hexanoic acid, 6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-,	37415-62-6 24280-93-1			Formulation, oral, enteric-coated	Transplant rejection, general
Myrophine		467-18-5				
N-(Hydroxymethyl)nicotinamide		3569-99-1				
N,N,N′,N′-Tetraethylphthalamide		83-81-8				
N_2-Formylsulfisomidine		795-13-1				
N_4-β-D-Glucosylsulfanilamide		53274-53-6				
N_4-Sulfanilylsulfanilamide		547-52-4				
Nabilone		51022-71-0				
nabumetone	2-Butanone, 4-(6-methoxy-2-naphthalenyl)- [CAS]	42924-53-8	GB	1476721	Anti-inflammatory	Arthritis, osteo
N-acetylcysteine	L-Cysteine, N-acetyl- [CAS]	616-91-1			Anticancer, other	Cancer, general
N-Acetylmethionine		65-82-7				
nadifloxacin	1H,5H-Benzo[ij]quinolizine-2-carboxylic acid, 9-fluoro-6,7-dihydro-8-(4-hydroxy-1-piperidinyl)-5-methyl-1-oxo-, (+/-)- [CAS]	124858-35-1	US	4399134	Quinolone antibacterial	Acne
nadolol	2,3-Naphthalenediol, 5-[3-[(1,1-dimethylethyl)amino]-2-hydroxypropoxy]-1,2,3,4-tetrahydro- [CAS]	42200-33-9	US	4346106	Antihypertensive, adrenergic	
Nadoxolol		54063-51-3				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
nafamostat	Benzoic acid, 4-[(aminoiminomethyl)amino]-, 6-(aminoiminomethyl)-2-naphthalenyl ester-[CAS]	80251-32-7 81525-10-2 82956-11-4	EP	450232	GI inflammatory/bowel disorders	Pancreatitis
nafarelin	Luteinizing hormone-releasing factor (pig), 6-[3-(2-naphthalenyl)-D-alanine]-[CAS]	76932-56-4 86220-42-0	EP	21234	Releasing hormones	Endometriosis
Nafcillin		147-52-4				
Nafronyl		31329-57-4				
naftidrofuryl	2-Furanpropanoic acid, tetrahydro-Alpha-(1-naphthalenylmethyl)-, 2-(diethylamino)ethyl ester	31329-57-4			Formulation, modified-release, other	Unspecified
naftifine	1-Naphthalenemethanamine, N-methyl-N-(3-phenyl-2-propenyl)-, (E)- [CAS]	65472-88-0 65473-14-5	US	4282251	Antifungal	Infection, dermatological
naftopidil	1-Piperazineethanol, 4-(2-methoxyphenyl)-Alpha-[(1-naphthalenyloxy)methyl]- [CAS]	57149-07-2	US	3997666	Antihypertensive, adrenergic	Hypertension, general
nalbuphine	Morphinan-3,6,14-triol, 17-(cyclobutylmethyl)-4,5-epoxy-, (5Alpha,6Alpha)- [CAS]	20594-83-6 23277-43-2	US	3393197	Analgesic, other	Pain, general
Nalidixic Acid		389-08-2				
nalmefene	Morphinan-3,14-diol, 17-(cyclopropylmethyl)-4,5-epoxy-6-methylene-,(5Alpha)-[CAS]	55096-26-9	JP	56167687	Dependence treatment	Poisoning, drug
Nalorphine		62-67-9				
naloxone	Morphinan-6-one, 17-allyl-4,5Alpha-epoxy-3,14-dihydroxy-, hydrochloride [CAS]	357-08-4 465-65-6			Septic shock treatment	
naltrexone	Morphinan-6-one, 17-(cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxy-, (5Alpha)-[CAS]	16590-41-3 16676-29-2	US	3332950	Dependence treatment	Addiction, narcotic/opiate
NAMI	Imidazolium trans(imidazole)(dimethylsulfoxide)tetrachlororuthenate (III)				Anticancer, other	Cancer, general

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
naminidil	Guanidine, N-cyano-N'-(4-cyanophenyl)-N"-[(1R)-1,2,2-trimethylpropyl]-[CAS]	220641-11-2			Dermatological	Alopecia, general
Nandrolone		434-22-0				
Naphazoline		835-31-4				
Naphthalene		91-20-3				
naproxen betainate	Methanaminium, 1-carboxy-N, N, N-trimethyl- salt with (R)-6-methoxy- Alpha-methyl-2-naphthaleneacetic acid (1:1), sodium salt [CAS]	104124-26-7	US	4672077	Antiarthritic, other	Arthritis, rheumatoid
naproxen	2-Naphthaleneacetic acid, 6-methoxy-Alpha-methyl-, [CAS]	26159-34-2 22204-53-1	GB	1211134	Analgesic, NSAID	Pain, general
naratriptan	1H-Indole-5-ethanesulfonamide, N-methyl-3-(1-methyl-4-piperidinyl)- [CAS]	121679-13-8	EP	303507	Antimigraine	Migraine
Narceine		131-28-2				
Narcobarbital		125-55-3				
Natamycin		7681-93-8				
nateglinide	D-phenylalanine, N-((4-(1-methylethyl)cyclohexyl)carbonyl)-, trans-[CAS]	105816-04-4	EP	196222	Antidiabetic	Diabetes, Type II
N-Butyldeoxynojirimycin		72599-27-0				
N-Butylscopolammonium Bromide		149-64-4				
NC-503			US	5643562	Anti-inflammatory	Amytoidosis
NC-531			US	5643562	Cognition enhancer	Alzheimer's disease
NCX-1000			WO	0061604	Hepatoprotective	Cirrhosis, hepatic
NCX-4016	Benzoic acid, 2-(acetyloxy)-, 2-((nitrooxy)methyl)phenyl ester [CAS]	175033-36-0	WO	9716405	Symptomatic antidiabetic	Insulin-related metabolic syndrome
NCX-456	Benzoic acid, 5-amino-2-hydroxy-, 4-(nitrooxy)butyl ester [CAS]	256499-26-0			GI inflammatory/bowel disorders	Inflammatory bowel disease

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
NCX-950	Alpha'-[[(1,1-dimethylethyl)amino]methyl]-4-hydroxyl-1,3-benzenedimethanol nitrate				Antiasthma	Asthma
n-Docosanol		661-19-8				
NE-100	Benzeneethanamine, 4-methoxy-3-(2-phenylethoxy)-N,N-dipropyl-, hydrochloride [CAS]	149409-57-4	WO	9307113	Neuroleptic	Schizophrenia
Nealbarbital		561-83-1				
nebivolol	2H-1-Benzopyran-2-methanol, Alpha,Alpha'-[iminobis(methylene)]bis[6-fluoro-3,4-dihydro]-, (2R*(R*(R*(S*))))-(1+)- [CAS]	118457-14-0 99200-09-6	EP	145067	Antihypertensive, adrenergic	Hypertension, general
nebostinel	N1-(4,4-Dimethylcyclohexyl)-L-isoglutamine	163000-63-3	EP	0688312	Cognition enhancer	Unspecified
Nebracetam		97205-34-0				
nedaplatin	Platinum, diammine[hydroxyacetato(2-)-O1,O2]-, (SP-4-3)- [CAS]	95734-82-0	EP	216362	Anticancer, alkylating	
nedocromil	4H-Pyrano[3,2-g]quinoline-2,8-dicarboxylic acid, 9-ethyl-6,9-dihydro-4,6-dioxo-10-propyl- [CAS]	69049-73-6 69049-74-7	EP	555718	Antiasthma, Ophthalmological	Rhinitis, allergic, general, Ocular disorder, general
nefazodone	3H-1,2,4-Triazol-3-one, 2-[3-[4-(3-chlorophenyl)-1-piperazinyl]propyl]-5-ethyl-2,4-dihydro-4-(2-phenoxyethyl)-, [CAS]	82752-99-6 83366-66-9	US	4338317	Antidepressant	Depression, general
nefiracetam	1-Pyrrolidineacetamide, N-(2,6-dimethylphenyl)-2-oxo- [CAS]	77191-36-7	US	4341790	Cognition enhancer	Dementia, senile, general
nefopam	1H-2,5-Benzoxazocine, 3,4,5,6-tetrahydro-5-methyl-1-phenyl- [CAS]	13669-70-0 23327-57-3	US	3487153	Analgesic, NSAID	
Negamycin		33404-78-3				
nelfinavir	3-Isoquinolinecarboxamide, N-(1,1-dimethylethyl)decahydro-2-(2-hydroxy-3-((3-hydroxy-2-methylbenzoyl)amino)-4-(phenylthio)butyl)-, (3S-(2(2S*,3S*),3Alpha,4aß,8aß))-, [CAS]	159989-65-8 159989-64-7			Antiviral, anti-HIV	Infection, HIV/AIDS
Nemonapride		75272-39-8				
Neostigmine		59-99-4				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
nepadutant	Cyclo[3-amino-L-alanyl-L-leucyl-N-[2-(acetylamino)-2-deoxy-ß-D-glucopyranosyl]-L-asparaginyl-L-Alpha-aspartyl-L-tryptophyl-L-phenylalanyl], (4-1)-lactam [CAS]	183747-35-5	WO	9628467	Antiasthma	Asthma
neramexane	1,3,3,5,5-pentamethylcyclohexylamine	202807-80-5 219810-59-0			Dependence treatment	Addiction, alcohol
neridronic acid	Phosphonic acid, (6-amino-1-hydroxyhexylidene)bis- [CAS]	79778-41-9			Musculoskeletal	Osteogenesis imperfecta
Nerlifolin		466-07-9				
N-Ethylamphetamine		457-87-4				
neticonazole	1H-Imidazole, 1-[2-(methylthio)-1-[2-(pentyloxy)phenyl]ethenyl]-, monohydrochloride, (E)- [CAS]	130773-02-3 130726-68-0	EP	445540	Antifungal	Infection, Candida, general
netilmicin	D-Streptamine, O-3-deoxy-4-C-methyl-3-(methylamino)-ß-L-arabinopyranosyl-(1-6)-O-[2,6-diamino-2,3,4,6-tetradeoxy-Alpha-D glycero-hex-4-enopyranosyl-(1-4)]-2-deoxy-N1-ethyl- [CAS]	56391-56-1 56391-57-2	GB	1473733	Aminoglycoside antibiotic	Infection, general
nevirapine	6H-Dipyrido[3,2-b:2',3'-e][1,4]diazepin-6-one, 11-cyclopropyl-5,11-dihydro-4-methyl- [CAS]	129618-40-2	EP	429987	Antiviral, anti-HIV	Infection, HIV/AIDS
NGD-98-2			WO	9635689	Anxiolytic	Anxiety, general
Nialamide		51-12-7				
Niaprazine		27367-90-4				
Nicametate		3099-52-3				
nicaraven	3-Pyridinecarboxamide, N,N'-(1-methyl-1,2-ethanediyl)bis- [CAS]	79455-30-4	EP	29602	Neuroprotective	Haemorrhage, subarachnoid
nicardipine	3,5-Pyridinedicarboxylic acid, 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-, methyl 2-[methyl(phenylmethyl)amino]ethyl ester [CAS]	54527-84-3 55985-32-5	US	3985758	Neuroprotective	Hypertension, general
nicergoline	Ergoline-8-methanol, 10-methoxy-1,6-dimethyl-, (8/b)-, 5-bromo-3-pyridinecarboxylate(ester)	27848-84-6			Formulation, modified-release, other	Unspecified

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Niceritrol		5868053				
Niclosamide		50-65-7				
Nicoclonate		10571-59-2				
Nicofuranose		15351-13-0				
Nicomol		27959-26-8				
Nicomorphine		639-48-5				
nicorandil	3-Pyridinecarboxamide, N-[2-(nitrooxy)ethyl]- [CAS]	65141-46-0	US	4792564	Vasodilator, coronary	Hypertension, general
Nicotinamide		98-92-0				
nicotine	Pyridine, 3-(1-methyl-2-pyrrolidinyl)-, (S)- [CAS]	54-11-5			Formulation, inhalable, other	Addiction, nicotine
Nicotinic Acid		59-67-6				
Nicotinic Acid Benzyl Ester		94-44-0				
Nicotinyl Alcohol		100-55-0				
nifedipine	4-(2'-nitrophenyl)-2,6-dimethyl-3,5-dicarbomethoxy-1,4-dihydropyridine	21829-25-4	GB	1173862	Vasodilator, coronary	Hypertension, general
nifekalant	2,4(1H,3H)-Pyrimidinedione, 6-[[2-[(2-hydroxyethyl)[3-(4-nitrophenyl)propyl]amino]ethyl]amino]-1,3-dimethyl-, [CAS]	130636-43-0 130656-51-8	EP	369627	Antiarrhythmic	Arrhythmia, general
Nifenalol		7413-36-7				
Niflumic Acid		4394-00-7				
Nifuratel		4936-47-4				
Nifurfoline		3363-58-4				
Nifuroxazide		965-52-6				
Nifuroxime		6236051				
Nifurpirinol		13411-16-0				
Nifurprazine		1614-20-6				
Nifurtimox		23256-30-6				
Nifurtoinol		1088-92-2				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
nifurzide	2-Thiophenecarboxylic acid, 5-nitro-, [3-(5-nitro-2-furanyl)-2-propenylidene]hydrazide [CAS]	39978-42-2	US	3847911	Antidiarrhoeal	Infection, GI tract
NIK-254	Gentamicin, sulfate (salt) [CAS]	1405-41-0			Formulation, other	Infection, general
Nikethamide		59-26-7				
nilutamide	2,4-Imidazolidinedione, 5,5-dimethyl-3-[4-nitro-3-(trifluoromethyl)phenyl]-[CAS]	63612-50-0	US	4472382	Anticancer, hormonal	Cancer, prostate
nilvadipine	3,5-Pyridinedicarboxylic acid, 2-cyano-1,4-dihydro-6-methyl-4-(3-nitrophenyl)-, 3-methyl 5-(1-methylethyl) ester [CAS]	75530-68-6	US	4338322	Antihypertensive, other	Hypertension, general
nimesulide	Methanesulfonamide, N-(4-nitro-2-phenoxyphenyl)- [CAS]	51803-78-2	US	3840597	Anti-inflammatory	Pain, general
Nimetazepam		2011-67-8				
nimodipine	3,5-Pyridinedicarboxylic acid, 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-, 2-methoxyethyl 1-methylethyl ester [CAS]	66085-59-4	EP	533014	Neuroprotective	
Nimorazole		6506-37-2				
nimustine	Urea, N'-[(4-amino-2-methyl-5-pyrimidinyl)methyl]-N-(2-chloroethyl)-N-nitroso-[CAS]	103745-00-2 42471-28-3 55661-38-6	GB	1374344	Anticancer, alkylating	Cancer, brain
Ninopterin		2179-16-0				
NIP-142	N-[4(S)-(Cyclopropylamino)-3-(R)-hydroxy-2,2-dimethyl-7-nitro-3,4-dihydro-2H-1-benzopyran-6-yl]-4-methoxybenzeneacetamide		WO	9804542	Antiarrhythmic	Fibrillation, atrial
NIP-531	N'-[3,5-Bis(trifluoromethyl)benzyl]-N-[3-[N-[1-(4-fluorobenzyl)benzimidazol-2-yl]-amino]propyl-N-methylurea hydrochloride				Antipruritic/inflamm, allergic	Eczema, atopic
niperotidine	N-[2-[[5-[(dimethylamino)methyl]furfuryl]thio]ethyl]-2-nitro-N'-piperonyl-1,1-ethenediamine	84845-75-0	GB	2104071	Antiulcer	Ulcer, GI, general

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
nipradilol	2H-1-Benzopyran-3-ol, 3,4-dihydro-8-[2-hydroxy-3-[(1-methylethyl)amino]propoxy]-, 3-nitrate [CAS]	81486-22-8 86247-86-1	EP	42299	Formulation, mucosal, topical	Glaucoma
Niridazole		61-57-4				
nisoldipine	3,5-Pyridinedicarboxylic acid, 1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-, methyl 2-methylpropyl ester- [CAS]	63675-72-9	GB	1516793	Antihypertensive, other	Hypertension, general
nitazoxanide	Benzamide, 2-(acetyloxy)-N-(5-nitro-2-thiazolyl)- [CAS]	55981-09-4	US	5387598	Protozoacide	Infection, GI tract
nitisinone	1,3-Cyclohexanedione, 2-[2-nitro-4-(trifluoromethyl)benzoyl]- [CAS]	104206-65-7	EP	186118	Metabolic and enzyme disorders	Cirrhosis, hepatic
nitracrine	1,3-Propanediamine, N,N-dimethyl-N'-(1-nitro-9-acridinyl)- [CAS]	4533-39-5 6514-85-8	FR	1458183	Anticancer, other	Cancer, ovarian
Nitrazepam		146-22-5				
nitrendipine	3,5-Pyridinedicarboxylic acid, 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-, ethyl methyl ester- [CAS]	39562-70-4	GB	1358951	Antihypertensive, other	Hypertension, general
nitroflurbiprofen	(1,1'-Biphenyl)-4-acetic acid, 2-fluoro-Alpha-methyl-, 4-(nitrooxy)butyl ester [CAS]	158836-71-6	EP	670825	Urological	Incontinence
Nitrofurantoin		67-20-9				
Nitrofurazone		59-87-0				
nitroglycerin	1,2,3-Propanetriol, trinitrate [CAS]	55-63-0			Formulation, transdermal, patch	Angina, general
Nitromersol		133-58-4				
nitronaproxen	2-Napthaleneacetic acid, 6-methoxy-Alpha-methyl 4-(nitrooxy)butyl ester (AlphaS)- [CAS]	163133-43-5	WO	9509831	Analgesic, NSAID	Pain, post-operative
nitroxazepine	Dibenz[b,f][1,4]oxazepin-11(10H)-one, 10-[3-(dimethylamino)propyl]-2-nitro-, monohydrochloride [CAS]	16398-39-3	NL	6608671	Antidepressant	
Nitroxoline	—	4008-48-4				
nizatidine	1,1-Ethenediamine, N-[2-[[[2-[(dimethylamino)methyl]-4-thiazolyl]methyl]thio]ethyl]-N'-methyl-2-nitro- [CAS]	76963-41-2	EP	49618	Antiulcer	Ulcer, duodenal

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Nizofenone		54533-85-6				
NM-3	3-(2-methylcarboxymethyl)-6-methoxy-8-hydroxy-isocoumarin		JP	08176138	Anticancer, other	Cancer, general
NM-702	4-Bromo-5-(3-pyridylmethylamino)-6-[3-(4-chlorophenyl)propoxy]-3(2H)pyridazinone hydrochloride				Antithrombotic	Peripheral vascular disease
N-Methylephedrine		552-79-4				
N-Methylepinephrine		554-99-4				
N-Methylglucamine		6284-40-8				
NN-414	6-chloro-3-(1-methylcyclopropylamino)-4H-thieno[3,2-e]-[1,2,4]thiadiazine-1,1-dioxide				Antidiabetic	Diabetes, Type II
NNC-05-1869	(R)-1-(3-(10,11-dihydro-5H-dibenzo[a,d]cycloheptен-5-ylidene)-1-propyl)-3-piperidine carboxylic acid				Symptomatic antidiabetic	Neuropathy, diabetic
Nogalamycin		1404-15-5				
nolatrexed	4(1H)-Quinazolinone, 2-amino-6-methyl-5-(4-pyridinylthio)-, [CAS]	152946-68-4 147149-76-6	WO	9320055	Anticancer, antimetabolite	Cancer, liver
nolomirole	Propanoic acid, 2-methyl-, 5,6,7,8-tetrahydro-6-(methylamino)-1,2-naphthalenediyl ester, hydrochloride, (+/-)- [CAS]	138531-51-8	WO	9529147	Cardiostimulant	Heart failure
nolpitantium	1-Azoniabicyclo[2.2.2]octane, 1-[2-[3-(3,4-dichlorophenyl)-1-[[3-(1-methylethoxy)phenyl]acetyl]-3-piperidinyl]ethyl]-4-phenyl-, chloride, (S)- [CAS]	153050-21-6	EP	591040	GI inflammatory/bowel disorders	Inflammatory bowel disease
nomegestrol	19-Norpregna-4,6-diene-3,20-dione, 17-(acetyloxy)-6-methyl- [CAS]	58652-20-3	DE	2522533	Menstruation disorders	Menstrual disorder, general
Nomifensine		24526-64-5				
Noprylsulfamide		576-97-6				
Norbolethone		1235-15-0				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Nordazepam		1088-11-5				
Nordefrin		6539-57-7 (unspecified); 74812-63-8 (*R**,*S**)-(±)-form				
Nordihydroguaiaretic Acid		27686-84-6 (*meso*-form); 500-38-9 (unspecified)				
Norelgestromin, Ethinyl Estradiol						
Norepinephrine		51-41-2				
Norethandrolone		52-78-8				
Norethindrone		68-22-4				
Norethynodrel		68-23-5				
Norfenefrine		536-21-0				
norfloxacin	3-Quinolinecarboxylic acid, 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)- [CAS]	68077-27-0 70458-96-7	US	4146719	Quinolone antibacterial	Infection, general
Norgesterone		13563-60-5				
Norgestimate		35189-28-7				
Norgestrel		6533-00-2				
Norgestrienone		848-21-5				
Norlevorphanol		1531-12-0				
Normethadone		467-85-6				
Normethandrone		514-61-4				
Normorphine		466-97-7				
Norphenazone		89-25-8				
Norpipanone		561-48-8				
Norpseudoephedrine		492-39-7				
Nortriptyline		72-69-5				
Norvinisterone		6795-60-4				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Noscapine		128-62-1				
Novembichin		1936-40-9				
Novobiocin		303-81-1				
Noxiptilin		3362-45-6				
Noxythiolin		15599-39-0				
NS-1209	Butanoic acid, 2-[[[5-[4-[(dimethylamino)sulfonyl]phenyl]-1,2,6,7,8,9-hexahydro-8-methyl-2-oxo-3H-pyrrolo[3,2-h]isoquinolin-3-ylidene]amino]oxy]-3-hydroxy- [CAS]	254751-28-5	WO	9426747	Antiepileptic	Epilepsy, general
NS-1231	5-(4-chlorophenyl)-6,7,8,9-tetrahydro-1H-pyrolo-(3,2-h]naphthalene-2,3-dione-3-oxime				Neuroprotective	Ischaemia, cerebral
NS-126			US	5063222	Antiallergic, non-asthma	Rhinitis, allergic, general
NS-220	2-Methyl-c-5-[4-[5-methyl-2-(4-methylphenyl)-4-oxazolyl]butyl]-1,3-dioxane-r-2-carboxylic acid				Hypolipaemic/Antiatherosclerosis	Atherosclerosis
NS-2330	NS 2330 [CAS]	402856-42-2			Cognition enhancer	Alzheimer's disease
NS5A inhibitors			US	6030785	Antiviral, other	Infection, hepatitis-C virus
NS-7	Pyrimidine, 4-(4-fluorophenyl)-2-methyl-6-[[5-(1-piperidinyl)pentyl]oxy]-, monohydrochloride [CAS]	178429-67-9	WO	9607641	Neuroprotective	Ischaemia, cerebral
NS-8	2-Amino-5-(2-fluorophenyl)-4-methyl-1H-pyrrole-3-carbonitrile				Urological	Incontinence
NSC-330507	17-Allylaminogeldanamycin				Anticancer, antibiotic	Cancer, general
NSC-619534	2-chloroethyl phenyl selenone				Anticancer, alkylating	Cancer, general
NSC-697726	2,5-diazinidinyl-3-[hydroxymethyl]6-methyl-1,4-benzoquinone				Anticancer, antibiotic	Cancer, general
N-Sulfanilyl-3,4-xylamide		120-34-3				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
NU-6027	2,4-Pyrimidinediamine, 6-(cyclohexylmethoxy)-5-nitroso- [CAS]	220036-08-8			Anticancer, other	Cancer, general
NV-07	2,4,6(1H,3H,5H)-Pyrimidinetrione, 5-ethyl-5-sec-pentyl-, 2-oxime [CAS]	53745-16-7	US	6455032	Antipruritic/inflamm, non-allergic	Keratosis
NVP-SRA880	([3R,4aR,10aR]-1,2,3,4,4a,5,10,10a-Octahydro-6-methoxy-1-methyl-benz[g]quinoline-3-carboxylic acid-4-(4-nitrophenyl)piperazine amide, hydrogen maleate				Neurological	Unspecified
NW-1029	(S)-(+)-2-[4-(2-fluorobenzyloxy)benzylamino]propanamide methansulfonate				Analgesic, other	Pain, general
NXY-059	CPI 22 [CAS]	168021-79-2	US	5780510	Neuroprotective	Ischaemia, cerebral
Nylidrin		447-41-6				
NZ-314	1-Imidazolidineacetic acid, 3-[(3-nitrophenyl)methyl]-2,4,5-trioxo- [CAS]	128043-99-2	EP	353198	Symptomatic antidiabetic	Neuropathy, diabetic
NZ-419	5-hydroxy-1-methylimidazolidine-2,4-dione		EP	412940	Urological	Renal failure
Obidoxime Chloride		114-90-9				
OC-108	OC 108 [CAS]	162602-62-2			Vasoprotective, topical	Venous insufficiency
ocinaplon	Methanone, 2-pyridinyl[7-(4-pyridinyl)pyrazolo[1,5-a]pyrimidin-3-yl]- [CAS]	96604-21-6	EP	129847	Anxiolytic	Generalized anxiety disorder
Octabenzone		1843-05-6				
Octacaine		13912-77-1				
Octamoxin		4684-87-1				
Octaverine		549-68-8				
octenidine	1-Octanamine, N,N'-(1,10-decanediyldi-1(4H)-pyridinyl-4-ylidene)bis- [CAS]	70775-75-6 71251-02-0 86767-75-1	WO	8705501	Stomatological	Periodontitis
Octodrine		543-82-8				
Octopamine		104-14-3				
Octotiamine		137-86-0				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
octreotide	L-Cysteinamide, D-phenylalanyl-L-cysteinyl-L-phenylalanyl-D-tryptophyl-L-lysyl-L-threonyl-N-[2-hydroxy-1-(hydroxymethyl)propyl]-, cyclic (2-7)-disulfide, [R-(R*,R*)]- [CAS]	83150-76-9			Formulation, fixed-dose combinations	Cancer, general
Octyl Methoxycinnamate		5466-77-3				
ofloxacin	7H-Pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid, 9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-, (+/-)- [CAS]	82419-36-1	EP	47005	Quinolone antibacterial	
o-Iodohippurate		133-17-5				
olanzapine	10H-Thieno(2,3-b)(1,5)benzodiazepine, 2-methyl-4-(4-methyl-1-piperazinyl)- [CAS]	132539-06-1	EP	454436	Neuroleptic	Schizophrenia
Oleandrin		465-16-7				
Oleic Acid		112-80-1				
olmesartan medoxomil	1H-Imidazole-5-carboxylic acid, 4-(1-hydroxy-1-methylethyl)-2-propyl-1-((2'-(1H-tetrazol-5-yl)(1,1'-biphenyl)-4-yl)methyl)-, (5-methyl-2-oxo-1,3-dioxol-4-yl) methyl ester [CAS]	144689-63-4	EP	503785	Antihypertensive, renin system	Hypertension, general
olopatadine	11-[(Z)-3-(Dimethylamino)propylidene]-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid, monohydrochloride	113806-05-6 140462-76-6	EP	235796	Ophthalmological	Conjunctivitis
olpadronic acid	Monosodium 3-dimethylamino-1-(hydroxypropylidene)-1,1-bisphosphonate	63132-39-8	WO	9619998	Osteoporosis treatment	Osteoporosis
olsalazine	Benzoic acid, 3,3'-azobis[6-hydroxy- [CAS]	15722-48-2 53200-51-4	US	4559330	GI inflammatory/bowel disorders	Colitis, ulcerative
oltipraz	3H-1,2-Dithiole-3-thione, 4-methyl-5-pyrazinyl- [CAS]	64224-21-1	DE	2705641	Anticancer, other	Cancer, general

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
OM-294DP	2-[3(R)-(Dodecanoyloxy)tetradecanamido]-N-[4-[3(R)-hydroxytetradecanamido]-5-(phosphonooxy)pentyl]-4-(phosphonooxy)butyramide				Anticancer, immunological	Unspecified
Omacor	ethyl (5Z,8Z,11Z,14Z,17Z)-eicosa-5,8,11,14,17-pentaenoate + ethyl (4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenoate	81926-94-5 86227-47-6			Hypolipaemic/Antiatherosclerosis	Hypertriglyceridaemia
omapatrilat	7H-Pyrido(2,1-b)(1,3)thiazepine-7-carboxylic acid, octahydro-4-((2-mercapto-1-oxo-3-phenylpropyl)amino)-5-oxo, (4S-(4Alpha(R*),7Alpha,10aß))- [CAS]	167305-00-2	US	5508272	Antihypertensive, renin system	Hypertension, general
omeprazole	1H-Benzimidazole, 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]- [CAS]	73590-58-6	US	4255431	Antiulcer	Ulcer, GI, general
omiloxetine	Ethanone, 2-[(3R,4S)-3-[(1,3-benzodioxol-5-yloxy)methyl]-4-(4-fluorophenyl)-1-piperidinyl]-1-(4-fluorophenyl)-, rel- [CAS]	176894-09-0			Antidepressant	Depression, general
omoconazole	1H-Imidazole, 1-[2-[2-(4-chlorophenoxy)ethoxy]-2-(2,4-dichlorophenyl)-1-methylethenyl]-, (Z)- [CAS]	74512-12-2	EP	8804	Antifungal	Infection, dermatological
Onapristone		96346-61-1				
ondansetron	4H-Carbazol-4-one, 1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]- [CAS]	99614-01-4 99614-02-5	US	4847281	Antiemetic	Chemotherapy-induced nausea and vomiting
ONO-3403	Benzoic acid, 4-[(1E)-3-[(2-ethoxy-2-oxoethyl)-2-propenylamino]-2-methyl-3-oxo-1-propenyl]-, 4-(aminoiminomethyl)phenyl ester, monomethanesulfonate [CAS]	181586-07-2			GI inflammatory/bowel disorders	Unspecified

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
ONO-4128	1,4,9-Triazaspiro(5.5)undecane-2,5-dione, 1-butyl-3-(cyclohexylmethyl)-9-((2,3-dihydro-1,4-benzodioxin-6-yl)methyl- [CAS]	342394-93-8			Antiviral, anti-HIV	Infection, HIV/AIDS
ONO-8815 Ly	L-lysine (Z)-7-[(1R,2R,3R,5R)-5-chloro-3-hydroxy-2-[(E)-(S)-4-(1-ethylcyclobutyl)-4-hydroxy-1-butenyl]cyclopentyl]-5-heptenoate				Labour inhibitor	Labour, preterm
ONT-093			US	5756527	Radio/chemosensitizer	Cancer, general
OPC-14523	2(1H)-Quinolinone, 1-[3-[4-(3-chlorophenyl)-1-piperazinyl]propyl]-3,4-dihydro-5-methoxy- [CAS]	145969-30-8	EP	512525	Antidepressant	Depression, general
OPC-31260	Benzamide, N-[4-[[5-(dimethylamino)-2,3,4,5-tetrahydro-1H-1-benzazepin-1-yl]carbonyl]phenyl]-2-methyl-	137975-06-5	WO	9105549	Urological	Unspecified
OPC-51803	(5R)-2-[1-(2-chloro-4-(1-pyrolidinyl)benzoyl)-2,3,4,5-tetrahydro-1H-1-benzazepin-5-yl]-N-isopropylacetamide				Antidiabetic	Diabetes, insipidus
OPC-6535	2-Pyridinecarboxylic acid, 6-[2-(3,4-diethoxyphenyl)-4-thiazolyl]- [CAS]	145739-56-6	WO	9209586	GI inflammatory/bowel disorders	Inflammatory bowel disease
Opiniazide		2779-55-7				
opioid analgesics	2-(4-trifluoromethylphenyl)-N-methyl-[1-phenyl-2-(1-pyrolidinyl)ethylacetamide				Analgesic, other	Pain, general
Opipramol		315-72-0				
Orazamide		2574-78-9				
orazipone	2,4-Pentanedione, 3-((4-methylsulfonyl)phenyl)methylene)- [CAS]	137109-78-5	EP	440324	Antiasthma	Unspecified
Org-12962	Piperazine, 1-[6-chloro-5-(trifluoromethyl)-2-pyridinyl]-, monohydrochloride [CAS]	210821-63-9			Antidepressant	Depression, general
Org-24448			US	6166008	Neuroleptic	Schizophrenia

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
oritavancin	Vancomycin, 22-O-(3-amino-2,3,6-trideoxy-3-C-methyl-Alpha-L-arabino-hexopyranosyl)-N3"-[(4'-chloro[1,1'-biphenyl]-4-yl)methyl]-,(4"R)- [CAS]	171099-57-3	US	5840684	Peptide antibiotic	Infection, dermatological
orlistat	L-Leucine, N-formyl-, 1-[(3-hexyl-4-oxo-2-oxetanyl)methyl]dodecyl ester, [2S-[2Alpha(R*),3ß]]- [CAS]	96829-58-2	EP	129748	Anorectic/Antiobesity	Obesity
ormeloxifene	Pyrrolidine, 1-[2-(p-(7-methoxy-2,2-dimethyl-3-phenyl-4-chromanyl)phenoxy)ethyl]-, trans- [CAS]	31477-60-8	DE	2329201	Female contraceptive	Contraceptive, female
Ornidazole		16773-42-5				
Ornipressin		3397-23-7				
Ornithine		70-26-8				
ornoprostil	Prost-13-en-1-oic acid, 11,15-dihydroxy-17,20-dimethyl-6,9-dioxo-, methyl ester, (11Alpha,13E,15S,17S)- [CAS]	70667-26-4	US	4278688	Prostaglandin	Ulcer, gastric
Orotic Acid		65-86-1				
Orphenadrine		83-98-7				
Orthocaine		536-25-4				
Osalmid		526-18-1				
osanetant	Acetamide, N-[1-[3-[(3R)-1-benzoyl-3-(3,4-dichlorophenyl)-3-piperidinyl]propyl]-4-phenyl-4-piperidinyl]-N-methyl- [CAS]	160492-56-8	EP	673928	Neuroleptic	Schizophrenia
osaterone	2-Oxapregna-4,6-diene-3,20-dione, 17-(acetyloxy)-6-chloro- [CAS]	105149-00-6	EP	193871	Prostate disorders	Benign prostatic hyperplasia
oseltamivir	1-Cyclohexene-1-carboxylic acid, 4-(acetylamino)5-amino-3-(1-ethylpropoxy)-, ethyl ester, (3R-(3Alpha,(4ß,5Alpha))- [CAS]	196618-13-0	WO	9626933	Antiviral, other	Infection, influenza virus
OSI-7836	4'-Thio-ß-D-arabinofuranosylcytosine				Anticancer, antimetabolite	Cancer, general

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
OSI-7904	Pentanedioic acid, 2-[5-[[(1,2-dihydro-3-methyl-1-oxobenzo[f]quinazolin-9-yl)methyl]amino]-1,3-dihydro-1-oxo-2H-isoindol-2-yl]-, (S)- [CAS]	139987-54-5	WO	9119700	Formulation, optimized, liposomes	Cancer, general
ospemifene	Ethanol, 2-[4-[(1Z)-4-chloro-1,2-diphenyl-1-butenyl]phenoxy]- [CAS]	128607-22-7	WO	9607402	Menopausal disorders	Osteoporosis
otilonium bromide	Ethanaminium, N,N-diethyl-N-methyl-2-[[4-[[2-(octyloxy)benzoyl]amino]benzoyl]oxy]-, bromide [CAS]	26095-59-0	GB	1181406	Antispasmodic	Irritable bowel syndrome
Ouabain		630-60-4				
Oxaceprol		33996-33-7				
Oxacillin		66-79-5				
Oxaflozane		26629-87-8				
oxaliplatin	Platinum, (1,2-cyclohexanediamine-N,N')[ethanedioato(2-)-O,O']-, [SP-4-2-(1R-trans)]- [CAS]	61825-94-3	EP	393575	Anticancer, alkylating	Cancer, colorectal
Oxalyt-C	1,2,3-Propanetricarboxylic acid, 2-hydroxy-, potassium sodium salt [CAS]	28060-67-5	DE	2249274	Urological	
Oxamarin		15301-80-1				
Oxametacine		27035-30-9				
Oxamniquine		21738-42-1				
oxandrolone	2-Oxaandrostan-3-one, 17-hydroxy-17-methyl-, (5Alpha,17ß)- [CAS]	53-39-4	US	3128283	Reproductive/gonadal, general	Sex-chromosome abnormality, Turner's syndrome
Oxantel		36531-26-7				
Oxapropanium		541-66-2				
oxaprozin	2-Oxazolepropanoic acid, 4,5-diphenyl- [CAS]	21256-18-8	GB	1206403	Antiarthritic, other	Arthritis, osteo
oxatomide	2H-Benzimidazol-2-one, 1-[3-[4-(diphenylmethyl)-1-piperazinyl]propyl]-1,3-dihydro- [CAS]	60607-34-3	GB	1579365	Antiallergic, non-asthma	Rhinitis, allergic, general
oxazepam	7-Chloro-1,3-dihydro-3-hydroxy-5-phenyl-2H-1,4-benzodiazepin-2-one	604-75-1			Formulation, oral, orally-disintegrating	Anxiety, general

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
oxazolam	Oxazolo[3,2-d][1,4]benzodiazepin-6(5H)-one, 10-chloro-2,3,7,11b-tetrahydro-2-methyl-11b-phenyl- [CAS]	27167-30-2	US	3772371	Anxiolytic	
oxcarbazepine	5H-Dibenz[b,f]azepine-5-carboxamide, 10,11-dihydro-10-oxo- [CAS]	28721-07-5 29331-92-8	DE	2011087	Antiepileptic	Epilepsy, general
Oxeladin		468-61-1				
Oxendolone		33765-68-3				
Oxethazaine		126-27-2				
Oxetorone		26020-55-3				
oxiconazole	Ethanone, 1-(2,4-dichlorophenyl)-2-(1H-imidazol-1-yl)-, O-[(2,4-dichlorophenyl)methyl]oxime, (Z)- [CAS]	64211-45-6	GB	1514870	Antifungal	Infection, fungal, general
Oxidronic Acid		15468-10-7				
Oxiniacic Acid		2398-81-4				
Oxiracetam		62613-82-5				
oxitropium	3-Oxa-9-azoniatricyclo[3.3.1.02,4]nonane, 9-ethyl-7-(3-hydroxy-1-oxo-2-phenylpropoxy)-9-methyl-, bromide, [7(S)-(1Alpha,2ß,4ß,5Alpha,7ß)]- [CAS]	30286-75-0	GB	1178305	Antiasthma	
Oxolamine		959-14-8				
Oxolinic Acid		14698-29-4				
Oxophenarsine		538-03-4				
Oxprenolol		6452-71-7				
Oxybenzone		131-57-7				
oxybutynin	Benzeneacetic acid, Alpha-cyclohexyl-Alpha-hydroxy-, 4-(diethylamino)-2-butynyl ester- [CAS]	5633-20-5			Formulation, modified-release, other	Incontinence
Oxycinchophen		485-89-2				
oxycodone	Morphinan-6-one, 4,5-epoxy-14-hydroxy-3-methoxy-17-methyl-, (5Alpha)-	76-42-6			Formulation, transmucosal, nasal	Pain, general

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Oxyfedrine		15687-41-9				
Oxygent	Octane, 1-bromo-1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-heptadecafluoro- [CAS]	423-55-2			Haematological	Surgery adjunct
Oxymesterone		145-12-0				
Oxymetazoline		1491-59-4				
oxymetholone	Androstan-3-one, 17-hydroxy-2-(hydroxymethylene)-17-methyl-, (5Alpha,17ß)- [CAS]	434-07-1			Hormone	Anaemia, general
Oxymethurea		140-95-4				
oxymorphone	(5Alpha)-4,5-Epoxy-3,14-dihydroxy-17-methylmorphinan-6-one [CAS]	76-41-5			Formulation, modified-release, immediate	Pain, general
Oxypendyl		5585-93-3				
Oxypertine		153-87-7				
Oxyphenbutazone		129-20-4				
Oxyphencyclimine		125-53-1				
Oxyphenisatin		115-33-3				
Oxyphenonium		50-10-2				
Oxypinocamphone		10136-65-9				
oxypurinol	1H-Pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione [CAS]	2465-59-0			Antigout	Hyperuricaemia
Oxytetracycline		79-57-2				
ozagrel	2-Propenoic acid, 3-[4-(1H-imidazol-1-ylmethyl)phenyl]-, (E)- [CAS]	78712-43-3 82571-53-7	GB	2025946	Antithrombotic	Vasospasm, cerebral
p-(Benzylsulfonamido)benzoic Acid		536-95-8				
P-100			US	6313177	Antiviral, anti-HIV	Infection, HIV/AIDS
P-1202	Pentanoic acid, 5-amino-4-oxo, methyl ester, hydrochloride [CAS]	79416-27-6	US	6034267	Dermatological	Keratosis
P32/98	Di-(3N-[(2S,3S)-2-amino-3-methyl-pentanoyl]-1,3-thiazolidine)fumarate				Antidiabetic	Diabetes, Type II
PA-824			WO	9701562	Antimycobacterial	Infection, tuberculosis

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
PACAP 38	Pituitary adenylate cyclase-activating peptide-38 [CAS]	128606-20-2	US	5128242	Neuroprotective	Nerve injury, general
paclitaxel	5ß,20-Epoxy-1,2Alpha,4,7ß,10ß,13Alpha-hexahydroxytax-11-en-9-one-4,10-diacetate-2-benzoate-13-(Alpha-phenylhippurate)	33069-62-4			Formulation, optimized, nanoparticles	Cancer, breast
PADRE			US	6413935	Immunostimulant, other	Vaccine adjunct
pagoclone	1H-Isoindol-1-one, 2-(7-chloro-1,8-naphthyridin-2-yl)-2,3-dihydro-3-(5-methyl-2-oxohexyl)- (R)- [CAS]	133737-32-3	US	4960779	Anxiolytic	Panic disorder
PAI inhibs			WO	9404512	Antithrombotic	Thrombosis, venous
palindore	8H-1,4-dioxino[2,3-e]indol-8-one,2,3,7,9-tetrahydro-2-[(phenylmethyl)amino]methyl]-, 2(S)-, (2E)-2-butendioate (1:1)	189681-71-8			Neuroleptic	Schizophrenia
Palivizumab		188039-54-5				
palonosetron	3aS-2-[(S)-1-Azabicyclo[2.2.2]oct-3-yl]-2,3,3a,4,5,6-hexahydro-1-oxo-1H-benz[de]isoquinoline hydrochloride	135729-62-3	US	5202333	Antiemetic	Chemotherapy-induced nausea and vomiting
Pamabrom		606-04-2				
Pamaquine		491-92-9				
pamicogrel	1H-Pyrrole-1-acetic acid, 2-[4,5-bis(4-methoxyphenyl)-2-thiazolyl]-, ethyl ester [CAS]	101001-34-7	EP	159677	Antithrombotic	Thrombosis, cerebral
pamidronate	(3-Amino-1-hydroxypropylidene)diphosphonic acid-[CAS]	40391-99-9			Formulation, implant	Hypercalcaemia of malignancy
p-Aminobenzoic Acid		150-13-0				
p-Aminohippuric Acid		61-78-9				
p-Aminopropiophenone		70-69-9				
p-Aminosalicylic Acid		65-49-6				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Panavir	4,4'-isopropylidenedithiobis-2,6-di-t-butylphenol				Neuroprotective	Vasospasm, cerebral
Pancuronium		15500-66-0				
Panipenem		87726-17-8				
Pantethine		16816-67-4				
pantoprazole	1H-Benzimidazole, 5-(difluoromethoxy)-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]- [CAS]	102625-70-7	EP	166287	Antiulcer	Ulcer, duodenal
Pantothenic Acid		79-83-4				
Papain						
Papaverine		58-74-2				
paracetamol	Acetamide, N-(4-hydroxyphenyl)- [CAS]	103-90-2			Formulation, oral, other, modified-release	Pain, general
Paraflutizide		1580-83-2				
Paraldehyde		123-63-7				
Paramethadione		115-67-3				
Paramethasone		53-33-8				
Paranyline		1729-61-9				
Parathyroid Hormone		9002-64-6				
parecoxib	Propanamide, N-((4-(5-methyl-3-phenyl-4-isoxazolyl)phenyl)sulfonyl)-, sodium salt [CAS]	198470-85-8	WO	9738986	Analgesic, NSAID	Pain, post-operative
Parethoxycaine		94-23-5				
Pargyline		555-57-7				
paricalcitol	19-Nor-9,10-secoergosta-5,7,22-triene-1,3,25-triol, (1Alpha,3ß,7E,22E)- [CAS]	131918-61-1	EP	387077	Hormone	Hyperparathyroidism
paromomycin	O-2-Amino-2-deoxy-Alpha-D-glucopyranosyl-(1-4)-O-[O-2,6-diamino-2,6-dideoxy-ß-L-idopyranosyl-(1-3)-ß-D-ribofuranosyl-(1-5)]-2-deoxy-D-streptamine	7542-37-2			Protozoacide	Infection, leishmaniasis
paroxetine	Piperidine, 3-[(1,3-benzodioxol-5-yloxy)methyl]-4-(4-fluorophenyl)-, (3S-trans)- [CAS]	61869-08-7	EP	223403	Antidepressant, formulation, oral, orally-disintegrating	Depression, general

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Paroxypropione		70-70-2				
Parsalmide		30653-83-9				
PaTrin-2	4-Bromothenylguanine				Radio/chemosensitizer	Cancer, melanoma
Pazinaclone		103255-66-9				
pazufloxacin	7H-Pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid, 10-(1-aminocyclopropyl)-9-fluoro-2,3-dihydro-3-methyl-7-oxo-, (S)- [CAS]	127045-41-4 127046-45-1 136905-87-8	DE	3913245	Quinolone antibacterial	Infection, general
p-Bromoacetanilide		103-88-8				
PC-NSAIDs			US	4918063	Formulation, other	Arthritis, general
PD-0166285	6-(2,6-Dichlorophenyl)-2-[4-(diethylamino-ethoxy)-phenylamino]-8-pyrido[2,3-D]pyrimidine-7-one				Anticancer, other	Cancer, general
Pecilocin		19504-77-9				
pefloxacin	3-Quinolinecarboxylic acid, 1-ethyl-6-fluoro-1,4-dihydro-7-(4-methyl-1-piperazinyl)-4-oxo- [CAS]	70458-92-3	GB	1598915	Quinolone antibacterial	Infection, urinary tract
pegvisomant	Somatotropin (18-aspartic acid, 21-asparagine, 120-lysine, 167-asparagine, 168-alanine, 171-serine, 172-arginine, 174-serine, 179-threonine (human), pegylated [CAS]	218620-50-9			Somatostatin	Acromegaly
Pelletierine		4396-1-4				
pemetrexed	L-Glutamic acid, N-[4-[2-(2-amino-4,7-dihydro-4-oxo-1H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-, disodium salt [CAS]	137281-23-3 150399-23-8	US	5248775	Anticancer, antimetabolite	Cancer, mesothelioma
pemirolast	4H-Pyrido[1,2-a]pyrimidin-4-one, 9-methyl-3-(1H-tetrazol-5-yl)- [CAS]	100299-08-9 69372-19-6	US	4457932	Antiasthma	Asthma
Pemoline		2152-34-3				
Pempidine		79-55-0				
PEN-203			US	5955446	Antiviral, other	Infection, human papilloma virus
Penamecillin		983-85-7				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
penbutolol	2-Propanol, 1-(2-cyclopentylphenoxy)-3-[(1,1-dimethylethyl)amino]-,(S)-, sulfate (2:1) (salt) [CAS]	38363-32-5 38363-40-5	GB	1215751	Antihypertensive, adrenergic	
penciclovir	6H-Purin-6-one, 2-amino-1,9-dihydro-9-[4-hydroxy-3-(hydroxymethyl)butyl]- [CAS]	39809-25-1	JP	60058982	Antiviral, other	Infection, herpes simplex virus
Penethamate		808-71-9				
penfluridol	4-Piperidinol, 1-[4,4-bis(4-fluorophenyl)butyl]-4-[4-chloro-3-(trifluoromethyl)phenyl]- [CAS]	26864-56-2	DE	2040231	Neuroleptic	
Penicillamine		52-67-5				
Penicillin G		61-33-6				
Penicillin G Benzathine		1538-09-6				
Penicillin G Procaine		6130-64-9				
Penicillin N		525-94-0				
Penicillin O		87-09-2				
Penicillin V		87-08-1				
Penimepicycline		4599-60-4				
Penntuss			US	4221778	Formulation, modified-release, other	Rhinitis, allergic, general
Pentaerythritol Chloral		78-12-6				
Pentaerythritol Dichlorohydrin		2209-86-1				
Pentaerythritol		597-71-7				
Pentagastrin		5534-95-2				
Pentagestrone		7001-56-1				
PentaLyte	Starch, 2-hydroxyethyl ether [CAS]	9005-27-0	US	5407428	Plasma substitute	Surgery adjunct
Pentamethonium		541-20-8				
pentamidine	Benzenecarboximidamide, 4,4'-[1,5-pentanediylbis(oxy)]bis- [CAS]	100-33-4			Formulation, inhalable, systemic	Infection, Pneumocystis jiroveci prophylaxis
Pentazocine		359-83-1				
Pentetate		12111-24-9				
Pentetic Acid		67-43-6				
Pentetreotide		138661-02-6				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Penthienate		60-44-6				
Pentifylline		1028-33-7				
Pentigetide		62087-72-3				
Pentisomide		78833-03-1				
Pentobarbital		76-74-4				
Pentolinium		52-62-0				
Pentorex		434-43-5				
pentosan	Xylan, [CAS]	37319-17-8	US	5180715	Urological	Inflammation, urinary tract
pentostatin	Imidazo[4,5-d][1,3]diazepin-8-ol, 3-(2-deoxy-ß-D-erythro-pentofuranosyl)-3,6,7,8-tetrahydro-, (R)- [CAS]	53910-25-1	US	3923785	Anticancer, antimetabolite	Cancer, leukaemia, hairy cell
pentoxifylline	1H-Purine-2,6-dione, 3,7-dihydro-3,7-dimethyl-1-(5-oxohexyl)- [CAS]				Neuroprotective	Amyotrophic lateral sclerosis
Pentoxyl		147-61-5				
Pentrinitrol		1607-17-6				
Pentylenetetrazole		54-95-5				
peplomycin	Bleomycinamide, N1-[3-[(1-phenylethyl)amino]propyl]-, (S)- [CAS]	68247-85-8	US	4195018	Anticancer, antibiotic	
Perazine		84-97-9				
Perflubron		423-55-2				
Perfosfamide		62435-42-1; 39800-16-3 (unspecified)				
pergolide	Ergoline, 8-[(methylthio)methyl]-6-propyl-, (8ß)-, monomethanesulfonate- [CAS]	66104-22-1 66104-23-2	US	4797405	Antiparkinsonian	Parkinson's disease
Perhexiline		6621-47-2				
Pericyazine		2622-26-6				
perifosine	Piperidinium, 4-[[hydroxy(octadecyloxy)phosphinyl]oxy]-1,1-dimethyl-, inner salt [CAS]	157716-52-4	EP	594999	Anticancer, other	Cancer, prostate
perillyl alcohol	1-Cyclohexene-1-methanol, 4-(1-methylethenyl)- [CAS]	536-59-4	US	5110832	Anticancer, other	Cancer, breast
Perimethazine		13093-88-4				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
perindopril	1H-Indole-2-carboxylic acid, 1-[2-[[1-(ethoxycarbonyl)butyl],amino]-1-oxopropyl]octahydro-, [2S-[1[R*(R*)],2Alpha,3aß,7aß]]-, compd. with 2-methyl-2-propanamine (1:1) [CAS]	107133-36-8 82834-16-0 95153-31-4	EP	49658	Antihypertensive, renin system	Hypertension, general
Periodyl		53586-99-5				
perisoxal	1-Piperidineethanol, Alpha-(5-phenyl-3-isoxazolyl)-, 2-hydroxy-1,2,3-propanetricarboxylate (2:1) (salt) [CAS]	2139-25-5 2055-44-9	JP	04217925	Anti-inflammatory	
Perlapine		1977-11-3				
Permethrin		52645-53-1				
perospirone	1H-Isoindole-1,3(2H)-dione, 2-[4-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]butyl]hexahydro-, cis- [CAS]	129273-38-7 150915-41-6	CA	2167004	Neuroleptic	Schizophrenia
Perphenazine		58-39-9				
Petroleum Benzin		8030-30-6				
PH-10			US	6331286	Antipsoriasis	Psoriasis
Phanquinone		84-12-8				
Pharmaprojects No. 4994			WO	9638482	Immunological	Unspecified
Pharmaprojects No. 5325			WO	9703986	Neuroleptic	Schizophrenia
Pharmaprojects No. 5972			WO	0204426	Antiasthma	Asthma
Pharmaprojects No. 6362			US	6057346	Antiviral, anti-HIV	Infection, HIV/AIDS
Pharmaprojects No. 6446	(R)-N-[4-[2-[[2-Hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[4-[4-(trifluoromethyl)phenyl]thiazol-2-yl]benzenesulfonamide				Anorectic/Antiobesity	Obesity
Pharmaprojects No. 6590			WO	0206223	Psychostimulant	Attention deficit disorder
Pharmaprojects No. 6656			US	6455026	Genomics-based drug discovery	Cancer, brain
Pharmaprojects No. 6691			US	6299900	Formulation, other	Pain, general
Pharmaprojects No. 6743	3-(6-Aminopyridin-3-yl)-N-methyl-N-[(1-methyl-1H-indol-2-yl)methyl]acrylamide				Antibacterial, other	Infection, general

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Pharmaprojects No. 6748	1,2,3,4,10,14b-Hexahydro-6-methoxy-2-methyldibenzo[c,f]pyrazino[1,2-a]azepin				Antidepressant	Depression, general
Phenacaine		620-99-5				
Phenacemide		63-98-9				
Phenacetin		62-44-2				
Phenadoxone		467-84-5				
Phenallymal		115-43-5				
Phenamet		3819-34-9				
Phenazocine		127-35-5				
Phenazopyridine		136-40-3				
Phenbutamide		3149-00-6				
Phencyclidine		77-10-1				
Phendimetrazine		634-03-7				
Phenelzine		51-71-8				
Phenesterine		3546-10-9				
Phenetharbital		357-67-5				
Phenethicillin		132-93-4				
Pheneturide		90-49-3				
Phenformin		114-86-3				
Phenglutarimide		1156-05-4				
Phenindamine		82-88-2				
Phenindione		83-12-5				
Pheniprazine		55-52-7				
Pheniramine		86-21-5				
Phenmetrazine		134-49-6				
Phenobarbital		50-06-6				
Phenobutiodil		554-24-5				
Phenocoll		103-97-9				
Phenoctide		78-05-7				
Phenolphthalein		77-09-8				
Phenolphthalol		81-92-5				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Phenolsulfonphthalein		143-74-8				
Phenoltetrachlorophthalein		639-44-1				
Phenoperidine		562-26-5				
Phenosulfazole		515-54-8				
Phenoxybenzamine		59-96-1				
Phenoxypropazine		3818-37-9				
Phenprobamate		673-31-4				
Phenprocoumon		435-97-2				
phenserine	Pyrrolo(2,3-b)indol-5-ol, 1,2,3,3a,8,8a-hexahydro-1,3a,8-trimethyl-, phenylcarbamate (ester), (3aS-cis)- [CAS]	101246-66-6			Cognition enhancer	Alzheimer's disease
Phensuximide		86-34-0				
Phentermine		122-09-8				
Phentetiothalein		18265-54-8				
phentolamine	Phenol, 3-(((4,5-dihydro-1H-imidazol-2-yl)methyl)(4-methylphenyl)amino)-, monomethanesulfonate (salt) [CAS]	65-28-1 50-60-2			Formulation, oral, other	Impotence
Phenyl Acetylsalicylate		134-55-4				
Phenyl Aminosalicylate		133-11-9				
Phenyl Salicylate		118-55-8				
Phenylbutazone		50-33-9				
Phenylephrine		61-76-7				
Phenylethanolamine		7568-93-6				
Phenylmercury		102-98-7				
Phenylmethylbarbituric Acid		76-94-8				
phenylpropanolamine	Benzenemethanol, Alpha-(1-aminoethyl)-, (R*,S*)-(+/-)- [CAS]	14838-15-4			Anorectic/Antiobesity, formulation, optimized, microparticles	
Phenylpropylmethylamine		93-88-9				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Phenyltoloxamine		92-12-6				
Phenyramidol		553-69-5				
phenytoin	2,4-Imidazolidinedione, 5,5-diphenyl- [CAS]	57-41-0			Formulation, oral, other	Epilepsy, general
Phethenylate		510-34-9				
Phloroglucinol		108-73-6				
Pholcodine		509-67-1				
Pholedrine		370-14-9				
Phosphocreatine		67-07-2				
Phosphocysteamine		5746-40-7				
Phosphorylcholine		107-73-3				
Phthalylsulfacetamide		131-69-1				
Phthalylsulfathiazole		85-73-4				
p-Hydroxyephedrine		365-26-4				
Phylloquinone		84-80-0				
Physostigmine		57-47-6				
Phytic Acid		83-86-3				
PI-88	D-Mannose, O-6-O-phosphono-Alpha-D-mannopyranosyl-(1-3)-O-Alpha-D-mannopyranosyl-(1-3)-O-Alpha-D-mannopyranosyl-(1-3)-O-Alpha-D-mannopyranosyl-(1-2)- hydrogen sulphate [CAS]	185077-23-0			Anticancer, other	Cancer, melanoma
Piberaline		39640-15-8				
piboserod	2H-(1,3)Oxazino(3,2-a)indole-10-carboxamide, N-((1-butyl-4-piperidinyl)methyl)-3,4-dihydro- [CAS]	152811-62-6	WO	9318036	Antiarrhythmic	Fibrillation, atrial
Picilorex		62510-56-9				
Picloxydine		5636-92-0				
Picoperine		21755-66-8				
Picosulfate		10040-45-6				
Picotamide		32828-81-2				
Picumast		39577-19-0				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
pidotimod	4-Thiazolidinecarboxylic acid, 3-[(5-oxo-2-pyrrolidinyl)carbonyl]- [CAS]	121808-62-6	EP	276752	Immunomodulator, anti-infective	Infection, respiratory tract, lower
Pifarnine		56208-01-6				
piketoprofen	Benzeneacetamide, 3-benzoyl-Alpha-methyl-N-(4-methyl-2-pyridinyl)- [CAS]	60576-13-8	GB	1436502	Anti-inflammatory, topical	
Pildralazine		64000-73-3				
pilocarpine	2(3H)-Furanone, 3-ethyldihydro-4-[(1-methyl-1H-imidazol-5-yl)methyl]-, (3S-cis)- [CAS]	92-13-7			Formulation, implant, Stomatological	
Piloplex	2-Propenoic acid, 2-methyl-, dodecyl ester, polymer with 2-propenoicacid, compd. with (3S-cis)-3-ethyldihydro-4-[(1-methyl-1H-imidazol-5-yl)methyl]-2(3H)-furanone [CAS]	62783-28-2	DE	2636559	Formulation, mucosal, topical	Glaucoma
pilsicainide	1H-Pyrrolizine-7a(5H)-acetamide, N-(2,6-dimethylphenyl)tetrahydro-, monohydrochloride [CAS]	88069-49-2 88069-67-4	US	4564624	Antiarrhythmic	Arrhythmia, general
Pimeclone		534-84-9				
pimecrolimus	15,19-Epoxy-3H-pyrido(2,1-c)(1,4)oxaazacyclotricosine-1,7,20,21(4H,23H)-tetrone, 3-(2-(4-chloro-3-methoxycyclohexyl)-1-methyletheny)-8-ethyl-5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5,19-dihydroxy-14,16-dimethoxy-4,10,12,18-tetramethyl-(3S-(3R*E(1S*,3S*,4R*)), 4S*,5R*,8S*,9E*,12R*,14R*,5S*,16R*,18S 8,19S*,26aR*))- [CAS]	137071-32-0	EP	626385	Antipruritic/inflamm, allergic	Eczema, atopic
Pimefylline		10001-43-1				
pimilprost	Acetic acid, [2-[octahydro-5-hydroxy-6-(3-hydroxy-5-methyl-1-nonenyl)-2-pentalenyl]ethoxy]-, methyl ester, [2R-[2Alpha,3Alpha,4Alpha(1E,3S*,5S*),5ß,6a Alpha]]- [CAS]	139403-31-9			Dermatological	Ulcer, general
Piminodine		13495-09-5				
Pimobendan		74150-27-9				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
pimozide	2H-Benzimidazol-2-one, 1-[1-[4,4-bis(4-fluorophenyl)butyl]-4-piperidinyl]-1,3-dihydro- [CAS]	2062-78-4	FR	M3695	Neuroleptic	
Pinacidil		85371-64-8				
pinaverium	Morpholinium, 4-[(2-bromo-4,5-dimethoxyphenyl)methyl]-4-[2-[2-(6,6-dimethylbicyclo[3.1.1]hept-2-yl)ethoxy]ethyl]-, [CAS]	53251-94-8 59995-65-2	EP	406743	Antispasmodic	Irritable bowel syndrome
pinazepam	2H-1,4-Benzodiazepin-2-one, 7-chloro-1,3-dihydro-5-phenyl-1-(2-propynyl)-[CAS]	52463-83-9	DE	2339790	Anxiolytic	
Pindolol		13523-86-9				
pioglitazone	2,4-Thiazolidinedione, 5-[[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methyl]-, monohydrochloride (+/-)- [CAS]	111025-46-8 112529-15-4	EP	193256	Antidiabetic	Diabetes, Type II
Pipacycline		1110-80-1				
Pipamazine		84-04-8				
Pipamperone		1893-33-0				
Pipazethate		2167-85-3				
Pipebuzone		27315-91-9				
Pipecurium		52212-02-9				
pipecuronium	Piperazinium, 4,4'-[(2ß,3Alpha,5Alpha,16ß,17ß)-3,17-bis(acetyloxy)androstane-2,16-diyl]bis[1,1]-dimethyl-, [CAS]	52212-02-9 68399-57-5	GB	1398050	Muscle relaxant	Anaesthesia, adjunct
pipemidic acid	Pyrido[2,3-d]pyrimidine-6-carboxylic acid, 8-ethyl-5,8-dihydro-5-oxo-2-(1-piperazinyl)- [CAS]	51940-44-4	GB	1451911	Antibacterial, other	Infection, urinary tract
Pipenzolate Bromide		125-51-9				
Piperacetazine		3819-00-9				
piperacillin	4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 6-[[[[(4-ethyl-2,3-dioxo-1-piperazinyl)carbonyl]amino]phenylacetyl]amino]-3,3-dimethyl-7-oxo-,[2S-[2Alpha,5Alpha,6ß(S*)]]- [CAS]	59703-84-3 61477-96-1	GB	1508062	Penicillin, injectable	Infection, general

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Piperazine Adipate		142-88-1				
Piperidione		77-03-2				
Piperidolate		82-98-4				
Piperilate		4546-39-8				
piperine analogues			WO	002544	Dermatological	Vitiligo
Piperocaine		136-82-3				
Piperonal		120-57-0				
Piperoxan		59-39-2				
Piperylone		25 31-4-6				
Pipobroman		54-91-1				
Piposulfan		2608-24-4				
pipotiazine	Hexadecanoic acid, 2-[1-[3-[2-[(dimethylamino)sulfonyl]-10H-phenothiazin-10-yl]propyl]-4-piperidinyl]ethyl ester [CAS]	37517-26-3 39860-99-6	US	4782077	Neuroleptic	
Pipoxolan		18174-58-8				
Pipradrol		467-60-7				
piprozolin	Acetic acid, [3-ethyl-4-oxo-5-(1-piperidinyl)-2-thiazolidinylidene]-, ethyl ester [CAS]	17243-64-0	US	3971794	GI inflammatory/bowel disorders	Motility dysfunction, GI, general
Piracetam		7491-74-9				
pirarubicin	5,12-Naphthacenedione, 10-[[3-amino-2,3,6-trideoxy-4-O-(tetrahydro-2H-pyran-2-yl)-Alpha-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-, [8S-[8Alpha,10Alpha(S*)]]- [CAS]	72496-41-4	US	4303785	Anticancer, antibiotic	Cancer, breast
Pirazolac		71002-09-0				
pirbuterol	2,6-Pyridinedimethanol, Alpha6-[[(1,1-dimethylethyl)amino]methyl]-3-hydroxy-, monoacetate (salt) [CAS]	38029-10-6 38677-81-5 65652-44-0	US	3786160	Antiasthma	Asthma
Pirenoxine		1043-21-6				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
pirenzepine	6H-Pyrido[2,3-b][1,4]benzodiazepin-6-one, 5,11-dihydro-11-[(4-methyl-1-piperazinyl)acetyl]- [CAS]	28797-61-7 29868-97-1	FR	1505795	Antiulcer	
piretanide	Benzoic acid, 3-(aminosulfonyl)-4-phenoxy-5-(1-pyrrolidinyl)- [CAS]	55837-27-9	US	4010273	Antihypertensive, diuretic	Hypertension, general
pirfenidone	2(1H)-Pyridinone, 5-methyl-1-phenyl- [CAS]	53179-13-8			Respiratory	Fibrosis, pulmonary
piribedil	Pyrimidine, 2-[4-(1,3-benzodioxol-5-ylmethyl)-1-piperazinyl]- [CAS]	3605-01-4	US	3299067	Vasodilator, peripheral	Parkinson's disease
Piridocaine		87-21-8				
Pirifibrate		55285-45-5				
Piritramide		302-41-0				
Piritrexim		72732-56-0				
pirlindole	1H-Pyrazino[3,2,1-jk]carbazole, 2,3,3a,4,5,6-hexahydro-8-methyl- [CAS]	16154-78-2 60762-57-4	SU	276060	Antidepressant	Depression, general
pirmenol	(2-Pyridinemethanol, Alpha-[3-(2,6-dimethyl-1-piperidinyl)propyl]-.Alpha.phenyl-, cis-(+)- [CAS]	61477-94-9 68252-19-7	US	4112103	Antiarrhythmic	Tachycardia, supraventricular
Piroctone		50650-76-5				
Piroheptine		16378-21-5				
Piromidic Acid		19562-30-2				
piroxicam	2H-1,2-Benzothiazine-3-carboxamide, 4-hydroxy-2-methyl-N-2-pyridinyl-, 1,1-dioxide [CAS]	36322-90-4	US	3862319	Anti-inflammatory	
piroxicam betadex	ß-Cyclodextrin, compd. with 4-hydroxy-2-methyl-N-2-pyridinyl-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxide- [CAS]	121696-62-6 96684-39-8	EP	153998	Formulation, other	Pain, musculoskeletal
piroxicam cinnamate	2-Propenoic acid, 3-phenyl-, 2-methyl-3-[(2-pyridinylamino)carbonyl]-2H-1,2-benzothiazin-4-yl ester, S,S-dioxide [CAS]	87234-24-0	EP	79639	Antiarthritic, other	Inflammation, general
Pirozadil		54110-25-7				
Pirprofen		31793-07-4				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
pitavastatin	6-Heptenoic acid, 7-[2-cyclopropyl-4-(4-fluorophenyl)-3-quinolinyl]-3,5-dihydroxy-, calcium salt (2:1), [S-[R*,S*-(E)]]- [CAS]	147526-32-7	EP	304063	Hypolipaemic/Antiatherosclerosis	Hyperlipidaemia, general
pivagabine	N-trimethylacetyl-4-aminobutyric acid	69542-93-4			Neurological	Anxiety, general
pivaloyloxymethyl	Butanoic acid, (2,2-dimethyl-1-oxopropoxy)methyl ester [CAS]	122110-53-6	EP	302349	Anticancer, other	Cancer, lung, non-small cell
Pivalylbenzhydrazine		306-19-4				
Pivampicillin		33817-20-8				
pivampicillin/pivmecillinam		98445-47-7			Penicillin, oral	Infection, general
Pivcefalexin		63836-75-9				
pivmecillinam	4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 6-[[(hexahydro-1H-azepin-1-yl)methylene]amino]-3,3-dimethyl-7-oxo-, (2,2-dimethyl-1-oxopropoxy)methyl ester, [2S-(2Alpha,5Alpha,6ß)]- [CAS]	32886-97-8	GB	1293590	Penicillin, oral	Infection, general
pixantrone	Benz[g]isoquinoline-5,10-dione, 6,9-bis[(2-aminoethyl)amino]-, (2Z)-2-butenedioate(1:2) [CAS]	144675-97-8	EP	503537	Anticancer, other	Cancer, lymphoma, non-Hodgkin's
pizotifen	4-(9,10-dihydro-4H-benzo[4,5]cyclohepta[1,2-b]thien-4-ylidene)-1-methylpiperidine	15574-96-6	DE	2346747	Antimigraine	
Pizotyline		15574-96-6				
PKI-166	Phenol, 4-(4-(((1R)-1-phenylethyl)amino)-1H-pyrrolo(2,3-d)pyrimidin-6-yl)- [CAS]	187724-61-4			Anticancer, other	Cancer, general
p-Lactophenetide		539-08-2				
Plafibride		63394-05-8				
plasminogen activator	Plasminogen activator [CAS]	105913-11-9	EP	151996	Fibrinolytic	Infarction, myocardial
Plasmocid		551-01-9				
Platonin		3571-88-8				
Plaunotol		64218-02-6				
PLD-118	Cyclopentanecarboxylic acid, 2-amino-4-methylene-, (1R,2S)- [CAS]	198022-65-0	EP	805145	Antifungal	Infection, Candida, general

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
PLD-147	(OC-6-43)-Bis(acetato)(1-adamantylamine)ammine-dichloro-platinum (IV)				Anticancer, alkylating	Cancer, general
pleconaril	1,2,4-Oxadiazole, 3-(3,5-dimethyl-4-(3-(3-methyl-5-isoxazolyl)propoxy)phenyl)-5-(trifluoromethyl)- [CAS]	153168-05-9	US	5464848	Antiviral, other	Infection, respiratory tract, general
Plicamycin		18378-89-7				
p-Methyldiphenhydramine		19804-27-4				
PMS-601			WO	0001677	Antiviral, anti-HIV	Infection, HIV/AIDS
Pneumococcal Vaccine, Diphtheria Conjugate						
Pneumococcal Vaccine, Polyvalent						
PNU-288034	N-[[(5s)-3[4[(1,1-dioxido-4-thiomorpholinyl)3,5-difluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide]				Antibiotic, other	Infection, general
Podophyllotoxin		518-28-5				
polaprezinc	Zinc, bis(N-ß-alanyl-L-histidinato-N3,OAlpha)-, (T-4)- [CAS]	107667-60-7	EP	303380	Antiulcer	Ulcer, duodenal
Poldine Methylsulfate		545-80-2				
Policresulen		9011-2-3				
Polidexide		9064-92-0				
polidocanol	Polyethylene glycol monododecyl ether	3055-99-0 9002-92-0			Vasoprotective, systemic	Venous insufficiency
Poliovirus Vaccine Inactivated						

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
poly-ADPRT inhibitors			WO	9845253	Anticancer, other	Cancer, general
Polyestradiol Phosphate		28014-46-2				
Polyphenon E	Polyphenon E [CAS]	188265-33-0			Antiviral, other	Infection, human papilloma virus
Polythiazide		346-18-9				
porfimer	Photofrin [CAS]	87806-31-3	US	4882234	Anticancer, other	Cancer, lung, non-small cell
Porfiromycin		801-52-5				
posaconazole	D-threo-Pentitol, 2,5-anhydro-1,3,4-trideoxy-2-C-(2,4-difluorophenyl)-4-((4-(4-(4-(1(1S,2S)-1-ethyl-2-hydroxypropyl)-1,5-dihydro-5-oxo-4H-1,2,4-triazol-4-yl)phenyl)-1-piperazinyl)phenoxy)methyl)-1-(1H-1,2,4-triazol-1-yl)- [CAS]	171228-49-2	US	5714490	Antifungal	Infection, fungal, general
Posatirelin		78664-73-0				
potassium chloride	Potassium chloride (KCl) [CAS]	7447-40-7			Formulation, oral, enteric-coated	
Potassium Gluconate		299-27-4				
Potassium Guaiacolsulfonate		1321-14-8				
Potassium p-Aminobenzoate		138-84-1				
Potassium Permanganate		7722-64-7				
Povidone		9003-39-8				
Povidone-Iodine		25655-41-8				
PP-117	3-Pyridinemethanol, hydrofluoride [CAS]	62756-44-9	DE	2633028	Formulation, oral, other	Unspecified
PR-2699	(-)-(E)-[4-(2,4-dichlorophenyl)-1,3-dithiolan-2-ylidene]-1-imidazolylacetonitrile				Antifungal	Infection, fungal, general

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
PR-608	(S)-(-)-1-[4,4-bis(4-fluorophenyl)butyl]-4-(2-hydroxy-3-phenylaminopropyl)piperazine trihydrochloride				Antiparkinsonian	Parkinson's disease
Practolol		6673-35-4				
Prajmaline		35080-11-6				
Pralidoxime		51-15-0				
pralnacasan	6H-Pyridazino(1,2-a)(1,2)diazepine-1-carboxamide, N-((2R,3S)-2-ethoxytetrahydro-5-oxo-3-furanyl)octahydro-9-((1-isoquinolinylcarbonyl)amino)-6,10-dioxo-, (1S,9S)- [CAS]	192755-52-5			Antiarthritic, immunological	Arthritis, rheumatoid
pramipexole	2,6-Benzothiazolediamine, 4,5,6,7-tetrahydro-N6-propyl-, (S)- [CAS]	104632-26-0	EP	186087	Antiparkinsonian	Parkinson's disease
pramiracetam	1-Pyrrolidineacetamide, N-[2-[bis(1-methylethyl)amino]ethyl]-2-oxo-, monohydrochloride [CAS]	68497-62-1 72869-16-0 75733-50-5	US	4145347	Cognition enhancer	Amnesia
Pramiverin		14334-40-8				
pramlintide	1,2-Dithia-5,8,11,14,17-pentaazacycloeicosane, cyclic peptide deriv. [CAS]	151126-32-8	US	5124314	Antidiabetic	Diabetes, Type I
Pramoxine		140-65-8				
pranidipine	3,5-Pyridinedicarboxylic acid, 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-, methyl 3-phenyl-2-propenyl ester, (E)- [CAS]	99522-79-9	EP	173126	Antihypertensive, other	Hypertension, general
Pranlukast		103177-37-3				
pranoprofen	5H-[1]Benzopyrano[2,3-b]pyridine-7-acetic acid, Alpha-methyl- [CAS]	52549-17-4			Formulation, mucosal, topical	Ocular disorder, general
prasterone	Androst-5-en-17-one, 3-hydroxy-, (3ß)- [CAS]	53-43-0			Labour inducer	
pratosartan	4(3H)-Cycloheptimidazolone, 5,6,7,8-tetrahydro-2-propyl-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]- [CAS]	153804-05-8	US	5409947	Antihypertensive, renin system	Hypertension, general

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
pravastatin	1-Naphthaleneheptanoic acid, 1,2,6,7,8,8a-hexahydro-ß,delta,6-trihydroxy-2-methyl-8-(2-methyl-1-oxobutoxy)-, monosodium salt, [1S-[1Alpha(ßS*,deltaS*),2Alpha,6Alpha,8ß(R*),8aAlpha]]- [CAS]	81093-37-0 81131-70-6	US	4346227	Hypolipaemic/Antiatherosclerosis	Atherosclerosis
Prazepam		2955-38-6				
praziquantel	4H-Pyrazino[2,1-a]isoquinolin-4-one, 2-(cyclohexylcarbonyl)-1,2,3,6,7,11b-hexahydro- [CAS]	55268-74-1	US	4001411	Schistosomicide	
prazosin	Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(2-furanylcarbonyl)-[CAS]	19216-56-9 19237-84-4	US	4092315	Antihypertensive, adrenergic	Hypertension, general
Prednicarbate		73771-04-7				
prednimustine	Pregna-1,4-diene-3,20-dione, 21-[4-[4-[bis(2-chloroethyl)amino]phenyl]-1-oxobutoxy]-11,17-dihydroxy-, (11ß)- [CAS]	29069-24-7	GB	1272841	Anticancer, alkylating	
Prednisolone		50-24-8				
Prednisolone 21-Diethylaminoacetate		5626-34-6				
prednisolone farnesil	Pregna-1,4-diene-3,20-dione, 11,17-dihydroxy-21-[(3,7,11-trimethyl-1-oxo-2,6,10-dodecatrienyl)oxy]-, [11ß,21(2E,6E)]- [CAS]	118244-44-3	EP	332143	Antiarthritic, other	Arthritis, rheumatoid
Prednisolone Sodium Phosphate		125-02-0				
Prednisone		53-03-2				
Prednival		15180-00-4				
Prednylidene		599-33-7				
pregabalin	Hexanoic acid, 3-(aminomethyl)-5-methyl, (S)- [CAS]	148553-50-8			Antiepileptic	Epilepsy, general
Pregnan-3α-ol-20-one		128-20-1				
Premarin + trimegestone	Estra-4,9-dien-3-one, 17-(2-hydroxy-1-oxopropyl)-17-methyl-, [17ß (S)]- [CAS]	74513-62-5			Menopausal disorders	Hormone replacement therapy

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
prenalterol	Phenol, 4-[2-hydroxy-3-[(1-methylethyl)amino]propoxy]-, hydrochloride, (S)-[CAS]	57526-81-5 61260-05-7	GB	1470039	Cardiostimulant	
Prenoxdiazine		982-43-4				
Prenylamine		390-64-7				
prezatide	Cuprate(1-), (N2-(N-glycyl-L-histidyl)-L-lysinato)(N2-(N-glycyl-L-histidyl)-L-lysinato(2-))-, hydrogen, [CAS]	130120-57-9			Vulnerary	Wound healing
Pridinol		511-45-5				
Prifinium		4630-95-9				
Prilocaine		721-50-6				
Primaquine		90-34-6				
Primidone		125-33-7				
Prinomastat		192329-42-3				
PRO-2000			US	5614599	Antiviral, anti-HIV	Infection, HIV prophylaxis
Probenecid		57-66-9				
Probucol		23288-49-5				
procainamide	Benzamide, 4-amino-N-[2-(diethylamino)ethyl]- [CAS]	51-06-9 614-39-1			Formulation, other	Arrhythmia, general
Procaine		59-46-1				
Procarbazine		671-16-9				
procaterol	2(1H)-Quinolinone, 8-hydroxy-5-[1-hydroxy-2-[(1-methylethyl)amino]butyl]-, monohydrochloride [CAS]	59828-07-8 60443-17-6 72332-33-3	GB	1496766	Antiasthma	
prochlorperazine	10H-Phenothiazine,2-chloro-10-[3-(4-methyl-1-piperazinyl)propyl]-, (Z)-2-butenedioate	58-38-8 84-02-6			Formulation, oral, other	Nausea and vomiting, general
procodazol	1H-Benzimidazole-2-propanoic acid [CAS]	23249-97-0	ES	407882	Anticancer, immunological	Cancer, general
Procyclidine		77-37-2				
Procymate		13931-64-1				
Prodipine		31314-38-2				
Proflavine		92-62-6				
Progabide		62666-20-0				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
progesterone	Pregn-4-ene-3,20-dione [CAS]	57-83-0			Formulation, transmucosal, systemic	Amenorrhoea
proglumetacin	1H-Indole-3-acetic acid, 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-, 2-(4-(3-((4-(benzoylamino)-5-(dipropylamino)-1,5-dioxopentyl)oxy)propyl)-1-piperazinyl)ethylester, (+/-)- [CAS]	57132-53-3 59209-40-4	GB	1467568	Anti-inflammatory	Inflammation, general
proglumide	Pentanoic acid, 4-(benzoylamino)-5-(dipropylamino)-5-oxo-, (+/-)- [CAS]	6620-60-6	DE	1518125	Antiulcer	Ulcer, gastric
Proheptazine		77-14-5				
Prolactin		9002-62-4				
Prolintane		493-92-5				
Prolonium		123-47-7				
Promazine		58-40-2				
Promedol		64-39-1				
Promegestone		34184-77-5				
promestriene	Estra-1,3,5(10)-triene, 17-methoxy-3-propoxy-, (17ß)- [CAS]	39219-28-8	GB	1337198	Reproductive/gonadal, general	Acne
Promethazine		60-87-7				
Pronethalol		54-80-8				
propacetamol	Glycine, N,N-diethyl-, 4-(acetylamino)phenyl ester [CAS]	66532-85-2 66532-86-3	US	4127671	Formulation, parenteral, other	
propafenone	1-Propanone, 1-[2-[2-hydroxy-3-(propylamino)propoxy]phenyl]-3-phenyl- [CAS]	54063-53-5	GB	1307455	Antiarrhythmic	Fibrillation, ventricular
Propagermanium		12758-40-6				
Propallylonal		545-93-7				
Propamidine		104-32-5				
propane-1,2-diol	1,2-propanediol	57-55-6			Formulation, dermal, topical	Infection, fungal, general
Propanidid		1421-14-3				
Propantheline		50-34-0				
Proparacaine		499-67-2.				
Propatyl		2921-92-8				
propenidazole	ethyl trans-Alpha-acetyl-1-methyl-5-nitroimidazole-2-acrylate	76448-31-2			Antifungal	Infection, trichomoniasis

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
propentofylline	1H-Purine-2,6-dione, 3,7-dihydro-3-methyl-1-(5-oxohexyl)-7-propyl- [CAS]	55242-55-2	GB	1470220	Neuroprotective	Ischaemia, cerebral
Propicillin		551-27-9				
Propiomazine		362-29-8				
Propionic Acid		79-09-4				
propionyl L-carnitine	1-Propanaminium, 3-carboxy-N,N,N-trimethyl-2-(1-oxopropoxy)-, chloride, (R)- [CAS]	119793-66-7 20084-19-1	GB	2008578	Vasodilator, peripheral	Peripheral vascular disease
Propipocaine		3670-68-6				
Propiram		15686-91-6				
propiverine	2,2-diphenyl-2-(1-propoxy)acetic acid (1-methylpiperid-4-yl) ester hydrochloride	54556-98-8 60569-19-9			Urological	Incontinence
Propizepine		10321-12-7				
propofol	Phenol, 2,6-bis(1-methylethyl)- [CAS]	2078-54-8	US	4056635	Anaesthetic, injectable	Anaesthesia
Propoxycaine		550-83-4				
Propoxyphene		469-62-5				
propranolol	2-Propanol, 1-[(1-methylethyl)amino]-3-(1-naphthalenyloxy)- [CAS]	318-98-9 525-66-6			Formulation, modified-release, <=24hr	Hypertension, general
Propylhexedrine		101-40-6				
Propyliodone		587-61-1				
Propylthiouracil		51-52-5				
Propyphenazone		479-92-5				
Proquazone		22760-18-5				
Proscillaridin		466-06-8				
Prostacyclin		35121-78-9				
Prostaglandin E_1		745-65-3				
Prostaglandin E_2		363-24-6				
Prostaglandin $F_{2\alpha}$		551-11-1				
Prosultiamine		59-58-5				
Protein C		60202-16-6				
Protheobromine		50-39-5				
Prothipendyl		303-69-5				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Protiofate		58416-00-5				
Protionamide		14222-60-7				
protizinic acid	10H-Phenothiazine-2-acetic acid, 7-methoxy-Alpha,10-dimethyl-, (+/-)- [CAS]	13799-03-6	US	3450698	Anti-inflammatory	
Protoanemonin		108-28-1				
Protokylol		136-70-9				
Protoporphyrin IX		553-12-8				
Protriptyline		438-60-8				
Pro-Urokinase		82657-92-9				
Proxazole		5696-9-3				
Proxibarbal		2537-29-3				
proxigermanium	Propanoic acid, 3,3'-(1,3-dioxo-1,3-digermoxanediyl)bis- [CAS]	12758-40-6	FR	2005110	Antiviral, other	Infection, hepatitis-B virus
Proxyphylline		603-00-9				
Prozapine		3426-8-2				
Prucalopride		179474-81-8				
prulifloxacin	1H,4H-[1,3]Thiazeto[3,2-a]quinoline-3-carboxylic acid, 6-fluoro-1-methyl-7-[4-[(5-methyl-2-oxo-1,3-dioxol-4-yl)methyl]-1-piperazinyl]-4-oxo- [CAS]	123447-62-1	EP	315828	Quinolone antibacterial	Infection, respiratory tract, general
Pseudococaine		478-73-9				
pseudoephedrine + triprolidine	Benzenemethanol, Alpha-[1-(methylamino)ethyl]-, hydrochloride, [S-(R*,R*)]-, mixt. with (E)-2-[1-(4-methylphenyl)-3-(1-pyrrolidinyl)-1-propenyl]pyridine monohydrochloride [CAS]				Formulation, modified-release, other	Rhinitis, allergic, general
pseudoephedrine	Benzenemethanol, Alpha-[1-(methylamino)ethyl]-, [S-(R*,R*)]- [CAS]	90-82-4, 8054-27-1, 345-78-8			Formulation, oral, other	Infection, respiratory tract, general
Psilocybin		520-52-5				
PSK-3841	Benzonitrile, 4-[3-(4-hydroxybutyl)-4,4-dimethyl-2,5-dioxo-1-imidazolidinyl]-2-(trifluoromethyl)- [CAS]	154992-24-2			Dermatological	Alopecia, general

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
p-Sulfanilylbenzylamine		4393-19-5				
PT-141			US	6051555	Male sexual dysfunction	Impotence
Pteropterin		89-38-3				
Puromycin		53-79-2				
PX-12	1-Methylpropyl 2-mercaptoimidazolyl disulfide				Anticancer, other	Cancer, general
Pyrantel		15686-83-6				
Pyrazinamide		98-96-4				
Pyridinol Carbamate		1882-26-4				
Pyridostigmine Bromide		101-26-8				
Pyridoxal 5-Phosphate		54-47-7				
Pyridoxine		58-56-0				
Pyrilamine		91-84-9				
Pyrimethamine		58-14-0				
Pyrinoline		1740-22-3				
Pyrisuccideanol		33605-94-6				
Pyrithione		1121-30-8				
Pyrithyldione		77-04-3				
Pyritinol		1098-97-1				
Pyrocatechol		120-80-9				
Pyrogallol		87-66-1				
Pyronaridine		74847-35-1				
Pyrovalerone		3563-49-3				
Pyroxylin		9004-70-0				
Pyrrobutamine		91-82-7				
Pyrrocaine		2210-77-7				
Pyrrolnitrin		1018-71-9				
Pyrvinium Pamoate		3546-41-6				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
quazepam	2H-1,4-Benzodiazepine-2-thione, 7-chloro-5-(2-fluorophenyl)-1,3-dihydro-1-(2,2,2-trifluoroethyl)- [CAS]	36735-22-5	US	3845039	Hypnotic/Sedative	Insomnia
Quercetin		117-39-5				
quetiapine	Ethanol, 2-[2-(4-dibenzo[b,f][1,4]thiazepin-11-yl-1-piperazinyl)ethoxy]-, (E)-2-butenedioate (2:1) (salt) [CAS]	111974-69-7 111974-72-2	EP	240228	Neuroleptic	Schizophrenia
Quinacillin		1596-63-0				
quinacrine	N-(6-Chloro-2-methoxy-9-acridinyl)-N,N-diethyl-1,4-pentanediamine + 10H-Phenothiazine-10-propanamine, 2-chloro-N,N-dimethyl	83-89-6			Neurofogical	Creutzfeldt-Jakob disease
quinagolide	Sulfamide, N,N-diethyl-N'-(1,2,3,4,4a,5,10,10a-octahydro-6-hydroxy-1-propylbenzo[g]quinolin-3-yl)-, (3Alpha,4aAlpha,10aß)- (+/-)- [CAS]	87056-78-8 94424-50-7 97805-49-7	EP	77754	Antiprolactin	Hyperprolactinaemia
quinapril	3-Isoquinolinecarboxylic acid, 2-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-, [3S-[2[R*(R*)],3R*]]- [CAS]	82586-55-8 85441-61-8 90243-99-5	EP	49605	Antihypertensive, renin system	Hypertension, general
quinaprilat	3-Isoquinolinecarboxylic acid, 2-[2-[(1-carboxy-3-phenylpropyl)amino]-1-oxopropyl]-1,2,3,4-tetrahydro-, [3S-[2[R*(R*)],3R*]]- [CAS]	82768-85-2	EP	46953	Antihypertensive, renin system	Hypertension, general
Quinapyramine		20493-41-8				
Quinbolone		2487-63-0				
Quinestradiol		1169-79-5				
Quinestrol		152-43-2				
Quinethazone		73-49-4				
quinfamide	2-Furancarboxylic acid, 1-(dichloroacetyl)-1,2,3,4-tetrahydro-6-quinolinyl ester [CAS]	62265-68-3	US	3997542	Amoebicide	
quinidine	Cinchonan-9-ol, 6'-methoxy-, (9S)-, sulfate (1:1) (salt) [CAS]	747-45-5 56-54-2			Formulation, modified-release, other	Arrhythmia, general

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Quinine		130-95-0				
Quinocide		525-61-1				
Quinupramine		31721-17-2				
Quinupristin		120138-50-3				
R-107500	cis-2,3,3a,8-tetrahydro-N,N-dimethyldibenz[c,f]isoxazolo[2,3-a]azepine-2-methanamine		WO	9614320	Anxiolytic	Anxiety, general
R-667			WO	0204439	COPD treatment	Emphysema, general
rabeprazole	1H-Benzimidazole, 2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]methyl]sulfinyl]-, sodium salt- [CAS]	117976-89-3 117976-90-6	EP	268956	Antiulcer	Ulcer, gastric
racecadotril	Glycine, N-[2-[(acetylthio)methyl]-1-oxo-3-phenylpropyl]-, phenylmethyl ester, (+/-)- [CAS]	112573-72-5 81110-73-8	EP	38758	Antidiarrhoeal	Diarrhoea, general
Racemethorphan		510-53-2				
raloxifene	Methanone, [6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]-, hydrochloride [CAS]	82640-04-8 84449-90-1	EP	62503	Osteoporosis treatment	Osteoporosis
raltitrexed	L-glutamic acid, N-[[5-[[(1,4-dihydro-2-methyl-4-oxo-6-quinazolinyl)methyl]methylamino]-2-thienyl]carbonyl]- [CAS]	112887-68-0	EP	239362	Anticancer, antimetabolite	Cancer, colorectal
ramatroban	9H-Carbazole-9-propanoic acid, 3-[[(4-fluorophenyl)sulfonyl]amino]-1,2,3,4-tetrahydro-, (R)- [CAS]	116649-85-5	EP	242518	Antiallergic, non-asthma	Rhinitis, allergic, perennial
Ramifenazone		3615-24-5				
ramipril	Cyclopenta[b]pyrrole-2-carboxylic acid, 1-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]octahydro-, [2S-[1[R*(R*)],2Alpha,3aß,6aß]]-[CAS]	87269-97-4 87333-19-5	EP	79022	Antihypertensive, renin system	Heart failure
ramosetron	Methanone, (1-methyl-1H-indol-3-yl)(4,5,6,7-tetrahydro-1H-benzimidazol-5-yl)-, monohydrochloride, (R)- [CAS]	132907-72-3 132036-88-5	EP	381422	Antiemetic	Nausea and vomiting, general

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Ramot project No. 1097			US	5730992	Dermatological	Unspecified
Ranimustine		58994-96-0				
ranitidine	1,1-Ethenediamine, N-[2-[[5-[(dimethylamino)methyl]-2-furanyl]methyl]thio]ethyl]-N'-methyl-2-nitro- [CAS]	66357-35-5	US	4128658	Antiulcer	Ulcer, duodenal
ranitidine bismuth citrate	1,2,3-Propanetricarboxylic acid, 2-hydroxy-, bismuth(3+) salt (1:1), compd. with N-(2-(((5-((dimethylamino)methyl)-2-furanyl)methyl)thio)ethyl)-N'-methyl-2-ni1-ethenediamine (1:1)- [CAS]	128345-62-0	EP	533281	Antiulcer	Ulcer, duodenal
ranolazine	1-Piperazineacetamide, N-(2,6-dimethylphenyl)-4-[2-hydroxy-3-(2-methoxyphenoxy)propyl]-, (+/-)- [CAS]	95635-55-5 95635-56-6	EP	126449	Antianginal	Angina, general
Ranpirnase		133737-96-9				
Rapacuronium		156137-99-4				
rasagiline	1H-Inden-1-amine, 2,3-dihydro-N-2-propynyl-, (R)-, [CAS]	161735-79-1	US	5457133	Antiparkinsonian	Parkinson's disease
Raubasine		483-04-5				
ravuconazole	Benzonitrile, 4-[2-[(1R,2R)-2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]-4-thiazolyl]- [CAS]	182760-06-1			Antifungal	Infection, meningitis, general
raxofelast	2-Benzofuranacetic acid, 5-(acetyloxy)-2,3-dihydro-4,6,7-trimethyl-, (+)- [CAS]	128232-14-4	US	4999350	Symptomatic antidiabetic	Nephropathy, diabetic
razoxane	2,6-Piperazinedione, 4,4'-(1-methyl-1,2-ethanediyl)bis- [CAS]	21416-67-1, 21416 87-5	GB	1234935	Anticancer, other	Cancer, general
RC-529	Tetradecanoic acid (1R)-1-(2-((2-((2-deoxy-3-O-((3R)-1-oxo-3-((1-oxotetradecyl)oxy)tetradecyl)amino-4-O-phosphono-ß-D-glucopyranosyl)oxy)ethyl)amino)-2-oxoethyl)dodecyl ester, compd. with N,N-diethylethanamine (1:1) [CAS]	216014-46-9			Immunostimulant, other	Vaccine adjunct
rebamipide	4-Quinolinepropanoic acid, Alpha-[(4-chlorobenzoyl)amino]-1,2-dihydro-2-oxo- [CAS]	90098-04-7	DE	3324034	Antiulcer	

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
rebimastat	L-Valinamide, N-((2S)-2-mercapto-1-oxo-4-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)butyl)-L-leucyl-N,3-dimethyl- [CAS]	259188-38-0			Anticancer, other	Cancer, lung, non-small cell
reboxetine	Morpholine, 2-[(2-ethoxyphenoxy)phenylmethyl]-, (R*,S*)- [CAS]	71620-89-8, 98769-81-4	US	4229449	Antidepressant	Depression, general
Remacemide		128298-28-2				
remifentanil	1-Piperidinepropanoic acid, 4-(methoxycarbonyl)-4-((1-oxopropyl)phenylamino)-methyl ester- [CAS]	132539-07-2, 132875-61-7	EP	383579	Analgesic, other	Pain, general
reminertant	Tricyclo[3.3.1.13,7]decane-2-carboxylic acid, 2-[[[1-(7-chloro-4-quinolinyl)-5-(2,6-dimethoxyphenyl)-1H-pyrazol-3-yl]carbonyl]amino]- [CAS]	146362-70-1	EP	699438	Neuroleptic	Schizophrenia
Remoxipride		80125-14-0				
renzapride	Benzamide, 4-amino-N-1-azabicyclo[3.3.1]non-4-yl-5-chloro-2-methoxy- [CAS]	109872-41-5 88721-77-1	JP	58188885	Gastroprokinetic	Irritable bowel syndrome
repaglinide	Benzoic acid, 2-ethoxy-4-[2-[[3-methyl-1-[2-(1-piperidinyl)phenyl]butyl]amino]-2-oxoethyl]-, (S)- [CAS]	135062-02-1	WO	9300337	Antidiabetic	Diabetes, Type II
repertaxin L-lysine salt	2(R)-4-Isobutylphenylpropionyl methanesulfonamide L-lysine salt		WO	0024710	Cardiovascular	Reperfusion injury
repinotan	1,2-Benzisothiazol-3(2H)-one, 2-(4-(((3,4-dihydro-2H-1-benzopyran-2-yl)methyl)amino)butyl)-, 1,1-dioxide, monohydrochloride [CAS]	144980-29-0 144980-77-8	US	5137901	Neuroprotective	Ischaemia, cerebral
repirinast	4H-Pyrano[3,2-c]quinoline-2-carboxylic acid, 5,6-dihydro-7,8-dimethyl-4,5-dioxo-, 3-methylbutyl ester [CAS]	73080-51-0	US	4298610	Antiasthma	
Reposal		3625-25-0				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
reproterol	1H-Purine-2,6-dione, 7-[3-[[2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]amino]propyl]-3,7-dihydro-1,3-dimethyl- [CAS]	13055-82-8 54063-54-6	FR	M5969	Antiasthma	Asthma
Rescimetol		73573-42-9				
Rescinnamine		24815-24-5				
Reserpiline		131-02-2				
Reserpine		50-55-5				
Resibufogenin		465-39-4				
resiquimod	1H-Imidazo(4,5-c)quinoline-1-ethanol(ethoxymethyl)-Alpha, Alpha-dimethyl- [CAS]	144875-48-9	US	5389640	Antiviral, other	Infection, hepatitis-C virus
Resorcinol		108-46-3				
Reteplase		133652-38-7				
retigabine	Carbamic acid, (2-amino-4-(((4-fluorophenyl)methyl)amino)phenyl)-, ethyl ester [CAS]	150812-12-7	DE	4200259	Antiepileptic	Epilepsy, general
retinoic acid	Retinoic acid [CAS]	302-79-4			Formulation, parenteral, other	Cancer, leukaemia, acute myelogenous
Revimid			US	6281230	Anticancer, other	Cancer, myeloma
R-flurbiprofen	[1,1'-Biphenyl]-4-acetic acid, 2-fluoro-Alpha-methyl	5104-49-4			Anticancer, other	Cancer, prostate
Rho (D) Immune Globulin (Human)						
Rho-kinase inhibitors			WO	0156988	Antiasthma	Unspecified
ribavirin	1H-1,2,4-Triazole-3-carboxamide, 1-ß-D-ribofuranosyl- [CAS]	36791-04-5	US	4211771	Antiviral, other	Infection, haemorrhagic fever
Riboflavin		146-17-8				
ribostamycin	D-Streptamine, O-2,6-diamino-2,6-dideoxy-Alpha-D-glucopyranosyl-(1-4)-O-[ß-D-ribofuranosyl-(1-5)]-2-deoxy- [CAS]	25546-65-0	GB	1254883	Aminoglycoside antibiotic	Infection, general
Ricinoleic Acid		141-22-0				
Ridogrel		110140-89-1				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
rifabutin	Rifamycin XIV, 1',4-didehydro-1-deoxy-1,4-dihydro-5'-(2-methylpropyl)-1-oxo-[CAS]	72559-06-9	US	4219478	Antimycobacterial	Infection, Mycobacterium avium complex
rifalazil	Rifamycin VIII, 1',4-didehydro-1-deoxy-1,4-dihydro-3'-hydroxy-5'-[4-(2-methylpropyl)-1-piperazinyl]-1-oxo- [CAS]	129791-92-0 129791-94-2 133633-12-2	EP	366914	Antimycobacterial	Infection, tuberculosis
rifametane	Rifamycin, 3-[[[1-(diethylamino)ethylidene]hydrazono]methyl]- [CAS]	94168-98-6	EP	119571	Antimycobacterial	Infection, general
Rifamide		2750-76-7				
rifampicin + trimethoprim	Rifamycin, 3-[[(4-methyl-1-piperazinyl)imino]methyl]-, mixt. with 5-[(3,4,5-trimethoxyphenyl)methyl]-2,4-pyrimidinediamine [CAS]	61498-94-0			Formulation, fixed-dose combinations	Infection, general
Rifampin		13292-46-1				
Rifamycin SV		6998-60-3				
rifapentine	Rifamycin, 3-[[(4-cyclopentyl-1-piperazinyl)imino]methyl]- [CAS]	61379-65-5	DE	2608218	Antibiotic, other	Infection, tuberculosis
rifaximin	Epoxypentadeca[1,11,13]trienimino)benzofuro[4,5-e]-pyrido[1,2-a]benzimidazole-1,15(2H)-dione, 25-(acetyloxy)-5,6,21,23-tetrahydroxy-27-methoxy-2,4,11,16,20,22,24,26-octamethyl-, [2S-(2R*,16Z,18E,20R*,22S*,23S*,24S*,25R*,26S*,27R*,28E)]	80621-81-4	GB	2079270	Antibiotic, other	Infection, GI tract
rifaximine cream	4-deoxy-4'-methylpyrido[1',2'-1,2]imidoazo[5,4-c]rifamycin SV	80621-81-4	BE	888895	Formulation, dermal, topical	Infection, dermatological
Rilmazafone		99593-25-6				
rilmenidine	2-Oxazolamine, N-(dicyclopropylmethyl)-4,5-dihydro- [CAS]	54187-04-1 54249-57-9	DE	2362754	Antihypertensive, adrenergic	Hypertension, general
riluzole	2-Benzothiazolamine, 6-(trifluoromethoxy)- [CAS]	1744-22-5	EP	50551	Neuroprotective	Amyotrophic lateral sclerosis
Rimantadine		13392-28-4				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
rimazolium	4H-Pyrido[1,2-a]pyrimidinium, 3-(ethoxycarbonyl)-6,7,8,9-tetrahydro-1,6-dimethyl-4-oxo-, [CAS]	28610-84-6 35615-72-6	DE	2461349	Analgesic, NSAID	
rimexolone	Androsta-1,4-dien-3-one,11-hydroxy-16,17-dimethyl-17-(1-oxopropyl)-, (11ß,16Alpha,17ß)- [CAS]	49697-38-3	DE	2301317	Ophthalmological	Inflammation, ocular
Rimiterol		32953-89-2				
rimonabant	1H-Pyrazole-3-carboxamide, 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-N-1-piperidinyl-, monohydrochloride [CAS]	158681-13-1	US	5624941	Anorectic/Antiobesity	Obesity
riodoxol	1,3-Benzenediol, 2,4,6-triiodo- [CAS]	19403-92-0	US	3755251	Antiviral, other	
Rioprostil		77287-05-9				
risedronate	Phosphonic acid, (1-hydroxy-2-(3-pyridinyl)ethylidene)bis-, monosodium salt	115436-72-1	EP	304961	Osteoporosis treatment	Paget's disease
Risedronic Acid		105462-24-6				
risperidone	4H-Pyrido[1,2-a]pyrimidin-4-one, 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl- [CAS]	106266-06-2	EP	196132	Neuroleptic, formulation, optimized, microencapsulate	Schizophrenia
Ritanserin		87051-43-2				
Ritipenem		84845-57-8				
ritodrine	Benzenemethanol, 4-hydroxy-Alpha-[1-[[2-(4-hydroxyphenyl)ethyl]amino]ethyl]-, (R*,S*)- [CAS]	23239-51-2 26652-09-5	US	3410944	Labour inhibitor	Labour, preterm
ritonavir	2,4,7,12-Tetraazatridecan-13-oic acid, 10-hydroxy-2-methyl-5-(1-methylethyl)-1-(2-(1-methylethyl)-4-thiazolyl)-3,6-dioxo-8,11-bis(phenylmethyl)-, 5-thiazolyl-methyl ester, (5S-(5R*,8R*,10R*,11R*))- [CAS]	155213-67-5	WO	9414436	Antiviral, anti-HIV	Infection, HIV/AIDS
Rituximab		174722-31-7				
rivastigmine	Carbamic acid, ethylmethyl-, 3-[1-(dimethylamino)ethyl]phenyl ester, (S)- [CAS]	123441-03-2 129101-54-8	DE	3805744	Cognition enhancer	Alzheimer's disease

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
rizatriptan	1H-Indole-3-ethanamine, N,N-dimethyl-5-(1H-1,2,4-triazol-1-ylmethyl)-, [CAS]	145202-66-0 159776-67-7 144034-80-0	EP	497512	Antimigraine	Migraine
RJR-2403	3-Buten-1-amine, N-methyl-4-(3-pyridinyl)-, (3E)-, (2E)-2-butenedioate (1:1) [CAS]	183288-99-5			Cognition enhancer	Alzheimer's disease
RNA Stealth Nucleosides	5-Formyluridine				Antiviral, other	Infection, hepatitis-C virus
Ro-0094889	2',3'-Di-O-acetyl-5'-vinylcytidine				Anticancer, antimetabolite	Cancer, general
Ro-61-1790	2-Pyridinesulfonamide, N-[6-(2-hydroxyethoxy)-5-(2-methoxyphenoxy)-2-[2-(1H-tetrazol-5-yl)-4-pyridinyl]-4-pyrimidinyl]-5-methyl- [CAS]	180384-56-9	WO	9619459	Cardiovascular	Haemorrhage, subarachnoid
Rociverine		53716-44-2				
rocuronium	Pyrrolidinium, 1-[(2ß,3Alpha,5Alpha,16ß,17ß)-17-(acetyloxy)-3-hydroxy-2-(4-morpholinyl)androstan-16-yl]-1-(2-propenyl)-, bromide- [CAS]	104855-17-6 104884-91-5 119302-91-9 143558-00-3	EP	287150	Muscle relaxant	Muscle spasm, general
rofecoxib	2(5H)-Furanone, 4-(4-(methylsulfonyl)phenyl)-3-phenyl- [CAS]	162011-90-7	US	5474995	Analgesic, NSAID	Arthritis, osteo
roflumilast	Benzamide, 3-(cyclopropylmethoxy)-N-(3,5-dichloro-4-pyridinyl)-4-(difluoromethoxy)- [CAS]	162401-32-3	WO	9501338	COPD treatment	Chronic obstructive pulmonary disease
rokitamycin	Leucomycin V, 4B-butanoate 3B-propanoate [CAS]	74014-51-0	US	4242504	Macrolide antibiotic	Infection, general
Rolipram		61413-54-5				
Rolitetracycline		751-97-3				
Romurtide		78113-36-7				
Ronifibrate		42597-57-9				
ropinirole	2H-Indol-2-one, 4-[2-(dipropylamino)ethyl]-1,3-dihydro-, monohydrochloride- [CAS]	91374-20-8 91374-21-9	EP	266033	Antiparkinsonian	Parkinson's disease

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
ropivacaine	2-Piperidinecarboxamide, N-(2,6-dimethylphenyl)-1-propyl-, (S)- [CAS]	84057-95-4 98717-15-8	EP	239710	Anaesthetic, local	Anaesthesia
Roquinimex		84088-42-6				
rosaprostol	Cyclopentaneheptanoic acid, 2-hexyl-5-hydroxy- [CAS]	56695-65-9	GB	1523355	Prostaglandin	
Rosaramicin		35834-26-5				
Rose Bengal		632-68-8				
rosiglitazone	2,4-Thiazolidinedione, 5-((4-(2-(methyl-2-pyridinylamino)ethoxy)phenyl)methyl)-, (Z)-2-butenedioate (1:1) [CAS]	122320-73-4 155141-29-0	US	5002953	Antidiabetic	Diabetes, Type II
rosoxacin	3-Quinolinecarboxylic acid, 1-ethyl-1,4-dihydro-4-oxo-7-(4-pyridinyl)- [CAS]	40034-42-2	US	3753993	Quinolone antibacterial	Infection, gonorrhoea
rostaporfin	Tin, dichloro[ethyl 3,4,20,21-tetradehydro-4,9,14,19-tetraethyl-18,19-dihydro-3,8,13,18-tetramethyl-20-phorbinecarboxylato(2-)-kappaN23,kappaN24,kappaN25,kappaN26]-, (OC-6-13)- [CAS]	114494-17-6			Ophthalmological	Macular degeneration
rosuvastatin	6-Heptenoic acid, 7-(4-(4-fluorophenyl)-6-(1-methylethyl)-2-(methyl(methylsulfonyl)amino)-5-pyrimdinyl)-3,5-dihydroxy- (S-(R*, S*-(E))) [CAS]	147098-20-2	JP	2648897	Hypolipaemic/Antiatherosclerosis	Hyperlipidaemia, general
rotigotine	1-Naphthalenol, 5,6,7,8-tetrahydro-6-[propyl[2-(2-thienyl)ethyl]amino]-, (S)- [CAS]	99755-59-6	US	4564628	Antiparkinsonian	Parkinson's disease
Rotraxate		92071-51-7				
Roxarsone		121-19-7				
roxatidine	Acetamide, 2-(acetyloxy)-N-[3-[3-(1-piperidinylmethyl)phenoxy]propyl]-, [CAS]	78628-28-1 93793-83-0	EP	24510	Antiulcer	Ulcer, gastric
roxifiban	L-Alanine, 3-(((3-(4-(aminoiminomethyl)phenyl)-4,5-dihydro-5-isoxazolyl)acetyl)amino)-N-(butoxycarbonyl)-, methyl ester, (R)-, [CAS]	176022-59-6	US	5849736	Antithrombotic	Thrombosis, general
Roxindole		112192-04-8				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
roxithromycin	Erythromycin, 9-[O-[(2-methoxyethoxy)methyl]oxime] [CAS]	80214-83-1 80214-86-4	EP	33255	Macrolide antibiotic	Infection, general
RPR-109881A	Benzenepropanoic acid, ß-(((1,1-dimethylethoxy)carbonyl)amino)-Alpha-hydroxy-(1S,2S,4S,7R,8aR,9aS,10aR,12aS,12bR)-7,12a-bis(acetyloxy)-1-(benzoyloxy)-1,3,47,8,9,9a,10,10a,12,12a,12b-dodecahydro-2-hydroxy-5,13,13-trimethyl-8-oxo-2,6-methano-2H-cyclodeca(3,4) cyclopropa (4,5) benz (1,2-b) oxet-4-yl ester, dihydrate Alpha R, betaS [CAS]	192573-38-9			Anticancer, other	Cancer, lung, general
RPR-130401	4,9-Ethano-3aH-benz[f]isoindole-3a-carboxylicacid, 1,2,3,4,9,9a-hexahydro-2-[2-(2-methoxyphenyl)-1-oxo-2-propenyl]-9-(4-methylphenyl)-, (3aR,4S,9S,9aR)-rel-[CAS]	210282-69-2	WO	9829390	Anticancer, other	Cancer, general
R-roscovitine			US	6316456	Anticancer, other	Cancer, lung, non-small cell
RS-0406	N'N'-bis(3-hydroxyphenyl)pyridazine-3,6-diamine				Neuroprotective	Alzheimer's disease
RSR-13		131179-95-8				
Rubijervine		79-58-3				
rubitecan	1H-Pyrano(3',4':6,7)indolizino(1,2-b)quinoline-3,14(4H,12H)-dione, 4-ethyl-4-hydroxy-10-nitro-, (S)- [CAS]	91421-42-0	US	6485514	Anticancer, other	Cancer, pancreatic
ruboxistaurin	9H,18H-5,21:12,17-Dimethenodibenzo(e,k)pyrrolo(3,4-h)(1,4,13)oxadiazacyclohexadecine-18,20(19H)-dione,9-((dimethylamino)methyl)-6,7,10,11-tetrahydro-, (S)- [CAS]	169939-94-0			Symptomatic antidiabetic	Retinopathy, diabetic
Rufinamide		106308-44-5				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
rufloxacin	7H-Pyrido[1,2,3-de]-1,4-benzothiazine-6-carboxylic acid, 9-fluoro-2,3-dihydro-10-(4-methyl-1-piperazinyl)-7-oxo- [CAS]	101363-10-4 102052-47-1 106017-08-7	EP	165375	Quinolone antibacterial	Infection, general
rupatadine	5H-Benzo[5,6]cyclohepta[1,2-b]pyridine, 8-chloro-6,11-dihydro-11-[1-[(5-methyl-3-pyridinyl)methyl]-4-piperidinylidene]-, trihydrochloride- [CAS]	156611-76-6	EP	0577957	Antiallergic, non-asthma	Rhinitis, allergic, seasonal
Rutin		153-18-4				
RWJ-54428	5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[[(2Z)-(2-amino-5-chloro-4-thiazolyl)(hydroxyimino)acetyl]amino]-3-[(3-[[(2-aminoethyl)thio]methyl]-4-pyridinyl]thio]-8-oxo-, (6R,7R)- [CAS]	189448-35-9	WO	9713772	Cephalosporin, injectable	Infection, beta-lactamase resistant
S-0139	Olean-12-en-28-oic acid, 27-[[3-[5-hydroxy-2-[(4-methoxy-1,4-dioxo-2-butenyl)amino]phenyl]-1-oxo-2-propenyl]oxy]-3-oxo- [CAS]	193969-54-9	WO	9727314	Cardiovascular	Ischaemia, cerebral
S-15535	Piperazine, 1-(2,3-dihydro-1,4-benzodioxin-5-yl)-4-(2,3-dihydro-1H-inden-2-yl)- [CAS]	146998-34-7			Cognition enhancer	Cognitive disorder, general
S-18886	1-Napthalenepropanoic acid, 6-(((4-chlorophenyl)sulfonyl)amino)-5,6,7,8-tetrahydro-2-methyl [CAS]	165537-73-5			Antithrombotic	Thrombosis, general
S-34730	7-chloro-6-sulfamoyl-2-(1H)-quinoleinone-3-phosphonic acid				Neuroprotective	Unspecified
S-3578	7ß-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2(Z)-ethoxyiminoacetamido]-3-(1-(N-methylaminopropyl)-1H-imidazo[4,5-b]pyridinium-4-methyl-3-cephem-4-carboxylate monosulfate				Cephalosporin, injectable	Infection, general

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
S-36496	2-{N-[4-(4-Chlorophenylsulfonylamino)butyl]-N-{3-[(4-isopropylthiazol-2-yl)methyloxy]benzyl}sulfamoyl}benzoic acid				Antiasthma	Asthma
S-36527	2-{N-[4-(4-Chlorophenylsulfonylamino)butyl]-N-{3-[2-(4-cyclobutylthiazol-2-yl)ethyl]benzyl}sulfamoyl}benzoic acid				Antiasthma	Asthma
S-5751	(1R,2R,3S,5S)-7-[2-(5-Hydroxybenzothiophen-3-ylcarboxamido)-6,6-dimethylbicyclo[3.1.1]hept-3yl]-5(Z)-heptenoic acid				Antiallergic, non-asthma	Allergy, general
S-8510	Imidazo[4,5-d]pyrano[4,3-b]pyridine, 1,6,7,9-tetrahydro-2-(3-isoxazolyl)-, phosphate (1:1) [CAS]	151466-23-8	EP	556008	Cognition enhancer	Alzheimer's disease
S-8921	2-Naphthalenecarboxylic acid, 1-(3,4-dimethoxyphenyl)-3-(3-ethyl-1-oxopentyl)-4-hydroxy-6,7,8-trimethoxy-, methyl ester [CAS]	151165-96-7	WO	9308155	Hypolipaemic/Antiatherosclerosis	Hypercholesterolaemia
Sabcomeline		159912-53-5				
Sabeluzole		104383-17-7				
S-Adenosylmethionine		29908-03-0				
safinamide	(S)-(+)-2-[4-(3-fluorobenzyloxy)benzylamino]propanamide methansulfonate	133865-89-1	AU	711309	Antiepileptic	Epilepsy, general
Salacetamide		487-48-9				
Salazosulfadimidine		2315-8-4				
salbutamol	1,3-Benzenedimethanol,Alpha1-[[(1,1-dimethylethyl)amino]methyl]-4-hydroxy- [CAS]	18559-94-9	EP	451745	Formulation, inhalable, topical, dry powder	Asthma
Salicin		138-52-3				
Salicyl Alcohol		90-01-7				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Salicylamide		65-45-2				
Salicylamide O-Acetic Acid		25395-22-6				
Salicylanilide		87-17-2				
Salicylic Acid		69-72-7				
Salicylsulfuric Acid		89-45-2				
Salinazid		495-84-1				
salmeterol	1,3-Benzenedimethanol, 4-hydroxy-Alpha1-[[[6-(4-phenylbutoxy)hexyl]amino]methyl]-, (±)- 1-hydroxy-2-naphthalenecarboxylate [CAS]	89365-50-4 94749-08-3	WO	9006775	Antiasthma	Asthma
Salsalate		552-94-3				
Salverine		6376-26-7				
Samarium ^{153}Sm Lexidronam		154427-83-5				
sampatrilat	L-Tyrosine, N2-(methylsulfonyl)-L-lysyl-1-[(2S)-3-amino-2-carboxypropyl]cyclopentanecarbonyl- [CAS]	129981-36-8	EP	358398	Antihypertensive, renin system	Hypertension, general
Sancycline		808-26-4				
Saperconazole		110588-57-3				
sapropterin	4(1H)-Pteridinone, 2-amino-6-(1,2-dihydroxypropyl)-5,6,7,8-tetrahydro-, dihydrochloride, [6R-[6R*(1R*,2S*)]]- [CAS]	69056-38-8 62989-33-7	EP	191335	Antidepressant	Hyperphenylalaninaemia
saquinavir	Butanediamide, N1-[3-[3-[[(1,1-dimethylethyl)amino]carbonyl]octahydro-2(1H)-isoquinolinyl]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(2-quinolinylcarbonyl)amino]-, [3S-[2[1R*(R*),2S*],3Alpha,4aß,8aß]]- [CAS]	127779-20-8	EP	432695	Antiviral, anti-HIV	Infection, HIV/AIDS
Saralasin		34273-10-4				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
saredutant	Benzamide, N-[4-[4-(acetylamino)-4-phenyl-1-piperidinyl]-2-(3,4-dichlorophenyl)butyl]-N-methyl-, (S)- [CAS]	142001-63-6	EP	474561	Antiasthma	Asthma
sarizotan	3-Pyridinemethanamine, N-((3,4-dihydro-2H-1-benzopyran-2-yl)methyl)-5-(4-fluorophenyl)- [CAS]	177975-08-5			Antiparkinsonian	Parkinson's disease
sarpogrelate	Butanedioic acid, mono[2-(dimethylamino)-1-[[2-[2-(3-methoxyphenyl)ethyl]phenoxy]methyl]ethyl] ester [CAS]	125926-17-2	EP	398326	Antithrombotic	
Satigrel		111753-73-2				
satraplatin	Platinum, bis(acetato-O)amminedichloro(cyclohexanamine)-, (OC-6-43)- [CAS]	129580-63-8	EP	328274	Anticancer, alkylating	Cancer, prostate
Satumomab		144058-40-2				
SB-237376	N-[3-[[2-(3,4-dimethoxyphenyl)ethyl]amino]propyl]-4-nitrobenzamide, HCl				Antiarrhythmic	Fibrillation, atrial
SB-238039	(5(-2-phenylamino-4-pyrimidinyl)-4-)(4-fluorophenyl)-1-(4-piperidinyl)imidazole				Anticancer, other	Cancer, general
SB-277011	trans-N-[4-[2-(6-Cyano-1,2,3,4-tetrahydroisoquinolin-2-yl)ethyl]cyclohexyl]-4-quinolinecarboxamide				Neuroleptic	Schizophrenia
Scarlet Red		85-83-6				
SCH-00013	Benzonitrile, 4-[2-[3,6-dihydro-4-(1,4,5,6-tetrahydro-6-oxo-3-pyridazinyl)-1(2H)-pyridinyl]-1-hydroxyethyl]- [CAS]	217963-18-3	EP	618204	Cardiostimulant	Heart failure
Sch-23863	(2-[10,11-Dihydro-5-ethoxy-5H-dibenzo [a,d] cyclohepten-S-yl]-N, N-dimethyl-ethanamine				Immunosuppressant	Inflammation, general

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Sch-57790	1-Piperazineacetonitrile, 4-cyclohexyl-alpha-[4-[(S)-(4-methoxyphenyl)sulfinyl]phenyl]- [CAS]	221660-80-6			Cognition enhancer	Alzheimer's disease
Sch-63390	7H-Pyrazolo[4,3-e][1,2,4]triazolo[1,5-c]pyrimidin-5-amine, 2-(2-furanyl)-7-(3-phenylpropyl)- [CAS]	174648-45-4			Antiparkinsonian	Parkinson's disease
Scillarenin		465-22-5				
Scopolamine		51-34-3				
Scopolamine N-Oxide		97-75-6				
scopolamine	Benzeneacetic acid, Alpha-(hydroxymethyl)-, 9-methyl-3-oxa-9-azatricyclo[3.3.1.02,4]non-7-yl ester, [7(S)-(1Alpha,2ß,4ß,5Alpha,7ß)]- [CAS]	51-34-3	US	4262003	Formulation, transdermal, other	Nausea and vomiting, general
SCS technology			US	6046188	Antiasthma	Unspecified
secalciferol	9,10-Secocholesta-5,7,10(19)-triene-3,24,25-triol, (3ß,5Z,7E,24R)- [CAS]	55721-11-4	EP	301167	Osteoporosis treatment	Osteodystrophy
secnidazole	1H-Imidazole-1-ethanol, Alpha,2-dimethyl-5-nitro- [CAS]	3366-95-8	FR	M3270	Protozoacide	Infection, trichomoniasis
Secobarbital		309-43-3				
selegiline	Benzeneethanamine, N,Alpha-dimethyl-N-2-propynyl-, (R)- [CAS]	14611-51-9	GB	1153578	Antiparkinsonian	
Selenomethionine		1464-42-2				
Sematilide		101526-83-4				
Semotiadil		116476-13-2				
seocalcitol	1,3-Cyclohexanediol, 5-((1-(6-ethyl-6-hydroxy-1-methyl-2,4-octadienyl)octahydro-7a-methyl-4H-inden-4-ylidene)ethylidene)-4-methylene-, (1R-(1Alpha(1R*,2E,4E),3aß,4E(1R*,3S*,5Z),7aAlpha))- [CAS]	134404-52-7	WO	9100855	Anticancer, other	Cancer, liver
Sepimostat		103926-64-3				
seratrodast	Benzeneheptanoic acid, zeta-(2,4,5-trimethyl-3,6-dioxo-1,4-cyclohexadien-1-yl)-, (+/-)- [CAS]	103187-07-1 112665-43-7	EP	232089	Antiasthma	Asthma

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
sertaconazole	1H-Imidazole, 1-[2-[(7-chlorobenzo[b]thien-3-yl)methoxy]-2-(2,4-dichlorophenyl)ethyl]- [CAS]	99592-32-2	EP	151477	Antifungal	Infection, dermatological
sertindole	2-Imidazolidinone, 1-[2-[4-[5-chloro-1-(4-fluorophenyl)-1H-indol-3-yl]-1-piperidinyl]ethyl]- [CAS]	106516-24-9	EP	392959	Neuroleptic	Schizophrenia
sertraline	1-Naphthalenamine, 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-, (1S-cis)- [CAS]	79559-97-0 79617-96-2 79617-97-3	EP	30081	Antidepressant	Depression, general
Setastine		64294-95-7				
sevelamer	2-Propen-1-amine polymer with (chloromethyl)oxirane, hydrochloride [CAS]	152751-57-0 52757-95-6	US	5496545	Urological	Renal failure
sevofturane	Propane, 1,1,1,3,3,3-hexafluoro-2-(fluoromethoxy)- [CAS]	28523-86-6	DE	1954268	Anaesthetic, inhalation	Anaesthesia
SG-210	2H-1,4-Benzothiazine-2-acetic acid, 3,4-dihydro-3-oxo-4-((4,5,7-trifluro-2-benzothiazolyl)methyl)- [CAS]	143162-65-6			Symptomatic antidiabetic	Neuropathy, diabetic
sibutramine	Cyclobutanemethanamine, 1-(4-chlorophenyl)-N,N-dimethyl-Alpha-(2-methylpropyl)- [CAS]	106650-56-0 84485-00-7	GB	2098602	Anorectic/Antiobesity	Obesity
siccanin	(4aS-(4aAlpha,6aAlpha,11bAlpha,13aR*,13bAlpha))-1,2,3,4,4a,5,6a,11b,13b-decahydro-4,4,6a,9-tetramethyl-13H-benzo[a]furo[2,3,4-mn]xanthen-11-ol	22733-60-4	JP	37003548	Antifungal	
sildenafil	Piperazine, 1-((3-(4,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo(4,3-d)pyrimidin-5-yl)-4-ethoxyphenyl)sulfonyl)-4-methyl, 2-hydroxy-1,2,3-propanetricarboxylate- (1:1) [CAS]	171599-83-0 139755-83-2	WO	9428902	Male sexual dysfunction	Impotence
silodosin	1H-Indole-7-carboxamide, 2,3-dihydro-1-(3-hydroxypropyl)-5-[(2R)-2-[[2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethyl]amino]propyl]- [CAS]	160970-54-7	EP	600675	Urological	Dysuria
Silver Lactate		128-00-7				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Silver Picrate		146-84-9				
silver sulfadiazine	N'-2-pyrimidinylsulfanilamide monosilver salt	22199-08-2 68-35-9			Anti-infective, other	Infection, general
Simetride		154-82-5				
Simfibrate		14929-11-4				
simvastatin	Butanoic acid, 2,2-dimethyl-, 1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1Alpha,3Alpha,7ß,8ß(2S*,4S*),8aß]]- [CAS]	79902-63-9	US	4444784	Hypolipaemic/Antiatherosclerosis	Hyperlipidaemia, general
Sincalide		25126-32-3				
Sintropium Bromide		79467-19-9				
Sisomicin		32385-11-8				
sitafloxacin	3-Quinolinecarboxylic acid, 7-(7-amino-5-azaspiro[2.4]hept-5-yl)-8-chloro-6-fluoro-1-(2-fluorocyclopropyl)-1,4-dihydro-4-oxo-, [1R-[1Alpha(S*),2Alpha]]-, hydrate	127254-12-0	EP	341493	Quinolone antibacterial	Infection, general
sitamaquine	1,6-Hexanediamine, N,N-diethyl-N'-(6-methoxy-4-methyl-8-quinolinyl)- [CAS]	5330-29-0 57695-04-2			Protozoacide	Infection, leishmaniasis
sitaxsentan	N-(4-Chloro-3-methyl-5-isoxazolyl)-2-[[4,5-(methylenedioxy)-o-toly]acetyl]-3-thiophenesulfonamide	184036-34-8	US	5464853	Antihypertensive, other	Hypertension, pulmonary
sivelestat	Glycine, N-[2-[[[4-(2,2-dimethyl-1-oxopropoxy)phenyl]sulfonyl]amino]benzoyl]- [CAS]	127373-66-4	EP	347168	Respiratory	Systemic inflammatory response syndrome
SJA-6017	Butanamide, 2-[[(4-fluorophenyl)sulfonyl]amino]-N-[(1S)-1-formyl-3-methylbutyl.).-3-methyl-, (2S)- [CAS]	190274-53-4	EP	771565	Ophthalmological	Cataract
SL-65-1498	6-Fluoro-9-methyl-2-phenyl-4-pyrrolidin-1-ylcarbonyl)-2,9-dihydro-1H-pyrido[3,4-b]indole-1-one		EP	607076	Anxiolytic	Anxiety, general

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference	Example of Therapeutic Use	Example of Indication
SLV-306	(3S,2'R)-3-[1-[2'-(Ethoxycarbonyl)-4'-phenyl-butyl-]-cyclopentan-1-carbonylamino]-2,3,4,5-tetra-hydro-2-oxo-1H-benzapin-1-acetic acid			Antihypertensive, diuretic	Hypertension, general
SLV-308	2(3H)-Benzoxazolone, 7-(4-methyl-1-piperazinyl)-, monohydrochloride	269718-83-4		Antiparkinsonian	Parkinson's disease
Sm153 lexidronam	Samarate(5-)-153Sm, (((1,2-ethanediylbis(nitrilobis(methylene)))tetrakis(phosphonato))(8-)-N,N',OP,OP',OP'',OP''')-, pentasodium, (OC-6-21)- [CAS]	160369-78-8		Analgesic, other	Pain, cancer
S-Methylmethionine		4727-40-6			
SMP-300	N-(Aminoiminomethyl)-11-chloro-5,6,7,8-tetrahydro-8-oxo-4H-pyrrolo[3,2,1-kl][1]benzazocine-2-carboxamide monomethanesulfonate monohydrate			Antianginal	Angina, general
SN-38	(4S)-4,7,11-triethyl-3,4,12,14-tetrahydro-4,10-dihydroxy-3,14-dioxo-1H-pyrano[3',4':6,7]indolizino[1,2-b]quindin-9-yl	100286-90-6		Formulation, optimized, liposomes	Cancer, colorectal
SNAP-7941	((+)-methyl (4S)-3-[[(3-{4-[3-(acetylamino)phenyl]-1-piperidinyl}propyl)amino] carbonyl]-4-(3,4-difluorophenyl)-6-(methoxymethyl)-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate hydrochloride)			Anxiolytic	Anxiety, general
SOA-132	2-Naphthalenecarboxamide, N-[2-[4-(diphenylmethoxy)-1-piperidinyl]ethyl]-3-hydroxy-5-(3-pyridinylmethoxy)- [CAS]	143964-80-1		Formulation, inhalable, topical	Asthma

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
soblidotin	L-valinamide, N,N-dimethyl-L-valyl-N-[2-methoxy-4-[2-[1-methoxy-2-methyl-3-oxo-3-[(2-phenylethyl)amino]propyl]-1-pyrrolidinyl]-1-(2-methylpropyl)-4-oxobutyl]-N-methyl-, [2S-[1[1R*(R*),2S*],2R*(1S*,2S*)]]- [CAS]	149606-27-9	WO	9303054	Anticancer, other	Cancer, lung, non-small cell
Sobrerol		498-71-5				
sobuzoxane	Carbonic acid, 1,2-ethanediylbis[(2,6-dioxo-4,1-piperazinediyl)methylene]bis(2-methylpropyl) ester [CAS]	98631-95-9	EP	140327	Anticancer, other	Cancer, lymphoma, T-cell
Sodium Arsanilate		127-85-5				
Sodium Arsphenamine		1936-28-3				
Sodium Chloride						
Sodium Dibunate		14992-59-7				
Sodium Folate		6484-89-5				
Sodium Formaldehydesulfoxylate		149-44-0				
Sodium Glycerophosphate		1334-74-3				
Sodium Hyaluronate						
Sodium Iodomethamate		519-26-6				
Sodium Nitrite		7632-00-0				
Sodium Nitroprusside		14402-89-2				
sodium oxybate	Butyric acid, 4-hydroxy monosodium salt [CAS]	502-85-2			Psychostimulant	Narcolepsy
Sodium Phenolsulfonate		1300-51-2				
sodium phenylbutyrate	Butyric acid, 4-phenyl-, sodium salt- [CAS]	1716-12-7			Formulation, other	Hyperammonaemia

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
sodium phosphate	Sodium phosphate monobasic monohydrate + sodium phosphate dibasic anhydrous		US	6162464	Formulation, oral, other	Surgery adjunct
sodium prasterone sulfate	3ß-hydroxy-5-androsten-17-one(sodium sulfate dihydrate)		EP	380036	Formulation, mucosal, topical	Labour, induction
Sodium Propionate		137-40-6				
sodium salicylate	Benzoic acid, 2-hydroxy-, monosodium salt [CAS]	54-21-7			Formulation, oral, solubility-enhanced	Pain, general
Sodium Tetradecyl Sulfate		139-88-8				
sofalcone	Acetic acid, [5-[(3-methyl-2-butenyl)oxy]-2-[3-[4-[(3-methyl-2-butenyl)oxy]phenyl]-1-oxo-2-propenyl]phenoxy]- [CAS]	64506-49-6	GB	1523241	Antiulcer	
Solasulfone		133-65-3				
solifenacin	Butanedioic acid compd with (1S)-(3R)-1-azabicyclo(2.2.2)oct-3-yl 3,4-dihydro-1-phenyl-2(1H)-isoquinolinecarboxylate (1:1) [CAS]	242478-38-2			Urological	Overactive bladder
Sorbinicate	D-Glucitol, hexa-3-pyridinecarboxylate [CAS]	6184-06-1	BE	883352	Hypolipaemic/Antiatherosclerosis	
Sorbitol		50-70-4				
Sorivudine		77181-69-2				
sotalol	Methanesulfonamide, N-[4-[1-hydroxy-2-[(1-methylethyl)amino]ethyl]phenyl]- [CAS]	3930-20-9 959-24-0			Antiarrhythmic	
Soterenol		13642-52-9				
Sozoiodolic Acid		554-71-2				
spaglumic acid	L-Glutamic acid, N-(N-acetyl-L-Alpha-aspartyl)- [CAS]	3106-85-2 80619-64-3			Formulation, mucosal, topical	Conjunctivitis
sparfloxacin	3-Quinolinecarboxylic acid, 5-amino-1-cyclopropyl-7-(3,5-dimethyl-1-piperazinyl)-6,8-difluoro-1,4-dihydro-4-oxo-, cis- [CAS]	110871-86-8	EP	221463	Quinolone antibacterial	Infection, respiratory tract, general
Sparteine		90-39-1				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
SPA-S-843	Candicin D, 18-decarboxy-40-demethyl-3,7-dideoxo-N3'-((dimethylamino)acetyl)-18-(((2-(dimethylamino)ethyl)amino)carbonyl)-3,7-dihydroxy-N47-methyl-5-oxo cyclic 15,19-hemiacetal, comp with L-ascorbic acid (1:2) [CAS]	202748-83-2	US	5298495	Antifungal	Infection, fungal, general
Spasmolytol		25333-96-4				
SPD-754	2(1H)-Pyrimidinone, 4-amino-1-(2-(hydroxymethyl)-1,3-oxathiolan-4-yl- (2R-cis)-	160707-69-7	US	6228860	Antiviral, anti-HIV	Infection, HIV/AIDS
Spectinomycin		1695-77-8				
SPI-339	4-[3-(4-Oxo-4,5,6,7-tetrahydroindol-yl)propionylamino]benzoic acid ethyl ester				Cognition enhancer	Alzheimer's disease
Spiperone		749-02-0				
spirapril	1,4-Dithia-7-azaspiro[4.4]nonane-8-carboxylic acid, 7-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-, [8S-[7[R*(R*)],8R*]]- [CAS]	83647-97-6	EP	50800	Antihypertensive, renin system	Hypertension, general
Spirogermanium		41992-23-8				
spironolactone	Pregn-4-ene-21-carboxylic acid, 7-(acetylthio)-17-hydroxy-3-oxo-,Gamma-lactone,(7Alpha,17Alpha)- [CAS]	52-01-7	EP	124147	Formulation, dermal, topical	Acne
SR-121463	Benzamide, N-(1,1-dimethylethyl)-4-[[cis-5'-ethoxy-4-[2-(4-morpholinyl)ethoxy]-2'-oxospiro[cyclohexane-1,3'-[3H]indol]-1'(2'H)-yl]sulfonyl]-3-methoxy- [CAS]	185913-78-4	WO	9715556	Cardiostimulant	Heart failure
SR-144190	Morpholine, 4-benzoyl-2-(3,4-difluorophenyl)-2-[2-[4-[[(dimethylamino)carbonyl]amino]-4-phenyl-1-piperidinyl]ethyl]-, (2R)- [CAS]	201152-86-5	WO	9623787	Anxiolytic	Anxiety, general

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
SR-146131	1H-Indole-1-acetic acid, 2-[[[4-(4-chloro-2,5-dimethoxyphenyl)-5-(2-cyclohexylethyl)-2-thiazolyl]amino]carbonyl]-5,7-dimethyl- [CAS]	221671-61-0	WO	9915525	Anorectic/Antiobesity	Obesity
SR-271425	N-[1-[2-(diethylamino)ethylamino]-7-methoxy-9-oxo-9H-thioxanthen-4-ylmethyl]formamide			–	Anticancer, alkylating	Cancer, general
SR-27897	1H-Indole-1-acetic acid, 2-[[[4-(2-chlorophenyl)-2-thiazolyl]amino]carbonyl]- [CAS]	136381-85-6	EP	432040	Anticancer, other	Cancer, pancreatic
SR-31747	Cyclohexanamine, N-(3-(3-chloro-4-cyclohexylphenyl)-2-propenyl)-N-ethyl-, hydrochloride, (Z)- [CAS]	132173-07-0	EP	376850	Anticancer, other	Cancer, myeloma
SR-58611	Acetic acid, [[(7S)-7-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]-5,6,7,8-tetrahydro-2-naphthalenyl]oxy]-, ethyl ester, hydrochloride [CAS]	121524-09-2	EP	303546	GI inflammatory/bowel disorders	Irritable bowel syndrome
SS732			US	5385900	Formulation, mucosal, topical	Infection, ocular
SS-750	(R)-(-)-2-(2,4-difluorophenyl)-1-(ethylsulfonyl)-1,1-difluoro-3-(1H-1,2,4-triazol-1-yl)-2-propanol		US	6083968	Antifungal	Infection, fungal, general
ß-alethine	Propanamide, N, N'(dithiodi-2,1-ethanediyl)bis(3-amino)- [CAS]	646-08-2			Anticancer, immunological	Cancer, myeloma
SSR-149415	(2S,4R)-1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxy-phenyl)-2-oxo-2,3-dihydro-1H-indol-3-yl]-4-hydroxy-N,N-dimethyl-2-pyrrolidine carboxamide		WO	0155130	Antidepressant	Depression, general
SSR-180575	2-(7-chloro-5-methyl-4-oxo-3-phenyl-4,5-dihydro-3H-pyridazino[4,5-6]indol-1-yl)-N,N-dimethylacetamide				Neuroprotective	Unspecified

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
SSR-181507	(3-Exo)-8-benzoyl-N-[[(2S)-7-chloro-2,3-dihydro-1,4-benzodioxin-2-yl]methyl]-8-azabicyclo[3.2.1]octane-3-methanamine HCl		US	6221879	Neuroleptic	Schizophrenia
SSR-591813	(5aS,8S,10aR)-5a,6,9,10-tetrahydro, 7H,11H-8,10a-methanopyrido[2',3':5,6]pyrano[2,3-d]azepine				Dependence treatment	Addiction, nicotine
SST-101	D-Glucitol, 1,4:3,6-dianhydro-, dinitrate [CAS]	87-33-2			Formulation, transdermal, other	Angina, general
SSY-726	(-)-(R)-3-Methyl-3-(methylsulfonyl)-1-(1,2,4-triazol-1-yl)-2-[4-(trifluoromethyl)phenyl]-2-butanol		US	5147886	Antifungal	Infection, fungal, general
ST-200	1-Propanaminium, 2-(acetyloxy)-3-carboxy-N,N,N-trimethyl-, chloride, (R)- [CAS]	5080-50-2	DE	3015635	Cognition enhancer	Dementia, senile, general
stachyflin			WO	9711947	Antiviral, other	Infection, influenza virus
Stallimycin		636-47-5				
Stampidine			US	6350736	Antiviral, anti-HIV	Infection, HIV/AIDS
Stannous Pyrophosphate		15578-26-4				
stannsoporfin	(OC-6-13)-Dihydrogen dichloro[7,12-diethyl-3,8,13,17-tetramethyl-21H,23H-porphine-2,18-dipropanoato(4-)-N21,N22,N23,N24]stannate(2-)	106344-20-1			Hepatoprotective	Hyperbilirubinaemia
Stanolone		521-18-6				
Stanozolol		10418-03-8 (2'*H* form); 302-96-5 (1'*H* form)				
Staph aureus ther			US	6376652	Genomics-based drug discovery	Infection, MRSA
STAT4 inhibitors			WO	9629341	Immunosuppressant	Unspecified

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
stavudine	Thymidine, 2',3'-didehydro-3'-deoxy- [CAS]	3056-17-5	EP	501511	Antiviral, anti-HIV	Infection, HIV/AIDS
Stenbolone		5197-58-0				
stepronin	Glycine, N-[1-oxo-2-[(2-thienylcarbonyl)thio]propyl]- [CAS]	72324-18-6	US	4242354	Antitussive	Cough
Stibocaptate		27279-76-1				
Stibophen		15489-16-4				
Stilbamidine		122-06-5				
stiripentol	1-Penten-3-ol, 1-(1,3-benzodioxol-5-yl)-4,4-dimethyl- [CAS]	49763-96-4			Antiepileptic	Epilepsy, general
Streptodornase		37340-82-2				
Streptomycin		57-92-1				
Streptonicozid		5667-71-0				
Streptonigrin		3930-19-6				
Streptozocin		18883-66-4				
strontium ranelate	3-Thiopheneacetic acid, 5-[bis(carboxymethyl)amino]-2-carboxy-4-cyano-, strontium salt (1:2)- [CAS]	135459-87-9	EP	415850	Osteoporosis treatment	Osteoporosis
strontium-89 chloride	Strontium chloride (89SrCl2) [CAS]	38270-90-5			Analgesic, other	Pain, cancer
Succimer		304-55-2				
Succinimide		123-56-8				
Succinylcholine		55-94-7				
Succinylcholine		71-27-2				
Succinylsulfathiazole		116-43-8				
Succisulfone		5934-14-5				
Suclofenide		30279-49-3				
sucralfate	Aluminium, hexadeca-μ-hydroxytetracosahydroxy(μ8-(1,3,4,6-tetra-O-sulfo-ß-D-fructofuranosyl-Alpha-D-glucopyranoside tetrakis(hydrogen sulfato)(8-)))hexadeca- [CAS]	54182-58-0	JP	58208233	Antiulcer, Formulation, oral, other	Ulcer, general
sufentanil	Propanamide, N-[4-(methoxymethyl)-1-[2-(2-thienyl)ethyl]-4-piperidinyl]-N-phenyl- [CAS]	56030-54-7	US	3998834	Analgesic, other, formulation implant	Pain, general

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
sulbactam	4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-, 4,4-dioxide, (2S-cis)- [CAS]	68373-14-8	GB	2000138	Antibiotic, other	Infection, general
sulbactam + ampicillin		117060-71-6	US	4234579	Antibiotic, other	Infection, general
sulbenicillin	4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylsulfoacetyl)amino]-, [2S-[2Alpha,5Alpha,6ß(S*)]]- [CAS]	28002-18-8 41744-40-5	GB	1289358	Penicillin, injectable	Infection, pseudomonal
Sulbentine		350-12-9				
sulbutiamine	Propanoic acid, 2-methyl-, dithiobis[3-[1-[[(4-amino-2-methyl-5-pyrimidinyl)methyl]formylamino]ethylidene]-3,1-propanediyl] ester [CAS]	3286-46-2 67-16-3			Neurological	Unspecified
sulconazole	1H-Imidazole, 1-[2-[[(4-chlorophenyl)methyl]thio]-2-(2,4-dichlorophenyl)ethyl]-, (+/-)- [CAS]	61318-90-9 61318-91-0	US	4055652	Antifungal	Infection, fungal, general
Sulesomab		167747-19-5				
Sulfabenzamide		127-71-9				
Sulfacetamide		144-80-9				
Sulfachlorpyridazine		80-32-0				
Sulfachrysoidine		485-41-6				
Sulfacytine		17784-12-2				
Sulfadiazine		68-35-9				
Sulfadicramide		115-68-4				
Sulfadimethoxine		122-11-2				
Sulfadoxine		2447-57-6				
Sulfaethidole		94-19-9				
Sulfaguanidine		57-67-0				
Sulfaguanole		27031-08-9				
Sulfalene		152-47-6				
Sulfaloxic Acid		14376-16-0				
Sulfamerazine		127-79-7				
Sulfameter		651-06-9				
Sulfamethazine		57-68-1				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference	Example of Therapeutic Use	Example of Indication
Sulfamethizole		144-82-1			
Sulfamethomidine		3772-76-7			
Sulfamethoxazole		723-46-6			
Sulfamethoxypyridazine		80-35-3			
Sulfametrole		32909-92-5			
Sulfamidochrysoidine		103-12-8			
Sulfamoxole		729-99-7			
Sulfanilamide		63-74-1			
Sulfanilic Acid		121-57-3			
Sulfanilylurea		547-44-4			
Sulfaperine		599-88-2			
Sulfaphenazole		526-08-9			
Sulfaproxyline		116-42-7			
Sulfapyrazine		116-44-9			
Sulfapyridine		144-83-2			
Sulfarside		1134-98-1			
Sulfarsphenamine		618-82-6			
sulfasalazine	Benzoic acid, 2-hydroxy-5-[[4-[(2-pyridinylamino)sulfonyl]phenyl]azo]- [CAS]	599-79-1		Formulation, oral, enteric-coated	Arthritis, rheumatoid
Sulfasomizole		632-00-8			
Sulfasymazine		1984-94-7			
Sulfathiazole		72-14-0			
Sulfathiourea		515-49-1			
Sulfinalol		66264-77-5			
Sulfinpyrazone		57-96-5			
Sulfiram		95-05-6			
Sulfisomidine		515-64-0			
Sulfisoxazole		127-69-5			
Sulfobromophthalein		71-67-0			
Sulfonethylmethane		76-20-0			

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Sulfoniazide		3691-81-4				
Sulfonmethane		115-24-2				
Sulforidazine		14759-06-9				
Sulfoxone		144-75-2				
sulindac	cis-5-fluoro-2-methyl-1-[(p-methylsulfinyl)benzylidene]indene-3-acetic acid	38194-50-2	US	3725548	Anti-inflammatory	Inflammation, general
Sulisatin		54935-03-4				
Sulisobenzone		4065-45-6				
Sulmarin		29334-07-4				
Sulmazole		73384-60-8				
Suloctidil		54063-56-8				
Sulphan Blue		129-17-9				
sulpiride	Benzamide, 5-(aminosulfonyl)-N-[(1-ethyl-2-pyrrolidinyl)methyl]-2-methoxy-[CAS]	15676-16-1			Alimentary/Metabolic, other	
sulprostone	5-Heptenamide, 7-[3-hydroxy-2-(3-hydroxy-4-phenoxy-1-butenyl)-5-oxocyclopentyl]-N-(methylsulfonyl)-, [1R-[1Alpha(Z),2ß(1E,3R*),3Alpha]]- [CAS]	60325-46-4	US	4024179	Prostaglandin	Abortion
sultamicillin	4-Thia-1-azabicyclo(3.2.0)heptane-2-carboxylic acid, 6-((aminophenylacetyl)amino)-3,3-dimethyl-7-oxo-, (((3,3-dimethyl-7-oxo-4-thia-1-azabicyclo(3.2.0)hept-2-yl)carbonyl)oxy)methyl ester, S, S-dioxide, (2S-(2.alpha.(2R*,5S*),5,alpha.,6.beta.(S*)))- [CAS]	117060-71-6 76497-13-7	GB	2044255	Penicillin, oral	Infection, general
Sulthiame		61-56-3				
sultopride	Benzamide, N-[(1-ethyl-2-pyrrolidinyl)methyl]-5-(ethylsulfonyl)-2-methoxy-[CAS]	53583-79-2	FR	M5916	Neuroleptic	Psychosis, general
Sultosilic Acid		57775-26-5				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
sumanirole	4H-Imidazo[4,5,1-ij]quinolin-2(1H)-one, 5,6-dihydro-5-(methylamino)-, (5R)-, (2Z)-2-butenedioate (1:1) [CAS]	179386-44-8	WO	9514020	Antiparkinsonian	Parkinson's disease
sumatriptan	1H-Indole-5-methanesulfonamide, 3-[2-(dimethylamino)ethyl]-N-methyl-, butanedioate (1:1)- [CAS]	103628-46-2 103628-48-4	EP	147107	Antimigraine	Migraine
SUN-N8075	1-(4-amino-2,3,5-trimethylphenoxy)-3-{4-[4-(4-fluorobenzyl)phenyl]piperazin-1-yl}propan-2(s)-ol dimethanesulfonate				Neuroprotective	Infarction, cerebral
suplatast	Sulfonium, [3-[[4-(3-ethoxy-2-hydroxypropoxy)phenyl]amino]-3-oxopropyl]dimethyl-, [CAS]	94055-76-2	JP	59167564	Antiasthma	Asthma
Suprofen		40828-46-4				
Suramin		129-46-4				
surfactant TA	Beractant [CAS]	108778-82-1	WO	9117766	Lung Surfactant	Respiratory distress syndrome, general
Suriclone		53813-83-5				
Suxibuzone		27470-51-5				
SYM-1010			US	5830998	Antiepileptic	Epilepsy, general
SYM-2081	L-Glutamic acid, 4-methyl-, (4R)- [CAS]	31137-74-3			Analgesic, other	Pain, general
SYM-2207	4-(Aminophenyl)-1-methyl-6,7-(methylenedioxy)-N-butyl-1,2-dihydrophthalazine-2-carboxamide				Neuroprotective	Ischaemia, cerebral
Symclosene		87-90-1				
Syn-1253	1-cyclopropyl-6-fluoro-8-methoxy-7-[3-(4-methyl-1,2,3-triazol-1-yl)pyrrolidin-1-yl]-4-oxo-1,4-dihydroquinoline 3-carboxylic acid				Quinolone antibacterial	Infection, peritoneum
Syn-2190	1-Azetidinesulfonic acid, 3-[[(2E)-[[(1,4-dihydro-1,5-dihydroxy-4-oxo-2-pyridinyl)methoxy]imino]-2-thienylacetyl]amino]-2-methyl-4-oxo, (2S,3S)- [CAS]	214963-75-4	WO	9847895	Antibacterial, other	Infection, general

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Syn-2869	3H-1,2,4-Triazol-3-one, 4-(4-(4-((1R,2R)-2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl)-1-piperazinyl)phenyl)-2,4-dihydro-2((4-(trifluoromethoxy)phenyl)methyl)- [CAS]	210562-98-4	US	6153616	Antifungal	Infection, Aspergillus
Synephrine		94-07-5				
Syrosingopine		84-36-6				
T-1095	1-Propanone, 3-(5-benzofuranyl)-1-(2-hydroxy-6-((6-O-methoxycarbonyl)-ß-D-glucopyranosyl)oxy)-4-methylphenyl- [CAS]	209746-59-8	EP	850948	Antidiabetic	Diabetes, general
T-1249	L-Phenylalaninamide, N-acetyl-L-tryptophyl-L-glutaminyl-L-Alpha-glutamyl-L-tryptophyl-L-Alpha-glutamyl-L-glutaminyl-L-lysyl-L-isoleucyl-L-threonyl-L-alanyl-L-leucyl-L-leucyl-L-Alpha-glutamyl-L-glutaminyl-L-alanyl-L-glutaminyl-L-isoleucyl-L-glutaminyl-L-glutaminyl-L-Alpha-glutamyl-L-lysyl-L-Alpha-glutamyl-asparaginyl-L-tyrosyl-L-Alpha-glutamyl-L-leucyl-L-glutaminyl-L-lysyl-L-leucyl-L-Alpha-aspartyl-L-lysyl-l-trytophyl-L-ananyl-L-seryl-L-leucyl-L-trytophyl-L-Alpha-glutamyl-L-tryptophyl- [CAS]	251562-00-2	WO	9959615	Antiviral, anti-HIV	Infection, HIV/AIDS
T-3912	1-cyclopropyl-8-methyl-7-[5-methyl-6-(methylamino)-3-pyridinyl]-4-oxo-1,4-dihydro-3-quinolinecarboxylic acid				Quinolone antibacterial	Infection, dermatological
T-588	Benzo(b)thiophene-5-methanol, Alpha-((2-(diethylamino)ethoxy)methyl)-, hydrochloride, (R)- [CAS]	142935-03-3	EP	565965	Cognition enhancer	Alzheimer's disease
T-67	Benzenesulfonamide, 2,3,4,5,6-pentafluoro-N-(3-fluoro-4-methoxyphenyl)- [CAS]	195533-53-0			Anticancer, other	Cancer, liver
T-82			US	5190951	Cognition enhancer	Alzheimer's disease

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
TA-2005	2(1H)-Quinolinone, 8-hydroxy-5-[1-hydroxy-2-[[2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]-, monohydrochloride, [R-(R*,R*)]- [CAS]	137888-11-0	US	4579854	Antiasthma	Asthma
TA-2005	2(1H)-Quinolinone, 8-hydroxy-5-[1-hydroxy-2-[[2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]-, monohydrochloride, [R-(R*,R*)]- [CAS]		WO	189480	Formulation, inhalable, solution	Asthma
TA-993	1,5-Benzothiazepin-4(5H)-one, 3-(acetyloxy)-5-[2-(dimethylamino)ethyl]-2,3-dihydro-8-methyl-2-(4-methylphenyl)-, (2R,3R)-rel-(-)-, (2Z)-2-butenedioate [CAS]	122024-98-0	JP	01045376	Antithrombotic	Peripheral vascular disease
tabimorelin	(R)-Alpha-[(E)-5-Amino-N,5-dimethyl-2-hexenamido]-N-methyl-N-[(R)-Alpha-(methylcarbamoyl)phenethyl]-2-napthalenepropionamide	170851-70-4 193079-69-5			Releasing hormones	Growth hormone deficiency
tacalcitol	9,10-Secocholesta-5,7,10(19)-triene-1,3,24-triol, (1Alpha,3ß,5Z,7E,24R)- [CAS]	57333-96-7 93129-94-3	EP	129003	Antipsoriasis	Keratosis
tacedinaline	Benzamide, 4-(acetylamino)-N-(2-aminophenyl)- [CAS]	112522-64-2	DE	3613571	Anticancer, other	Cancer, pancreatic
tacrine	9-Acridinamine, 1,2,3,4-tetrahydro- [CAS]	1684-40-8 321-64-2	EP	332147	Cognition enhancer	Alzheimer's disease
Tacrolimus		104987-11-3				
tadalafil	Pyrazino(1',2':1,6)pyrido(3,4-b)indole1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-, (6R-trans) [CAS]	171596-29-5	US	6143746	Male sexual dysfunction	Impotence
tafenoquine	1,4-Pentanediamine, N4-[2,6-dimethoxy-4-methyl-5-[3-(trifluoromethyl)phenoxy]-8-quinolinyl]- [CAS]	106635-80-7 106635-81-8 80065-55-0	US	4617394	Antimalarial	Infection, malaria
tafluposide		179067-42-6	WO	9612727	Anticancer, other	Cancer, general
TAK-375	(S)-N-[2-(1,6,7,8-Tetrahydro-2H-indeno-[5,4-b]furan-8-yl)]propionamide				Hypnotic/Sedative	Insomnia

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
TAK-427	2-[6-[[3-[4-(Diphenylmethoxy)-piperidino]imidazo[1,2-b]pyridazin-2-yl-2-methylpropionic acid dihydrate				Antipruritic/inflamm, allergic	Eczema, atopic
TAK-559	(E)-4-{4-[5-Methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyloxyimino}-4-phenylbutyric acid				Antidiabetic	Diabetes, general
Taka-Diastase		9001-19-8				
talampanel	7H-1,3-Dioxolo[4,5-h][2,3]benzodiazepine,7-acetyl-5-(4-aminophenyl)-8,9-dihydro-8-methyl-,(8R)- [CAS]	161832-65-1	US	5639751	Antiepileptic	Epilepsy, general
Talampicillin		47747-56-8				
talaporfin	N-[[(2S,3S)-18-Carboxy-2-(2-carboxy-ethyl)-13-ethyl-2,3-dihydro-3,7,12,17-tetramethyl-8-vinyl porphyrin-20-yl]acetyl]-L-aspartic acid	220201-34-3			Radio/chemosensitizer	Cancer, lung, general
Talastine		16188-61-7				
Talbutal		115-44-6				
Talinolol		57460-41-0				
talipexole	4H-Thiazolo[4,5-d]azepin-2-amine, 5,6,7,8-tetrahydro-6-(2-propenyl)- [CAS]	101626-70-4 36085-73-1	DE	3503963	Antiparkinsonian	Schizophrenia
talnetant	4-Quinolinecarboxamide, 3-hydroxy-2-phenyl-N-[(1S)-1-phenylpropyl]- [CAS]	174636-32-9	WO	9532948	GI inflammatory/bowel disorders	Irritable bowel syndrome
talniflumate	3-Pyridinecarboxylic acid, 2-[[3-(trifluoromethyl)phenyl]amino]-, 1,3-dihydro-3-oxo-1-isobenzofuranyl ester [CAS]	66898-62-2	BE	858864	Anti-inflammatory	Inflammation, ocular
taltirelin	L-Prolinamide, N-[(hexahydro-1-methyl-2,6-dioxo-4-pyrimidinyl)carbonyl]-L-histidyl-, (S)- [CAS]	103300-74-9	JP	61033197	Neurological	Dyskinesia, general
tamoxifen	Ethanamine, 2-[4-(1,2-diphenyl-1-butenyl)phenoxy]-N,N-dimethyl-, (Z)- [CAS]	10540-29-1	US	4536516	Anticancer, hormonal	

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
tamsulosin	Benzenesulfonamide, 5-[2-[[2-(2-ethoxyphenoxy)ethyl]amino]propyl]-2-methoxy-, (R)- [CAS]	106133-20-4 80223-99-0	EP	34432	Prostate disorders	Benign prostatic hyperplasia
tandospirone	4,7-Methano-1H-isoindole-1,3(2H)-dione, hexahydro-2-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]-, (3aAlpha,4ß,7ß,7aAlpha)-, 2-hydroxy-1,2,3-propanetricarboxylate (1:1) [CAS]	112457-95-1 87760-53-0	EP	82402	Anxiolytic	Anxiety, general
Tannoform		9010-29-1				
Taprostene		108945-35-3				
tariquidar	3-Quinolinecarboxamide, N-[2-[[[4-[2-(3,4-dihydro-6,7-dimethoxy-2(1H)-isoquinolinyl)ethyl]phenyl]amino]carbonyl]-4,5-dimethoxyphenyl]- [CAS]	206873-63-4	WO	9817648	Radio/chemosensitizer	Cancer, lung, non-small cell
TAS-103	6-[[2-(Dimethyl-amino)ethyl]amino]-3-hydroxy-7H-indeno[2,1-c]quinolin-7-one dihydrochloride	174634-09-4	WO	9532187	Anticancer, other	Cancer, lung, non-small cell
Tasosartan		145733-36-4				
Taurocholic Acid		81-24-3				
Taurolidine		19388-87-5				
tazanolast	Acetic acid, oxo[[3-(1H-tetrazol-5-yl)phenyl]amino]-, butyl ester [CAS]	82989-25-1	US	4778816	Antiasthma	
tazarotene	3-Pyridinecarboxylic acid, 6-[(3,4-dihydro-4,4-dimethyl-2H-1-benzothiopyran-6-yl)ethynyl]-, ethyl ester [CAS]	118292-40-3	EP	284288	Antipsoriasis	Psoriasis
Tazobactam		89786-04-9				
tazobactam + piperacillin			JP	58225091	Antibiotic, other	Infection, general
TBC-3711		374680-51-0			Cardiovascular	Heart failure
TCH-346	N-Methyl-N-propargyl-10-aminomethyl-dibenzo(b,f)oxepin				Neuroprotective	Amyotrophic lateral sclerosis
tebipenem	5-Hexenoic acid, 4-hydroxy-, polymer with 4-ethenyl-1H-imidazole [CAS]	82200-24-6			Beta-lactam antibiotic	Infection, streptococcal

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
tecadenoson	Adenosine, N-[(3R)-tetrahydro-3-furanyl]- [CAS]	204512-90-3	WO	9808855	Antiarrhythmic	Tachycardia, supraventricular
tecastemizole	1H-Benzimidazol-2-amine, 1-((4-fluorophenyl)methyl)-N-4-piperidinyl- [CAS]	75970-99-9	US	4219559	Antiallergic, non-asthma	Rhinitis, allergic, seasonal
Technetium ^{99m}Tc Bicisate		121281-41-2				
Technetium ^{99m}Tc Mertiatide		125224-05-7; 104348-91-6				
Technetium ^{99m}Tc Sestamibi		109581-73-9				
Technetium ^{99m}Tc Teboroxime		104716-22-5				
Teclothiazide		4267-5-4				
Teclozan		5560-78-1				
tedisamil	Spiro[cyclopentane-1,9'-[3,7]diazabicyclo[3.3.1]nonane], 3',7'-bis(cyclopropylmethyl)- [CAS]	90961-53-8	EP	102833	Antiarrhythmic	Fibrillation, atrial
Teflurane		124-72-1				
tegafur	2,4(1H,3H)-Pyrimidinedione, 5-fluoro-1-(tetrahydro-2-furanyl)- [CAS]	17902-23-7	GB	1168391	Anticancer, antimetabolite	Cancer, general
tegafur + uracil	2,4(1H,3H)-Pyrimidinedione, 5-fluoro-1-(tetrahydro-2-furanyl)-, mixt. with 2,4(1H,3H)-pyrimidinedione- [CAS]	74578-38-4	EP	224885	Anticancer, antimetabolite	Cancer, breast
tegaserod	Hydrazinecarboximidamide, 2-((5-methoxy-1H-indol-3-yl)methylene)-N-pentyl-, (Z)-2-butenedioate [CAS]	189188-57-6 145158-71-0			GI inflammatory/bowel disorders	Irritable bowel syndrome
Teicoplanin		61036-64-4				
telbivudine	ß-L-2'-deoxythymidine	3424-98-4			Antiviral, other	Infection, hepatitis-B virus
Telenzepine		80880-90-6				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
telithromycin	3-De((2,6-dideoxy-3-C-methyl-3-O-methyl-Alpha-L-ribo-hexopyranosyl)oxy)-11,12-dideoxy-6-O-methyl-3-oxo-12,11-(oxycarbonyl((4-(4-(3-pyridinyl)-1H-imidazol-1-yl)butyl)imino))- [CAS]	191114-48-4	EP	680967	Macrolide antibiotic	Infection, respiratory tract, general
telmesteine	3,4-Thiazolidinedicarboxylic acid, 3-ethyl ester, (R)- [CAS]	122946-43-4			COPD treatment	Bronchitis, chronic
telmisartan	(1,1'-Biphenyl)-2-carboxylic acid, 4'-((1,4-dimethyl-2'-propyl(2,6'-bi-1H-benzimidazol)-1'-yl)methyl)- [CAS]	144701-48-4	EP	502314	Antihypertensive, renin system	Hypertension, general
telomerase inhibs			WO	9941261	Anticancer, other	Cancer, general
temazepam	7-chloro-1,3-dihydro-3-hydroxy-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one	846-50-4	US	3197467	Hypnotic/Sedative	Insomnia
temiverine	Benzeneacetic acid, Alpha-cyclohexyl-Alpha-hydroxy-, 4-(diethylamino)-1,1-dimethyl-2-butynyl ester, [CAS]	129927-33-9	GB	2222828	Urological	Pollakisuria
temocapril	1,4-Thiazepine-4(5H)-acetic acid, 6-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]tetrahydro-5-oxo-2-(2-thienyl)-, [2S-[2Alpha,6ß(R*)]]- [CAS]	102090-90-4 110221-44-8 111902-57-9	US	4495188	Antihypertensive, renin system	Hypertension, general
Temocillin		66148-78-5				
temoporfin	Phenol, 3,3',3",3'"-(2,3-dihydro-21H,23H-porphine-5,10,15,20-tetrayl)tetrakis- [CAS]	122341-38-2	EP	337601	Radio/chemosensitizer	Cancer, head and neck
temozolomide	Imidazo[5,1-d]-1,2,3,5-tetrazine-8-carboxamide, 3,4-dihydro-3-methyl-4-oxo- [CAS]	85622-93-1	DE	3231255	Anticancer, alkylating	Cancer, brain, general
tenatoprazole	1H-Imidazo(4,5-b)pyridine, 5-methoxy-2-(((4-methoxy-3,5-dimethyl-2-pyridinyl)methyl)sulfinyl)- [CAS]	113712-98-4	US	4808596	Antiulcer	Ulcer, gastric
Tenecteplase		191588-94-0				
Tenidap		120210-48-2				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
teniposide	Furo[3',4':6,7]naphtho[2,3-d]-1,3-dioxol-6(5aH)-one, 5,8,8a,9-tetrahydro-5-(4-hydroxy-3,5-dimethoxyphenyl)-9-[[4,6-O-(2-thienylmethylene)-ß-D-glucopyranosyl]oxy]-, [5R-[5Alpha,5aß,8aAlpha,9ß(R*)]]- [CAS]	29767-20-2	US	3524844	Anticancer, other	Cancer, lymphoma, non-Hodgkin's
tenofovir	Phosphonic acid, (((1R)-2-(6-amino-9H-purin-9-yl)-1-methylethoxy)methyl)- [CAS]	147127-20-6			Antiviral, anti-HIV	Infection, HIV/AIDS
tenofovir disoproxil	2,4,6,8-tetraoxa-5-phosphanonanedioic acid, 5-(2-(6-amino-9H-purin-9-yl)-1-methylethoxymethyl) bis(1-methylethyl)ester, 5-oxide (R)-, (E)-2-butenedioate	202138-50-9			Antiviral, anti-HIV	Infection, HIV/AIDS
Tenonitrozole		3810-35-3				
tenoxicam	2H-Thieno[2,3-e]-1,2-thiazine-3-carboxamide, 4-hydroxy-2-methyl-N-2-pyridinyl-, 1,1-dioxide [CAS]	59804-37-4	GB	1519811	Antiarthritic, other	
Tenuazonic Acid		610-88-8				
teprenone	5,9,13,17-Nonadecatetraen-2-one, 6,10,14,18-tetramethyl- [CAS]	3796-63-2 6809-52-5			Antiulcer	
terazosin	Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[(tetrahydro-2-furanyl)carbonyl]- [CAS]	63074-08-8 63590-64-7 70024-40-7	US	4112097	Antihypertensive, adrenergic	Hypertension, general
terbinafine	1-Naphthalenemethanamine, N-(6,6-dimethyl-2-hepten-4-ynyl)-N-methyl-, (E)- [CAS]	78628-80-5 91161-71-6	EP	24587	Antifungal	Infection, dermatological
terbutaline	1,3-Benzenediol, 5-[2-[(1,1-dimethylethyl)amino]-1-hydroxyethyl]- [CAS]	23031-25-6			Formulation, mucosal, topical	Dysmenorrhoea
terconazole	Piperazine, 1-[4-[[2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-4-(1-methylethyl)-, cis- [CAS]	67915-31-5	US	4358449	Antifungal	Vaginitis

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
terfenadine	1-Piperidinebutanol, Alpha-[4-(1,1-dimethylethyl)phenyl]-4-(hydroxydiphenylmethyl)- [CAS]	50679-08-8	US	3878217	Antiallergic, non-asthma	
terguride	Urea, N,N-diethyl-N'-[(8Alpha)-6-methylergolin-8-yl]- [CAS]	37686-84-3	EP	159522	Antiprolactin	Hyperprolactinaemia
Terlipressin		14636-12-5				
Terodiline		15793-40-5				
Terofenamate		29098-15-5				
Terpin		80-53-5				
tertatolol	2-Propanol, 1-[(3,4-dihydro-2H-1-benzothiopyran-8-yl)oxy]-3-[(1,1-dimethylethyl)amino]-, hydrochloride, (+\-)- [CAS]	33580-30-2 83688-84-0 34784-64-0	GB	1308191	Antihypertensive, adrenergic	Hypertension, general
tert-Pentyl Alcohol		75-85-4				
tesaglitazar	(2S)-2-ethoxy-3-[4-[2-[4-[(methylsulfonyl)oxy]phenyl]ethoxy]phenyl] propanoic acid				Antidiabetic	Diabetes, Type II
tesmilifene	Ethanamine, N,N-Diethyl-2-(4-(phenylmethyl)phenoxy)- [CAS]	92981-78-7			Radio/chemosensitizer	Cancer, breast
Testolactone		968-93-4				
Testosterone	androst-4-en-3-one, 17-hydroxy-, (17ß) - [CAS]	58-22-0 5949-44-0			Formulation, transdermal, systemic	Hormone replacement therapy
tetrabamate		60763-47-5	DE	2748794	Anxiolytic	Addiction, alcohol
Tetrabarbital		76-23-3				
Tetrabenazine		58-46-8				
Tetracaine		136-47-0				
Tetrachloroethylene		127-18-4				
tetracine	Benzoic acid, 4-(butylamino)-, 2-(dimethylamino)ethyl ester [CAS]	94-24-6			Formulation, transdermal, systemic	Pain, general
tetracycline	2-Naphthacenecarboxamide, 4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-, [4S-(4Alpha,4aAlpha,5aAlpha,6ß,12aAlpha)]- [CAS]	60-54-8			Formulation, oral, other	Infection, oral

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Tetrahydrozoline		84-22-0				
Tetrandrine		518-34-3				
Tetrantoin		52094-70-9				
Tetrazepam		10379-14-3				
Tetrofosmin		127502-06-1				
tetroxoprim	2,4-Pyrimidinediamine, 5-[[3,5-dimethoxy-4-(2-methoxyethoxy)phenyl]methyl]-[CAS]	53808-87-0 74515-38-1	US	3992379	Trimethoprim and analogues	Infection, general
Tevenel®		4302-95-8				
tezacitabine	Cytidine, 2'-deoxy-2'-(fluoromethylene)-, (2E)- [CAS]	130306-02-4	US	5616702	Anticancer, antimetabolite	Cancer, colorectal
tezosentan	2-Pyridinesulfonamide, N-(6-(2-hydroxyethoxy)-5-(2-methoxyphenoxy)-2-(2-(1H-tetrazol-5-yl)-4-pyridinyl)-4-pyrimidinyl)-5-(1-methylethyl)- [CAS]	180384-57-0			Cardiostimulant	Oedema, general
thalidomide	1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-3-piperidinyl)- [CAS]	50-35-1			Dermatological	Infection, dermatological
Thenaldine		86-12-4				
Thenyldiamine		91-79-2				
Theobromine		83-67-0				
Theofibrate		54504-70-0				
theophylline	1H-Purine-2,6-dione, 3,7-dihydro-1,3-dimethyl- [CAS]	58-55-9 5967-84-0			Formulation, modified-release, other	Asthma
Thiabendazole		148-79-8				
Thiacetazone		104-06-3				
thiacymserine	Carbamic acid, [4-(1-methylethyl)phenyl]-, (3aS,8aS)-3,3a,8,8a-tetrahydro-3a,8-dimethyl-2H-thieno[2,3-b]indol-5-yl ester [CAS]	145209-51-4			Cognition enhancer	Alzheimer's disease
Thialbarbital		467-36-7				
Thiamine		59-43-8				
Thiamine		154-87-0				
Thiamine		67-16-3				
Thiamiprine		5581-52-2				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Thiamphenicol		15318-45-3				
Thiamylal		77-27-0				
Thiazesim		5845-26-1				
Thiazinamium		58-34-4				
Thiazolinobutazone		54749-86-9				
Thiazolsulfone		473-30-3				
Thibenzazoline		6028-35-9				
Thiethylperazine		1420-55-9				
Thimerfonate		5964-24-9				
Thimerosal		54-64-8				
Thiobarbital		77-32-7				
Thiobutabarbital		2095-57-0				
Thiocarbamizine		91-71-4				
Thiocarbarsone		120-02-5				
Thiocolchicine		2730-71-4				
Thiocresol		26445-03-4				
Thioctic Acid		62-46-4				
Thioglycerol		96-27-5				
Thioguanine		154-42-7				
Thioimreg	L-Thiotyrosinyl-glycinyl-glycine				Anticancer, immunological	Cancer, general
Thiopental		71-73-8				
Thiopropazate		84-06-0				
Thioproperazine		316-81-4				
Thioridazine		50-52-2				
Thiothixene		5591-45-7				
Thiovir	Thiophosphonoformic acid				Antiviral, anti-HIV	Infection, HIV/AIDS
Thiphenamil		82-99-5				
Thiram		137-26-8				
Thonzylamine		63-56-9				
Thozalinone		655-05-0				
Thromboplastin		9035-58-9				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Thurfyl Nicotinate		70-19-9				
thymectacin			US	6245750	Anticancer, other	Cancer, colorectal
Thymol		89-83-8				
Thymopentin		69558-55-0				
Thymyl N-Isoamylcarbamate		578-20-1				
Thyropropic Acid		51-26-3				
Thyroxine		51-48-9				
Tiadenol		6964-20-1				
tiagabine	3-Piperidinecarboxylic acid, 1-[4,4-bis(3-methyl-2-thienyl)-3-butenyl]-, (R)- [CAS]	115103-54-3	WO	8700171	Antiepileptic	Epilepsy, general
Tiamenidine		31428-61-2				
tianeptine	Heptanoic acid, 7-[(3-chloro-6,11-dihydro-6-methyldibenzo[c,f][1,2]thiazepin-11-yl)amino]-, S,S-dioxide [CAS]	72797-41-2 66981-73-5	GB	1269551	Antidepressant	Depression, general
tiapride	Benzamide, N-[2-(diethylamino)ethyl]-2-methoxy-5-(methylsulfonyl)- [CAS]	51012-32-9	GB	1394563	Neuroleptic	
tiaprofenic acid	2-Thiopheneacetic acid, 5-benzoyl-Alpha-methyl- [CAS]	33005-95-7	GB	1331505	Antiarthritic, other	
Tiaramide		32527-55-2				
tiazofurin	4-Thiazolecarboxamide, 2-ß-D-ribofuranosyl- [CAS]	60084-10-8	EP	54432	Anticancer, antimetabolite	Cancer, leukaemia, chronic myelogenous
Tibezonium		54663-47-7				
tibolone	19-Norpregn-5(10)-en-20-yn-3-one, 17-hydroxy-7-methyl-, (7Alpha,17Alpha)- [CAS]	5630-53-5	EP	389035	Menopausal disorders	Hormone replacement therapy
Ticarcillin		34787-01-4				
ticlopidine	Thieno[3,2-c]pyridine, 5-[(2-chlorophenyl)methyl]-4,5,6,7-tetrahydro- [CAS]	53885-35-1 55142-85-3	GB	1554424	Antithrombotic	
Ticrynafen		40180-04-9				
tiemonium	4-(3-hydroxy-3-phenyl-3-thien-2-yl-propyl)-4-methylmorpholinium	6252-92-2 144-12-7			Antispasmodic	

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
tigecycline	2-Naphthacenecarboxamide, 4,7-bis(dimethylamino)-9-[[[(1,1-dimethylethyl)amino]acetyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-, (4S,4aS,5aR,12aS)- [CAS]	220620-09-7	EP	582829	Tetracycline	Infection, general
Tigemonam		102507-71-1				
Tigloidine		495-83-0				
Tilidine		20380-58-9				
Tilisolol		85136-71-6				
tilmacoxib	Benzenesulfonamide, 4-(4-cyclohexyl-2-methyl-5-oxazolyl)-2-fluoro- [CAS]	180200-68-4	WO	9619463	Alimentary/Metabolic, other	Polyp
tiludronic acid	Phosphonic acid, [[(4-chlorophenyl)thio]methylene]bis- [CAS]	89987-06-4	EP	100718	Osteoporosis treatment	Paget's disease
Timentin		86482-18-0			Antibiotic, other	Infection, general
timepidium	Piperidinium, 3-(di-2-thienylmethylene)-5-methoxy-1,1-dimethyl-, [CAS]	35035-05-3	GB	1358446	Antispasmodic	
Timiperone		57648-21-2				
timolol	(-)-1-(t-butylamino)-3-[(4-morpholino-1,2,5-thiadiazol-3-yl)oxy]-2-propanolmaleate (1:1) salt	26839-75-8 26921-17-5	GB	1253709	Antihypertensive, adrenergic, antiglaucoma	
Timonacic		444-27-9				
Tin Ethyl Etiopurpurin		113471-15-1				
tinazoline	1H-Indole, 3-[(4,5-dihydro-1H-imidazol-2-yl)thio]- [CAS]	62882-99-9	US	3376311	Vasodilator, peripheral	
Tinidazole		19387-91-8				
Tinoridine		24237-54-5				
Tiocarlide		910-86-1				
Tioclomarol		22619-35-8				
tioconazole	1H-Imidazole, 1-[2-[(2-chloro-3-thienyl)methoxy]-2-(2,4-dichlorophenyl)ethyl]-[CAS]	61675-64-7 65899-73-2	US	4062966	Antifungal	Infection, fungal, general
tiopronin	Glycine, N-(2-mercapto-1-oxopropyl)- [CAS]	1953-02-2	US	3246025	Urological	Homocystinuria

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
tiotropium	3-Oxa-9-azoniatricyclo(3.3.1.02,4)nonane, 7-((hydroxydi-2-thienylacetyl)oxy)-9,9-dimethyl-, [CAS]	136310-93-5	EP	418716	COPD treatment	Chronic obstructive pulmonary disease
Tioxolone		4991-65-5				
Tipepidine		5169-78-8				
tipifarnib	2(1H)-Quinolone, 6-(amino(4-chlorophenyl)(1-methyl-1H-imidazol-5-yl)methyl)-4-(3-chlorophenyl)-1-methyl [CAS]	192185-68-5 192185-72-1	WO	9716443	Anticancer, other	Cancer, breast
tipranavir	N-[3-[1(R)-[4-Hydroxy-2-oxo-6(R)-(2-phenylethyl)-6-propyl-5,6-dihydro-2H-pyran-3-yl]propyl]phenyl]-5-(trifluoromethyl)pyridine-2-sulfonamide	174484-41-4			Antiviral, anti-HIV	Infection, HIV/AIDS
tiquizium	2H-Quinolizinium, 3-(di-2-thienylmethylene)octahydro-5-methyl-, [CAS]	71731-58-3	US	4205074	Antispasmodic	
tirapazamine	1,2,4-Benzotriazin-3-amine, 1,4-dioxide- [CAS]	20028-80-2 27314-97-2 5424-06-6	DE	2204574	Radio/chemosensitizer	Cancer, lung, non-small cell
Tiratricol		51-24-1				
tirilazad	Pregna-1,4,9(11)-triene-3,20-dione, 21-[4-(2,6-di-1-pyrrolidinyl-4-pyrimidinyl)-1-piperazinyl]-16-methyl-, (16Alpha)-, [CAS]	110101-65-0 110101-67-2 110101-66-1	WO	8701706	Neuroprotective	Haemorrhage, subarachnoid
tirofiban	L-Tyrosine, N-(butylsulfonyl)-O-[4-(4-piperidinyl)butyl]-, [CAS]	142373-60-2 144494-65-5	EP	478363	Antithrombotic	Infarction, myocardial
tiropramide	Benzenepropanamide, Alpha-(benzoylamino)-4-[2-(diethylamino)ethoxy]-N,N-dipropyl-, (+\-)- [CAS]	55837-29-1	DE	2503992	Antispasmodic	Muscle spasm, general
Titanium Sulfate		13825-74-6				
tixocortol	Pregn-4-ene-3,20-dione, 21-[(2,2-dimethyl-1-oxopropyl)thio]-11,17-dihydroxy-, (11ß)- [CAS]	55560-96-8 61951-99-3	GB	1475795	Antiallergic, non-asthma, mucosal, topical	Rhinitis, allergic, general

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
tizanidine	2,1,3-Benzothiadiazol-4-amine, 5-chloro-N-(4,5-dihydro-1H-imidazol-2-yl)-[CAS]	51322-75-9	GB	1429926	Muscle relaxant	Spastic paralysis
TLK-199	Glycine, L-Gamma-glutamyl-S-(phenylmethyl)-L-cysteinyl-2-phenyl-, diethyl ester, (2R)- [CAS]	168682-53-9	US	5679643	Immunostimulant, other	Myelodysplastic syndrome
TLK-286	Glycine, L-Gamma-glutamyl-3-[[2-([bis[bis(2-chloroethyl)amino]phosphinyl]oxy)ethyl]sulfonyl]-L-alanyl-2-phenyl-, (2R)- [CAS]	158382-37-7	US	5545621	Anticancer, other	Cancer, ovarian
TNF-ß analogue			RU	2035185	Anticancer, immunological	Cancer, general
TNP-470		129298-91-5				
TO-186	Pregna-1,4-diene-3,20-dione, 9-fluoro-11ß,17,21-trihydroxy-16.beta.-methyl-, 17-butyrate 21-propionate [CAS]	5534-02-1			Antipruritic/inflamm, allergic	
tobramycin	O-3-amino-3-deoxy-Alpha-D-glucopyranosyl-(1,6)-O-(2,6-diamino-2,3,6-trideoxy-Alpha-D-ribo-hexopyranosyl-(1-4)-2-deoxy- [CAS]	32986-56-4			Formulation, inhalable, topical	Infection, respiratory tract, general
tocainide	Propanamide, 2-amino-N-(2,6-dimethylphenyl)- [CAS]	41708-72-9	US	4218477	Antiarrhythmic	Fibrillation, ventricular
Tocamphyl		5634-42-4				
tocladesine	8-Chloroadenosine 3'5'-cyclic phosphate	41941-56-4			Anticancer, other	Cancer, colorectal
Tocoretinate		40516-48-1				
Todralazine		14679-73-3				
Tofenacin		15301-93-6				
tofimilast	5H-Pyrazolo[3,4-c]-1,2,4-triazolo[4,3-a]pyridine,9-cyclopentyl-7-ethyl-6,9-dihydro-3-(2-thienyl)-	185954-27-2			Antiasthma	Asthma
tofisopam	5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl-[CAS]	22345-47-7	GB	1334271	Anxiolytic	Anxiety, general
Tolazamide		1156-19-0				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Tolazoline		59-98-3				
Tolbutamide		64-77-7				
tolcapone	Methanone, (3,4-dihydroxy-5-nitrophenyl)(4-methylphenyl)- [CAS]	134308-13-7	EP	237929	Antiparkinsonian	Parkinson's disease
tolciclate	Carbamothioic acid, methyl(3-methylphenyl)-, O-(1,2,3,4-tetrahydro-1,4-methanonaphthalen-6-yl) ester [CAS]	50838-36-3	GB	1364407	Antifungal	Infection, dermatological
Tolcyclamide		664-95-9				
tolevamer	Benzenesulfonic acid, 4-ethenyl-, homopolymer,	28038-50-8			Antibacterial, other	Infection, Clostridium, general
tolfenamic acid	Benzoic acid, 2-[(3-chloro-2-methylphenyl)amino]- [CAS]	13710-19-5	DE	1543295	Anti-inflammatory	Inflammation, general
Tolindate		27877-51-6				
Toliprolol		2933-94-0				
Tolmetin		26171-23-3				
Tolnaftate		2398-96-1				
Tolonidine		4201-22-3				
Tolonium		92-31-9				
toloxatone	2-Oxazolidinone, 5-(hydroxymethyl)-3-(3-methylphenyl)- [CAS]	29218-27-7	GB	1250538	Antidepressant	
Tolperisone		728-88-1				
Tolpropamine		5632-44-0				
Tolrestat		82964-04-3				
tolserine	Carbamic acid, (2-methylphenyl)-, (3aS,8aR)-1,2,3,3a,8,8a-hexahydro-1,3a,8-trimethylpyrrolo[2,3-b]indol-5-yl ester [CAS]	145209-30-9			Cognition enhancer	Alzheimer's disease
tolterodine	Phenol, 2-(3-(bis(1-methylethyl)amino)-1-phenylpropyl)-4-methyl-, (R)- [CAS]	124937-51-5	EP	325571	Urological	Incontinence
tolvaptan	Benzamide, N-[4-[(7-chloro-2,3,4,5-tetrahydro-5-hydroxy-1H-1-benzazepin-1-yl)carbonyl]-3-methylphenyl]-2-methyl- [CAS]	150683-30-0	EP	450097	Cardiovascular	Heart failure

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Tolycaine		3686-58-6				
Topiramate	Beta-D-Fructopyranose, 2,3:4,5-bis-O-(1-methylethylidene)-, sulfamate [CAS]	97240-79-4	EP	533483	Antiepileptic	Epilepsy, generalized, tonic-clonic
topoisomerase inhibitors			US	5733880	Anticancer, other	Cancer, general
topotecan	1H-Pyrano[3',4':6,7]indolizino[1,2-b]quinoline-3,14(4H,12H)-dione, 9-[(dimethylamino)methyl]-4-ethyl-4,10-dihydroxy-, (S)- [CAS]	123948-87-8	EP	321122	Anticancer, other	Cancer, ovarian
torasemide	3-Pyridinesulfonamide, N-[[(1-methylethyl)amino]carbonyl]-4-[(3-methylphenyl)amino]- [CAS]	56211-40-6	US	4018929	Antihypertensive, diuretic	Hypertension, general
torcetrapib	ethyl (2R,4S)-4-[[3,5-bis(trifluoromethyl) benzyl](methoxycarbonyl)amino]-2-ethyl-6-(trifluoromethyl)-3,4-dihydroquinoline-1(2H)-carboxylate	262352-17-0			Hypolipaemic/Antiatherosclerosis	Atherosclerosis
torcitabine	ß-L-2'Deoxycytidine				Antiviral, other	Infection, hepatitis-B virus
toremifene	Ethanamine, 2-[4-(4-chloro-1,2-diphenyl-1-butenyl)phenoxy]-N,N-dimethyl-, (Z)-[CAS]	89778-26-7 89778-27-8	EP	95875	Anticancer, hormonal	Cancer, breast
Torsemide		56211-40-6				
Tositumomab		208921-02-2				
tosufloxacin	1,8-Naphthyridine-3-carboxylic acid, 7-(3-amino-1-pyrrolidinyl)-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-, [CAS]	100490-36-6 115964-29-9	US	4704459	Quinolone antibacterial	Infection, urinary tract
tramadol	Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, cis-(+/-)-[CAS]	27203-92-5 36282-47-0			Analgesic, other	Pain, general
Tramazoline		1082-57-1				
trandolapril	1H-Indole-2-carboxylic acid, 1-[2-[(1-carboxy-3-phenylpropyl)amino]-1-oxopropyl]octahydro-, [2S-[1[R*(R*)],2Alpha,3aAlpha,7aß]]- [CAS]	87679-71-8 87679-37-6 52-53-9	DE	3151690	Antihypertensive, renin system	Hypertension, general

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
tranexamic acid	Cyclohexanecarboxylic acid, 4-(aminomethyl)-, trans- [CAS]	1197-18-8	US	3950405	Antifibrinolytic	Menstrual disorder, general
tranilast	Benzoic acid, 2-[[3-(3,4-dimethoxyphenyl)-1-oxo-2-propenyl]amino]- [CAS]	53902-12-8	US	3940422	Vulnerary	Wound healing
trans-retinoic acid	Retinoic acid [CAS]	302-79-4			Anticancer, other	Cancer, general
Tranylcypromine		155-09-9				
trapidil	[1,2,4]Triazolo[1,5-a]pyrimidin-7-amine, N,N-diethyl-5-methyl- [CAS]	15421-84-8	DD	55956	Vasodilator, coronary	
Trastuzumab		180288-69-1				
travoprost	5-Heptenoic acid, 7-(3,5-dihydroxy-2-(3-hydroxy-4-(3-(trifluoromethyl)phenoxy)-1-butenyl)cyclopentyl)-, 1-methylethylester (1R(1Alpha(Z),2ß(1E,3R*),3Alpha,5Alpha) [CAS]	157283-68-6			Formulation, mucosal, topical	Glaucoma
Traxanox		58712-69-9				
traxoprodil	1-Piperidineethanol, 4-hydroxy-Alpha-(4-hydroxyphenyl)-ß-methyl-4-phenyl-, (AlphaS,ßS)- [CAS]	134234-12-1 188591-67-5			Analgesic, other	Pain, general
trazodone	1,2,4-Triazolo[4,3-a]pyridin-3(2H)-one, 2-[3-[4-(3-chlorophenyl)-1-piperazinyl]propyl]- [CAS]	19794-93-5 25332-39-2	US	4215104	Antidepressant	
Tremacamra		155576-45-7				
Trenbolone		10161-33-8				
Trengestone		5192-84-7				
treosulfan	1,2,3,4-Butanetetrol, 1,4-dimethanesulfonate, [S-(R*,R*)]- [CAS]	299-75-2	WO	8401506	Anticancer, alkylating	
trepibutone	Benzenebutanoic acid, 2,4,5-triethoxy-Gamma-oxo- [CAS]	41826-92-0	GB	1387733	Antispasmodic	
treprostinol	Prosta-5,13-dien-1-oic acid, 6,9-epoxy-11,15-dihydroxy-, [5Z,9Alpha,11Alpha,13E,15S]- [CAS]	35121-78-9 61849-14-7	US	6054486	Formulation, parenteral, other	Hypertension, pulmonary
tretinoin	Retinoic acid [CAS]	302-79-4			Formulation, dermal, topical	Acne

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
tretoquinol	6,7-Isoquinolinediol, 1,2,3,4-tetrahydro-1-[(3,4,5-trimethoxyphenyl)methyl]-, (S)-[CAS]	18559-59-6 30418-38-3 21650-42-0	ZA	6802416	Antiasthma	
TRH		24305-27-9				
TRI-50b	TRI 50b [CAS]	226214-49-9			Antithrombotic	Thrombosis, general
Triacetin		102-76-1				
Triamcinolone Acetonide		76-25-5				
Triamcinolone Benetonide		31002-79-6				
Triamcinolone Hexacetonide		5611-51-8				
triamcinolone	Pregna-1,4-diene-3,20-dione, 9-fluoro-11,21-dihydroxy-16,17-[(1-methylethylidene)bis(oxy)]-, (11ß,16Alpha)-[CAS]	76-25-5 124-94-7			Formulation, inhalable, topical	Asthma
Triamterene		396-01-0				
triapine	Triapine [CAS]	236392-56-6	US	6458816	Anticancer, antimetabolite	Cancer, leukaemia, general
Triaziquone		68-76-8				
triazolam	8-chloro-6-(2-chlorophenyl)-1-methyl-4H-[1,2,4]-triazolo[4,3-a][1,4]benzodiazepine	28911-01-5	US	3980790	Hypnotic/Sedative	Insomnia
Tribenoside		10310-32-4				
Trichlorfon		52-68-6				
Trichlormethiazide		133-67-5				
Trichlormethine		555-77-1				
Trichloroethylene		79-01-6				
Triclobisonium		79-90-3				
Triclocarban		101-20-2				
Triclofenol Piperazine		5714-82-9				
Triclofos		306-52-5				
Triclosan		3380-34-5				
Tricromyl		85-90-5				
Tridihexethyl Iodide		125-99-5				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
trientine	1,2-Ethanediamine, N,N2-bis(2aminoethyl)-, [CAS]	38260-01-4 112-24-3			Metabolic and enzyme disorders	Wilson's disease
Triethanolamine		102-71-6				
Triethylenemelamine		51-18-3				
Triethylenephosphoramide		545-55-1				
Triethylenethiophosphoramide		52-24-4				
Trifluoperazine		117-89-5				
Trifluperidol		749-13-3				
Triflupromazine		146-54-3				
trifluridine	Thymidine, Alpha,Alpha,Alpha-trifluoro- [CAS]	70-00-8	US	3201387	Antiviral, other	Infection, herpes virus, general
triflusal	Benzoic acid, 2-(acetyloxy)-4-(trifluoromethyl)- [CAS]	322-79-2	US	4096252	Antithrombotic	Thrombosis, general
Trihexyphenidyl		52-49-3				
trilostane	Androst-2-ene-2-carbonitrile, 4,5-epoxy-3,17-dihydroxy-, (4Alpha,5Alpha,17ß)- [CAS]	13647-35-3	US	3296255	Anticancer, hormonal	Cancer, breast
Trimazosin		35795-16-5				
trimebutine	Benzoic acid, 3,4,5-trimethoxy-, 2-(dimethylamino)-2-phenylbutyl ester, (Z)-2-butenedioate (1:1) [CAS]	34140-59-5 39133-31-8	DE	2151716	Antispasmodic	
Trimecaine		616-68-2				
Trimeprazine		84-96-8				
Trimetazidine		5011-34-7				
Trimethadione		127-48-0				
Trimethaphan		68-91-7				
Trimethobenzamide		138-56-7				
Trimethoprim		738-70-5				
Trimetozine		635-41-6				
trimetrexate	2,4-Quinazolinediamine, 5-methyl-6-[[(3,4,5-trimethoxyphenyl)amino]methyl]- [CAS]	52128-35-5 82952-64-5	US	4391809	Antifungal	Infection, Pneumocystis jiroveci

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
trimipramine	5H-Dibenz[b,f]azepine-5-propanamine, 10,11-dihydro-N,N,ß-trimethyl-, (Z)-2-butenedioate (1:1) [CAS]	521-78-8 739-71-9			Antidepressant	
Trimoprostil		69900-72-7				
Trioxsalen		3902-71-4				
tripamide	Benzamide, 3-(aminosulfonyl)-4-chloro-N-(octahydro-4,7-methano-2H-isoindol-2-yl)-, (3aAlpha,4Alpha,7Alpha,7aAlpha)- [CAS]	73803-48-2	JP	7305585	Antihypertensive, diuretic	Hypertension, general
Triparanol		78-41-1				
Tripelennamine		91-81-6				
Triprolidine		486-12-4				
triptorelin	Luteinizing hormone-releasing factor (pig), 6-D-tryptophan- [CAS]	124508-66-3 57773-63-4	US	4010125	Releasing hormones	Cancer, prostate
tritiozine	Morpholine, 4-[thioxo(3,4,5-trimethoxyphenyl)methyl]- [CAS]	35619-65-9	US	3862138	Antiulcer	
Tritoqualine		14504-73-5				
TRK-530	Phosphonic acid, [[[4-(methylthio)phenyl]thio]methylene]bis-, disodium salt [CAS]	151425-92-2	WO	9410181	Antiarthritic, other	Arthritis, rheumatoid
TRK-820	2-Propenamide, N-[(5Alpha,6ß)-17-(cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxymorphinan-6-yl]-3-(3-furanyl)-N-methyl-, monohydrochloride, (2E)- [CAS]	152658-17-8	WO	9315081	Antipruritic/inflamm, non-allergic	Pruritus
Troclosene		2244-21-5				
trofosfamide	3-2-(chloroethyl)-2-[bis(2-chloroethyl)amino]tetrahydro-2H-1,3,2-oxazaphosphorin 2-oxide	22089-22-1	GB	1188159	Anticancer, alkylating	
Troglitazone		97322-87-7				
Troleandomycin		2751-9-9				
Trolnitrate		588-42-1				
tromantadine	N-(1-adamantyl)-2-(2-dimethylamine ethoxy)acetamide	53783-83-8	DE	1941218	Antiviral, other	Infection, herpes simplex virus
Tromethamine		77-86-1				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Tropacine		6878-98-4				
Tropesin		65189-78-8				
Tropicamide		1508-75-4				
tropine	1H-Indole-3-acetic acid, 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-, 2-carboxy-2-phenylethyl ester, (+/-)- [CAS]	65189-78-8			Antiarthritic, other	
tropisetron	1H-Indole-3-carboxylic acid, 8-methyl-8-azabicyclo[3.2.1]oct-3-yl ester, endo-[CAS]	89565-68-4	GB	2125398	Antiemetic	Chemotherapy-induced nausea and vomiting
Trospectomycin		88669-04-9				
trospium	3Alpha-Hydroxyspiro[1AlphaH,5AlphaH-nortropane-8,1'-pyrrolidinium] benzilate	10405-02-4			Urological	Pollakisuria
trovafloxacin	1,8-Naphthyridine-3-carboxylic acid, 7-(6-amino-3-azabicyclo[3.1.0]hex-3-yl)-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-, (1Alpha,5Alpha,6Alpha)-, [CAS]	147059-72-1 147059-75-4	US	5164402	Quinolone antibacterial	Infection, respiratory tract, general
troxacitabine	2(1H)-Pyrimidinone, 4-amino-1-(2-(hydroxymethyl)-1,3-dioxolan-4-yl)-, (2S-cis)-[CAS]	145918-75-8			Anticancer, other	Cancer, leukaemia, acute myelogenous
Troxerutin		7085-55-4				
troxipide	Benzamide, 3,4,5-trimethoxy-N-3-piperidinyl-, (+/-)- [CAS]	30751-05-4 99777-81-8	US	3647805	Antiulcer	Ulcer, gastric
Trypan Red		574-64-1				
Tryparsamide		554-72-3				
Tryptophan		73-22-3				
TSH		9002-71-5				
TSN-09	6,14-Ethenomorphinan-7-methanol, 17-(cyclopropylmethyl)-Alpha-(1,1-dimethylethyl)-,5-epoxy-18,19-dihydro-3-hydroxy-6-methoxy-Alpha-methyl-, [5Alpha,7Alpha,(S)]- [CAS]	52485-79-7			Formulation, transdermal, patch	Pain, cancer
TU-2100	Nonanedioic acid, bis[(2-(ethoxycarbonyl)phenyl] ester		US	6180669	Antiacne	Acne

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example *of Indication*
Tuaminoheptane		123-82-0				
Tubercidin		69-33-0				
Tubocurarine Chloride		57-94-3				
tulobuterol	Benzenemethanol, 2-chloro-Alpha-[[(1,1-dimethylethyl)amino]methyl]- [CAS]	41570-61-0	DE	2244737	Antiasthma	Asthma
TV-3326	N-(Propargyl-(3R)aminoindan-5-yl)-ethyl methyl carbamate				Cognition enhancer	Alzheimer's disease
TY-11223	Acetic acid, [2-[2,3,3a,6,7,7a-hexahydro-2-hydroxy-1-(3-hydroxy-4,4-dimethyl-1,6-nonadiynyl)-1H-inden-5-yl]ethoxy]-, [1S-[1Alpha(R*),2ß,3aAlpha,7aAlpha]]- [CAS]	140694-43-5	US	4837342	Antithrombotic	Unspecified
TY-12533	6,7,8,9-Tetrahydro-2-methyl-5H-cyclohepta[b]pyridine-3-carbonylguanidine maleate		US	6258829	Antiarrhythmic	Unspecified
TYB-3215	D-Glucitol, 1,4:3,6-dianhydro-, dinitrate [CAS]	87-33-2			Formulation, modified-release, other	Angina, general
Tybamate		4268-36-4				
tyloxapol	4-(1,1,3,3-Tetramethylbutyl)phenol polymer with formaldehyde and oxirane [CAS]	25301-02-4			Formulation, inhalable, topical	Cystic fibrosis
Tymazoline		24243-97-8				
Tyramine		51-67-2				
Tyropanoate		7246-21-1				
Ubenimex		58970-76-6				
ufenamate	Benzoic acid, 2-[[3-(trifluoromethyl)phenyl]amino]-, butyl ester [CAS]	67330-25-0	BE	861852	Antipruritic/inflamm, non-allergic	
Undecylenic Acid		112-38-9				
Unoprostone		120373-36-6				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
UR-8880	4-[4-Chloro-5-(3-fluoro-4-methoxyphenyl)imidazol-1-imidazol-1-yl]benzenesulfonamide- [CAS]				Anti-inflammatory	Inflammation, general
Uracil Mustard		66-75-1				
Uralyt-U	1,2,3-Propanetricarboxylic acid, 2-hydroxy-, potassium sodium salt (5:6:6), hydrate [CAS]	55049-48-4	US	4400535	Urological	
urapidil	2,4(1H,3H)-Pyrimidinedione, 6-[[3-[4-(2-methoxyphenyl)-1-piperazinyl]propyl]amino]-1,3-dimethyl- [CAS]	34661-75-1	GB	1309324	Antihypertensive, adrenergic	Hypertension, general
urea	Urea [CAS]	57-13-6			Antipsoriasis	
Uredepa		302-49-8				
Urethan		51-79-6				
Uridine 5'-Triphosphate		63-39-8				
Urinastatin		80449-31-6				
ursodeoxycholic acid	3Alpha,7ß-dihydroxy-5ß-cholan-24-oic acid [CAS]	128-13-2			Formulation, other, Cirrhosis, primary biliary, hepatic dysfunction, biliary calculus	Cirrhosis, primary biliary
Ursodiol		128-13-2				
Ushercell			US	6063773	Formulation, mucosal, topical	Contraceptive, female
Uzarin		20231-81-6				
valaciclovir	L-Valine, 2-[(2-amino-1,6-dihydro-6-oxo-9H-purin-9-yl)methoxy]ethyl ester [CAS]	124832-26-4	EP	308065	Antiviral, other	Infection, herpes simplex virus
Valacyclovir		124832-26-4				
valdecoxib	Benzenesulfonamide, 4-(5-methyl-3-phenyl-4-isoxazolyl)- [CAS]	181695-72-7	US	5859257	Antiarthritic, other	Arthritis, rheumatoid
Valdetamide		512-48-1				
Valethamate		90-22-2				
valganciclovir	L-Valine, 2-((2-amino-1,6-dihydro-6-oxo-9H-purin-9-yl)methoxy)-3-hydroxypropyl ester [CAS]	175865-59-5 175865-60-8	EP	694547	Antiviral, other	Infection, cytomegalovirus
Valnoctamide		4171-13-5				

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
valomaciclovir	L-Valine (3R)-3-((2-amino-1,6-dihydro-6-oxo-9H-purin-9-yl)methyl)-4-((1-oxooctadecyl)oxy)butyl ester [CAS]	195156-77-5			Antiviral, other	Infection, herpes simplex virus
valproate	Pentanoic acid, 2-propyl-, [CAS]	76584-70-8 1069-66-5	US	4988731	Antiepileptic	Epilepsy, generalized, tonic-clonic
Valproic Acid		99-66-1				
Valpromide		2430-27-5				
valrocemide	Pentanamide, N-(2-amino-2-oxoethyl)-2-propyl- [CAS]	92262-58-3	US	5585358	Antiepileptic	Epilepsy, general
valrubicin	Pentanoic acid, 2-(1,2,3,4,6,11-hexahydro-2,5,12-trihydroxy-7-methoxy-6,11-dioxo-4-((2,3,6-trideoxy-3-((trifluoroacetyl)amino)-Alpha-L-lyxo-hexopyranosyl)oxy)-2-naphthacenyl)-2-oxoethyl ester (2S-cis)- [CAS]	56124-62-0	US	4035566	Anticancer, antibiotic	Cancer, bladder
valsartan	L-Valine, N-(1-oxopentyl)-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]- [CAS]	137862-53-4	EP	443983	Antihypertensive, renin system	Hypertension, general
Valspodar		121584-18-7				
vardenafil	Piperazine, 1-(3-(1,4-dihydro-5-methyl(-4-oxo-7-propylimidazo(5,1-f)(1,2,4)-triazin-2-yl)-4-ethoxyphenyl)sulfonyl)-4-ethyl- [CAS]	224785-90-4			Male sexual dysfunction	Sexual dysfunction, male, general
varespladib	Acetic acid, ((3-(aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl)oxy)- [CAS]	172732-68-2 172733-42-5	EP	675110	Septic shock treatment	Sepsis
Varicella Virus Vaccine						
vatanidipine	3,5-Pyridinedicarboxylic acid, 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-, 2-[4-[4-(diphenylmethyl)-1-piperazinyl]phenyl]ethyl methyl ester, [CAS]	116308-55-5 133743-71-2	EP	257616	Neuroprotective	Hypertension, general
VEA			US	6007817	Radio/chemosensitizer	Cancer, general

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
vecuronium	Piperidinium, 1-[(2ß,3Alpha,5Alpha,16ß,17ß)-3,17-bis(acetyloxy)-2-(1-piperidinyl)androstan-16-yl]-1-methyl-, [CAS]	50700-72-6	US	4237126	Muscle relaxant	Anaesthesia, adjunct
Velnacrine		104675-29-8				
venlafaxine	Cyclohexanol, 1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]-, [CAS]	93413-69-5 99300-78-4	GB	2227743	Antidepressant	Depression, general
Veralipride		66644-81-3				
verapamil	Benzeneacetonitrile, Alpha-[3-[[2-(3,4-dimethoxyphenyl)ethyl]methylamino]propyl]-3,4-dimethoxy-Alpha-(1-methylethyl)- [CAS]	52-53-9			Formulation, modified-release, other	Hypertension, general
verteporfin	23H,25H-Benzo[b]porphine-9,13-dipropanoic acid, 18-ethenyl-4,4a-dihydro-3,4-bis(methoxycarbonyl)-4a,8,14,19-tetramethyl-, monomethyl ester, trans- [CAS]	129497-78-5	US	5238940	Ophthalmological	Macular degeneration
vesnarinone	Piperazine, 1-(3,4-dimethoxybenzoyl)-4-(1,2,3,4-tetrahydro-2-oxo-6-quinolinyl)- [CAS]	81840-15-5	GB	2086896	Cardiostimulant	Heart failure
Vetrabutine		3735-45-3				
VF-233	Benzene carboximidamide, N,3,4,5-tetrahydroxy- [CAS]	95933-74-7	US	4623659	Cardiovascular	Reperfusion injury
VI-0134			US	6403597	Male sexual dysfunction	Premature ejaculation
vidarabine	9H-Purin-6-amine, 9-ß-D-arabinofuranosyl- [CAS]	24356-66-9 5536-17-4	GB	1159290	Antiviral, other	Infection, herpes virus, general
vigabatrin	5-Hexenoic acid, 4-amino- [CAS]	68506-86-5 60643-86-9	GB	1472525	Antiepileptic	Epilepsy, partial (focal, local)
vilazodone	2-Benzofurancarboxamide, 5-[4-[4-(5-cyano-1H-indol-3-yl)butyl]-1-piperazinyl]- [CAS]	163521-12-8	EP	648767	Antidepressant	Depression, general
Viloxazine		46817-91-8				
Viminol		21363-18-8				
Vinbarbital		125-44-0				
Vinblastine		865-21-4				
vinburnine	Eburnamenin-14(15H)-one, (3Alpha,16Alpha)- [CAS]	474-00-0 4880-88-0	DE	1932245	Cognition enhancer	

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Vincamine		1617-90-9				
Vinconate		70704-03-9				
vincristine	Vincaleukoblastine, 22-oxo-, sulfate (1:1) (salt) [CAS]	2068-78-2 57-22-7	EP	207831	Formulation, parenteral, other	Cancer, general
vindesine	Vincaleukoblastine, 3-(aminocarbonyl)-O4-deacetyl-3-de(methoxycarbonyl)- [CAS]	53643-48-4 59917-39-4	GB	1463575	Anticancer, other	Cancer, leukaemia, acute lymphocytic
vinflunine	Aspidospermidine-3-carboxylic acid, 4-(acetyloxy)-6,7-didehydro-15-[(2R,4R,6S,8S)-4-(1,1-difluoroethyl)-1,3,4,5,6,7,8,9-octahydro-8-(methoxycarbonyl)-2,6-methano-2H-azecino[4,3-b]indol-8-yl]-3-hydroxy-16-methoxy-1-methyl-, methyl ester, (2ß,3ß,4ß,5Alpha,12ß,19Alpha) - [CAS]	162652-95-1	FR	2707988	Anticancer, other	Cancer, general
vinorelbine	C'-Norvincaleukoblastine, 3',4'-didehydro-4'-deoxy- [CAS]	71486-22-1	EP	10458	Anticancer, other	Cancer, lung, non-small cell
vinpocetine	Eburnamenine-14-carboxylic acid, ethyl ester, (3Alpha,16Alpha)- [CAS]	42971-09-5	GB	1405127	Cognition enhancer	Cognitive disorder, general
Vinyl Ether		109-93-3				
Vinylbital		2430-49-1				
Viquidil		84-55-9				
Viridin		3306-52-3				
Visnadine		477-32-7				
Vitamin A		68-26-8				
vitamin B12	Vitamin B12 [CAS]	68-19-9			Formulation, transmucosal, nasal	Anaemia, general
vitamin C	L-Ascorbic acid [CAS]	50-81-7			Formulation, modified-release, <=24hr	Nutrition
Vitamin D_2		50-14-6				
Vitamin D_3		67-97-0				
Vitamin K_5		83-70-5				
Vitamins, Prenatal						

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
VLA-4 antagonists	((R,S)-4-(4-(Amino-imino-methyl)-phenyl)-3-((4-biphenylyl)-methyl)-4-methyl-2,5-dioxoimidazolidin-1-yl)-acetyl-L-N-methyl-aspartyl-L-phenylglycine		EP	842943	Antiasthma	Asthma
VNP-40101M	1,2-Bis(methylsulfonyl)-1-(2-chloroethyl)-2-(methylamino)carbonylhydrazine		US	6040338	Anticancer, alkylating	Cancer, general
voglibose	D-epi-Inositol, 3,4-dideoxy-4-[[2-hydroxy-1-(hydroxymethyl)ethyl]amino]-2-C-(hydroxymethyl)- [CAS]	83480-29-9	EP	56194	Antidiabetic	Diabetes, Type II
voriconazole	4-Pyrimidineethanol, Alpha-(2,4-difluorophenyl)-5-fluoro-ß-methyl-Alpha-(1H-1,2,4-triazol-1-ylmethyl)-, (R-(R*,S*))- [CAS]	137234-62-9	EP	440372	Antifungal	Infection, fungal, general
Vorozole		129731-10-8				
VUF-K-8788	7-[3-[4-(2-Quinolinylmethyl)-1-piperazinyl]propoxy]-3,4-dihydro-2H-1,4-benzothiazine-3-one				Antiasthma	Asthma
Warfarin		81-81-2				
WF-10	Tetrachlorodecaoxide [CAS]	92047-76-2			Radio/chemoprotective	Chemotherapy-induced injury, bone marrow, general
WMC-79	2-(3-[4-[3-(6-oxo-6H-2,10b-diaza-aceanthrenylen-5-ylamino)propyl]-piperazin-1-yl]propyl)-5-nitro-2-aza-phenalene-1,3-dione				Anticancer, other	Cancer, colorectal
wound healing matrix			US	5897880	Formulation, transdermal, patch	Ulcer, diabetic
WP-170			US	6531121	Cytokine	Unspecified
xaliproden	Pyridine, 1,2,3,6-tetrahydro-1-[2-(2-naphthalenyl)ethyl]-4-[3-(trifluoromethyl)phenyl]-, [CAS]	90494-79-4 135354-020-8	EP	101381	Neuroprotective	Amyotrophic lateral sclerosis
xamoterol	4-Morpholinecarboxamide, N-[2-[[2-hydroxy-3-(4-hydroxyphenoxy)propyl]amino]ethyl]-, (+/-)- [CAS]	73210-73-8 81801-12-9	GB	2002748	Cardiostimulant	Heart failure

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
Xanomeline		131986-45-3				
Xanthinol Niacinate		437-74-1				
Xemilofiban		149820-74-6				
Xenbucin		959-10-4				
Xibenolol		81584-06-7				
xibornol	Phenol, 4,5-dimethyl-2-(1,7,7-trimethylbicyclo[2.2.1]hept-2-yl)-, exo- [CAS]	13741-18-9	GB	1206774	Antibacterial, other	Infection, general
ximelagatran	Glycine, N-((R)-cyclohexyl-2-((2S)-2-((((4-(hydroxyamino)iminomethyl)phenyl)methyl)amino)carbonyl)-1-azetidinyl)2-oxoethyl ethyl ester [CAS]	192939-46-1			Antithrombotic	Thrombosis, venous
Ximoprofen		56187-89-4				
xipamide	Benzamide, 5-(aminosulfonyl)-4-chloro-N-(2,6-dimethylphenyl)-2-hydroxy- [CAS]	14293-44-8	US	3567777	Antihypertensive, diuretic	
xorphanol	Morphinan-3-ol, 17-(cyclobutylmethyl)-8-methyl-6-methylene-, (8ß)- [CAS]	77287-89-9			Analgesic, other	Pain, cancer
XR-5118	2,5-Piperazinedione, 3-[[5-[[2-(dimethylamino)ethyl]thio]-2-thienyl]methylene]-6-(phenylmethylene)-, monohydrochloride, (3Z,6Z)- [CAS]	174766-49-5	WO	9532190	Anticancer, other	Cancer, general
XR-5944	N,N'-(1,2-Ethanediyl)bis(imino-2,1-ethanediyl)bis(9-methylphenazine-1-carboxamide)		EP	934278	Anticancer, other	Cancer, general
Xylometazoline		526-36-3				
Xylose		58-86-6				
YH-1885	2-Pyrimidinamine, 4-(3,4-dihydro-1-methyl-2(1H)-isoquinolinyl)-N-(4-fluorophenyl)-5,6-dimethyl-, monohydrochloride [CAS]	178307-42-1	WO	9605177	Antiulcer	Ulcer, GI, general
YM-511	Benzonitrile, 4-[[(4-bromophenyl)methyl]-4H-1,2,4-triazol-4-ylamino]- [CAS]	148869-05-0	WO	9305027	Anticancer, hormonal	Cancer, breast

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
YM-598	potassium(E)-N-[6-methoxy-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl)pyrimidin-4-yl]-2-phenylethenesulfonamidate				Anticancer, other	Cancer, prostate
Yohimbine		146-48-5				
YT-146	Adenosine, 2-(1-octynyl)- [CAS]	90596-75-1	US	5270304	Anti-inflammatory	Inflammation, general
Z-321	Thiazolidine, 3-((2,3-dihydro-1H-inden-2-yl)acetyl)-4-(1-pyrrolidinylcarbonyl)-, (R)- [CAS]	130849-58-0	EP	372484	Cognition enhancer	Dementia, senile, general
Z-335	(1H-Indene-5-acetic acid, 2[[[(4-chlorophenyl)sulfonyl]amino]methyl]-2,3-dihydro, monosodium salt) [CAS]	146731-14-8	JP	92506077	Antithrombotic	Peripheral vascular disease
zafirlukast	Carbamic acid, [3-[[2-methoxy-4-[[[(2-methylphenyl)sulfonyl]amino]carbonyl]phenyl]methyl]-1-methyl-1H-indol-5-yl]-, cyclopentyl ester [CAS]	107753-78-6	EP	199543	Antiasthma	Asthma
zalcitabine	Cytidine, 2',3'-dideoxy- [CAS]	7481-89-2	US	4879277	Antiviral, anti-HIV	Infection, HIV/AIDS
Zaldaride		109826-26-8				
zaleplon	Acetamide, N-[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-ethyl- [CAS]	151319-34-5	EP	776898	Hypnotic/Sedative	Insomnia
zaltoprofen	Dibenzo[b,f]thiepin-2-acetic acid, 10,11-dihydro-Alpha-methyl-10-oxo- [CAS]	74711-43-6	JP	55053282	Anti-inflammatory	
zanamivir	5-Acetamido-2,6-anhydro-3,4,5-trideoxy-4-guanidino-D-glycero-D-galacto-non-2-enonic acid [CAS]	139110-80-8	WO	9116320	Antiviral, other	Infection, influenza virus
zanapezil	1-Propanone, 3-(1-(phenylmethyl)-4-piperidinyl)-1-(2,3,4,5-tetrahydro-1H-1-benzazepin-8-yl)- [CAS]	142852-50-4	EP	487071	Cognition enhancer	Alzheimer's disease
Zatebradine		85175-67-3				
ZD-0473	Platinum, amminedichloro(2-methylpyridine)- (SP-4-3)- [CAS]	181630-15-9	EP	727430	Anticancer, alkylating	Cancer, ovarian
ZD-0947			WO	9528388	Urological	Overactive bladder
ZD-6126	N-acetylcolchinol-O-phosphate				Anticancer, other	Cancer, general
ZD-9331	1H-Tetrazole-5-butanoic acid, Alpha-((4-(((1,4-dihydro-2,7-dimethyl-4-oxo-6-quinazolinyl)methyl)-2-propynylamino)-2-fluorobenzoyl)amino) (S)- [CAS]	153537-73-6	GB	2264946	Anticancer, antimetabolite	Cancer, pancreatic

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
zebularine	2(1H)-Pyrimidinone, 1-ß-D-ribofuranosyl- [CAS]	3690-10-6			Anticancer, other	Cancer, general
zelandopam	7,8-Isoquinolinediol, 4-(3,4-dihydroxyphenyl)-1,2,3,4-tetrahydro-, [CAS]	138086-00-7	JP	03190818	Vasodilator, renal	Hypertension, general
Zenarestat		112733-06-9				
Ziconotide		107452-89-1				
zidovudine	Thymidine, 3'-azido-3'-deoxy- [CAS]	30516-87-1	US	4724232	Antiviral, anti-HIV	Infection, HIV/AIDS
zileuton	Urea, N-(1-benzo[b]thien-2-ylethyl)-N-hydroxy- [CAS]	111406-87-2	EP	279263	Antiasthma	Asthma
Zimeldine		56775-88-3				
zinc acetate	hexakis(\m-acetato)-\m4-oxotetrazinc	12129-82-7			Antiviral, other	Infection, herpes simplex virus prophylaxis
zinc acexamate	Hexanoic acid, 6-(acetylamino)-, zinc salt (2:1)- [CAS]	70020-71-2	EP	369088	Antiulcer	Ulcer, duodenal
zinc ibuprofenate		78416-80-5			Anti-inflammatory, topical	Inflammation, dermal
Zinc p-Phenolsulfonate		127-82-2				
Zinc Salicylate		16283-36-6				
Zinostatin		9014-2-2				
zinostatin stimalamer		123760-07-6	EP	136791	Anticancer, antibiotic	Cancer, liver
Zipeprol		34758-83-3				
ziprasidone	2H-Indol-2-one, 5-(2-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)ethyl)-6-chloro-1,3-dihydro- [CAS]	122883-93-6 146939-27-7	EP	281309	Neuroleptic	Schizophrenia
zofenopril	L-Proline, 1-[3-(benzoylthio)-2-methyl-1-oxopropyl]-4-(phenylthio)-,[1(R*),2Alpha,4Alpha]- [CAS]	75176-37-3 81872-10-8 81938-43-4	GB	2028327	Antihypertensive, renin system	Hypertension, general
zofenopril + HCTZ	L-Proline, 1-[3-(benzoylthio)-2-methyl-1-oxopropyl]-4-(phenylthio)-,[1(R*),2Alpha,4Alpha]- + 6-Chloro-3,4-dihydro-2H-1,2,4-benzothiazide-7-sulfonamide 1,1-dioxide [CAS]				Formulation, fixed-dose combinations	Hypertension, general
zoledronic acid	Phosphonic acid, [1-hydroxy-2-(1H-imidazol-1-yl)ethylidene]bis- [CAS]	118072-93-8 165800-06-6	EP	531253	Osteoporosis treatment	Hypercalcaemia of malignancy

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
zolimidine	2-(p-methylsulfonylphenyl)imidazo[1,2-a]pyridine	1222-57-7	US	3318880	Antiulcer	Gastritis
zolmitriptan	2-Oxazolidinone, 4-((3-(2-(dimethylamino)ethyl)-1H-indol-5-yl)methyl)-, (S)- [CAS]	139264-17-8	WO	9118897	Antimigraine	Migraine
zolpidem	Imidazo[1,2-a]pyridine-3-acetamide, N,N,6-trimethyl-2-(4-methylphenyl)-(R-(R*,R*))-2,3-dihydroxybutanedioate (2:1) [CAS]	99294-93-6 82626 48-0	EP	50563	Hypnotic/Sedative	Insomnia
Zomepirac		33369-31-2				
zonampanel	1(2H)-Quinoxalineacetic acid, 3,4-dihydro-7-(1H-imidazol-1-yl)-6-nitro-2,3-dioxo- [CAS]	210245-80-0			Neuroprotective	Ischaemia, cerebral
zoniporide	1H-pyrazole-4-carboxamide,N-(aminoimino methyl)-5-cyclopropyl-1-(5-quinolinyl)-,	249296-45-5			Cardiovascular	Unspecified
zonisamide	1,2-Benzisoxazole-3-methanesulfonamide [CAS]	68291-97-4 68291-98-5	GB	2025931	Antiepileptic	Epilepsy, generalized, tonic-clonic
zopiclone	1-Piperazinecarboxylic acid, 4-methyl-, 6-(5-chloro-2-pyridinyl)-6,7-dihydro-7-oxo-5H-pyrrolo[3,4-b]pyrazin-5-yl ester [CAS]	43200-80-2	GB	1358680	Hypnotic/Sedative	Insomnia
Zopolrestat		110703-94-1				
Zorubicin		54083-22-6				
zosuquidar	1-Piperazineethanol, 4-(1,1-difluoro-1,1a,6,10b-tetrahydrodibenzo[a,e]cyclopropa[c]cyclohepten-6-yl)-Alpha-[(5-quinolinyloxy)methyl]-, [6(R)-(1aAlpha,6Alpha,10bAlpha)]- [CAS]	167465-36-3			Radio/chemosensitizer	Cancer, leukaemia, acute myelogenous
zotepine	Ethanamine, 2-[(8-chlorodibenzo[b,f]thiepin-10-yl)oxy]-N,N-dimethyl- [CAS]	26615-21-4	GB	1247067	Neuroleptic	Schizophrenia
ZP-123			WO	0162775	Antiarrhythmic	Arrhythmia, general
Z-tamoxifen	Ethanamine, 2-[4-(1,2-diphenyl-1-butenyl)phenoxy]-N,N-dimethyl-, (Z)- [CAS]	10540-29-1			Anticancer, hormonal	Cancer, colorectal

Table IV

API Generic Name	API Chemical Name	CAS No.	Patent Reference		Example of Therapeutic Use	Example of Indication
zuclopenthixol	1-Piperazineethanol, 4-[3-(2-chloro-9H-thioxanthen-9-ylidene)propyl]-, (Z)-[CAS]	53772-83-1 982-24-1 85721-05-7 64053-00-5	EP	270282	Neuroleptic	Psychosis, general

CLAIMS:

1. A pharmaceutical co-crystal composition, comprising: an API and a co-crystal former, wherein the API is a liquid or a solid at room temperature and the co-crystal former is a solid at room temperature, and wherein the API and co-crystal former are hydrogen bonded to each other.

2. The pharmaceutical co-crystal composition according to claim 1, wherein:

(a) the co-crystal former is selected from a co-crystal former of Table I or Table II;

(b) the API is selected from an API of Table IV;

(c) the API is selected from an API of Table IV and the co-crystal former is selected from a co-crystal former of Table I or Table II;

(d) the API is a liquid at room temperature;

(e) the API is a solid at room temperature;

(f) the API has at least one functional group selected from the group consisting of: ether, thioether, alcohol, thiol, aldehyde, ketone, thioketone, nitrate ester, phosphate ester, thiophosphate ester, ester, thioester, sulfate ester, carboxylic acid, phosphonic acid, phosphinic acid, sulfonic acid, amide, primary amine, secondary amine, ammonia, tertiary amine, imine, thiocyanate, cyanamide, oxime, nitrile, diazo, organohalide, nitro, S-heterocyclic ring, thiophene, N-heterocyclic ring, pyrrole, O-heterocyclic ring, furan, epoxide, peroxide, hydroxamic acid, imidazole, and pyridine;

(g) the co-crystal former has at least one functional group selected from the group consisting of: ether, thioether, alcohol, thiol, aldehyde, ketone, thioketone, nitrate ester, phosphate ester, thiophosphate ester, ester, thioester, sulfate ester, carboxylic acid, phosphonic acid, phosphinic acid, sulfonic acid, amide, primary amine, secondary amine, ammonia, tertiary amine, imine, thiocyanate, cyanamide, oxime, nitrile, diazo, organohalide, nitro, S-heterocyclic ring,

thiophene, N-heterocyclic ring, pyrrole, O-heterocyclic ring, furan, epoxide, peroxide, hydroxamic acid, imidazole, and pyridine;

(h) the difference in pK_a between the API and the co-crystal former does not exceed 2;

(i) the solubility of the co-crystal is increased as compared to the API;

(j) the dose response of the co-crystal is increased as compared to the API;

(k) the dissolution of the co-crystal is increased as compared to the API;

(l) the bioavailability of the co-crystal is increased as compared to the API;

(m) the stability of the co-crystal is increased as compared to the API;

(n) a difficult to salt or unsaltable API is incorporated into the co-crystal;

(o) the hygroscopicity of the co-crystal is decreased as compared to the API;

(p) an amorphous API is crystallized as a component of the co-crystal;

(q) the form diversity of the co-crystal is decreased as compared to the API; or

(r) the morphology of the co-crystal is modulated as compared to the API.

3. A pharmaceutical co-crystal composition, comprising: an API, a co-crystal former, and a third molecule; wherein the API is a liquid or a solid at room temperature and the co-crystal former is a solid at room temperature, and wherein the API and the third molecule are bonded to each other, and further wherein the co-crystal former and the third molecule are hydrogen bonded to each other.

4. The pharmaceutical co-crystal composition according to claim 3, wherein:

(a) the co-crystal former is selected from a co-crystal former of Table I or Table II;

(b) the API is selected from an API of Table IV;

(c) the API is selected from an API of Table IV and the co-crystal former is selected from a co-crystal former of Table I or Table II;

(d) the API is a liquid at room temperature;

(e) the API is a solid at room temperature;

(f) the API has at least one functional group selected from the group consisting of: ether, thioether, alcohol, thiol, aldehyde, ketone, thioketone, nitrate ester, phosphate ester, thiophosphate ester, ester, thioester, sulfate ester, carboxylic acid, phosphonic acid, phosphinic acid, sulfonic acid, amide, primary amine, secondary amine, ammonia, tertiary amine, imine, thiocyanate, cyanamide, oxime, nitrile, diazo, organohalide, nitro, S-heterocyclic ring, thiophene, N-heterocyclic ring, pyrrole, O-heterocyclic ring, furan, epoxide, peroxide, hydroxamic acid, imidazole, and pyridine;

(g) the co-crystal former has at least one functional group selected from the group consisting of: ether, thioether, alcohol, thiol, aldehyde, ketone, thioketone, nitrate ester, phosphate ester, thiophosphate ester, ester, thioester, sulfate ester, carboxylic acid, phosphonic acid, phosphinic acid, sulfonic acid, amide, primary amine, secondary amine, ammonia, tertiary amine, imine, thiocyanate, cyanamide, oxime, nitrile, diazo, organohalide, nitro, S-heterocyclic ring, thiophene, N-heterocyclic ring, pyrrole, O-heterocyclic ring, furan, epoxide, peroxide, hydroxamic acid, imidazole, and pyridine; or

(h) the difference in pK_a between the API and the co-crystal former does not exceed 2;

(i) the solubility of the co-crystal is increased as compared to the API;

(j) the dose response of the co-crystal is increased as compared to the API;

(k) the dissolution of the co-crystal is increased as compared to the API;

(l) the bioavailability of the co-crystal is increased as compared to the API;

(m) the stability of the co-crystal is increased as compared to the API;

(n) a difficult to salt or unsaltable API is incorporated into the co-crystal;

(o) the hygroscopicity of the co-crystal is decreased as compared to the API;

(p) an amorphous API is crystallized as a component of the co-crystal;

(q) the form diversity of the co-crystal is decreased as compared to the API; or

(r) the morphology of the co-crystal is modulated as compared to the API.

5. A pharmaceutical co-crystal composition, comprising: a first and a second API, wherein each API is either a liquid or a solid at room temperature, and wherein the APIs are hydrogen bonded to a molecule.

6. The pharmaceutical co-crystal composition according to claim 5, wherein:

(a) the first API is hydrogen bonded to the second API;

(b) an API is selected from an API of Table IV;

(c) each API is selected from an API of Table IV;

(d) an API is a liquid at room temperature and the other API is a solid at room temperature;

(e) each API is a solid at room temperature;

(f) an API has at least one functional group selected from the group consisting of: ether, thioether, alcohol, thiol, aldehyde, ketone, thioketone, nitrate ester, phosphate ester, thiophosphate ester, ester, thioester, sulfate ester, carboxylic acid, phosphonic acid, phosphinic acid, sulfonic acid, amide, primary amine, secondary amine, ammonia, tertiary amine, imine, thiocyanate, cyanamide, oxime, nitrile, diazo, organohalide, nitro, S-heterocyclic ring, thiophene, N-heterocyclic ring, pyrrole, O-heterocyclic ring, furan, epoxide, peroxide, hydroxamic acid, imidazole, and pyridine;

(g) each API has at least one functional group selected from the group consisting of: ether, thioether, alcohol, thiol, aldehyde, ketone, thioketone, nitrate ester, phosphate ester, thiophosphate ester, ester, thioester, sulfate ester, carboxylic acid, phosphonic acid, phosphinic acid, sulfonic acid, amide, primary amine, secondary amine, ammonia, tertiary amine, imine, thiocyanate, cyanamide, oxime, nitrile, diazo,

organohalide, nitro, S-heterocyclic ring, thiophene, N-heterocyclic ring, pyrrole, O-heterocyclic ring, furan, epoxide, peroxide, hydroxamic acid, imidazole, and pyridine;

(h) the difference in pK_a between the first API and the second API does not exceed 2;

(i) the solubility of the co-crystal is increased as compared to an API;

(j) the dose response of the co-crystal is increased as compared to an API;

(k) the dissolution of the co-crystal is increased as compared to an API;

(l) the bioavailability of the co-crystal is increased as compared to an API;

(m) the stability of the co-crystal is increased as compared to an API;

(n) a difficult to salt or unsaltable API is incorporated into the co-crystal;

(o) the hygroscopicity of the co-crystal is decreased as compared to an API;

(p) an amorphous API is crystallized as a component of the co-crystal;

(q) the form diversity of the co-crystal is decreased as compared to an API; or

(r) the morphology of the co-crystal is modulated as compared to an API.

7. A pharmaceutical co-crystal composition, comprising: a first and a second co-crystal former, wherein each co-crystal former is a solid at room temperature, and wherein both co-crystal formers are hydrogen bonded to a molecule.

8. The pharmaceutical co-crystal composition according to claim 7, wherein:

(a) the first co-crystal former is hydrogen bonded to the second co-crystal former;

(b) a co-crystal former is selected from a co-crystal former of Table I or Table II;

(c) each co-crystal former is selected from a co-crystal former of Table I or Table II;

(d) a co-crystal former has at least one functional group selected from the group consisting of: ether, thioether, alcohol, thiol, aldehyde, ketone, thioketone, nitrate ester, phosphate ester, thiophosphate ester, ester, thioester, sulfate ester, carboxylic acid, phosphonic acid, phosphinic acid, sulfonic acid, amide, primary amine, secondary amine, ammonia, tertiary amine, imine, thiocyanate, cyanamide, oxime, nitrile, diazo, organohalide, nitro, S-heterocyclic ring, thiophene, N-heterocyclic ring, pyrrole, O-heterocyclic ring, furan, epoxide, peroxide, hydroxamic acid, imidazole, and pyridine;

(e) each co-crystal former has at least one functional group selected from the group consisting of: ether, thioether, alcohol, thiol, aldehyde, ketone, thioketone, nitrate ester, phosphate ester, thiophosphate ester, ester, thioester, sulfate ester, carboxylic acid, phosphonic acid, phosphinic acid, sulfonic acid, amide, primary amine, secondary amine, ammonia, tertiary amine, imine, thiocyanate, cyanamide, oxime, nitrile, diazo, organohalide, nitro, S-heterocyclic ring, thiophene, N-heterocyclic ring, pyrrole, O-heterocyclic ring, furan, epoxide, peroxide, hydroxamic acid, imidazole, and pyridine;

(f) the difference in pK_a between the first co-crystal former and the second co-crystal former does not exceed 2;

(g) the solubility of the co-crystal is increased as compared to a co-crystal former;

(h) the dose response of the co-crystal is increased as compared to a co-crystal former;

(i) the dissolution of the co-crystal is increased as compared to a co-crystal former;

(j) the bioavailability of the co-crystal is increased as compared to a co-crystal former;

(k) the stability of the co-crystal is increased as compared to a co-crystal former;

(l) a difficult to salt or unsaltable API is incorporated into the co-crystal;

(m) the hygroscopicity of the co-crystal is decreased as compared to a co-crystal former;

(n) an amorphous API is crystallized as a component of the co-crystal;

(o) the form diversity of the co-crystal is decreased as compared to a co-crystal former; or

(p) the morphology of the co-crystal is modulated as compared to a co-crystal former.

9. The pharmaceutical co-crystal composition according to claim 1, wherein the API is selected from celecoxib, carbamazepine, itraconazole, olanzapine, topiramate, modafinil, 5-fluorouracil, hydrochlorothiazide, acetaminophen, aspirin, flurbiprofen, phenytoin, or ibuprofen.

10. The pharmaceutical co-crystal composition according to claim 1, 3, 5, or 7, further comprising a pharmaceutically acceptable diluent, excipient, or carrier.

11. A co-crystal comprising an API and a co-crystal former selected from the group consisting of:

(a) carbamazepine and saccharin;

(b) carbamazepine and nicotinamide;

(c) carbamazepine and trimesic acid;

(d) celecoxib and nicotinamide;

(e) olanzapine and nicotinamide;

(f) celecoxib and 18-crown-6;

(g) itraconazole and succinic acid;

(h) itraconazole and fumaric acid;

(i) itraconazole and L-tartaric acid;

(j) itraconazole and L-malic acid;

(k) itraconazoleHCl and DL-tartaric acid;

(l) modafinil and malonic acid;

(m) modafinil and glycolic acid;

(n) modafinil and maleic acid;

(o) topiramate and 18-crown-6;

(p) 5-fluorouracil and urea;

(q) hydrochlorothiazide and nicotinic acid;

(r) hydrochlorothiazide and 18-crown-6;

(s) hydrochlorothiazide and piperazine;

(t) acetaminophen and 4,4'-bipyridine;

(u) phenytoin and pyridone;

(v) aspirin and 4,4'-bipyridine;

(w) ibuprofen and 4,4'-bipyridine;

(x) flurbiprofen and 4,4'-bipyridine;

(y) flurbiprofen and trans-1,2-bis(4-pyridyl) ethylene;

(z) carbamazepine and p-phthalaldehyde;

(aa) carbamazepine and 2,6-pyridinecarboxylic acid;

(bb) carbamazepine and 5-nitroisophthalic acid;

(cc) carbamazepine and 1,3,5,7-adamantane tetracarboxylic acid; and

(dd) carbamazepine and benzoquinone.

12. A process for preparing a pharmaceutical co-crystal composition comprising an API and a co-crystal former, comprising:

(a) providing an API and a co-crystal former, wherein the API is a liquid or a solid at room temperature and the co-crystal former is a solid at room temperature;

(b) grinding, heating, co-subliming, co-melting, or contacting in solution the API with the co-crystal former under crystallization conditions, so as to form a solid phase, wherein the API and co-crystal former are hydrogen bonded to each other;

(c) isolating co-crystals formed thereby; and

(d) incorporating the co-crystals into a pharmaceutical composition.

13. The process of claim 12, wherein:

(a) the co-crystal former is selected from a co-crystal former of Table I or Table II;

(b) the API is selected from an API of Table IV;

(c) the API is selected from an API of Table IV and the co-crystal former is selected from a co-crystal former of Table I or Table II;

(d) the API is a liquid at room temperature;

(e) the API is a solid at room temperature;

(f) the API has at least one functional group selected from the group consisting of: ether, thioether, alcohol, thiol, aldehyde, ketone, thioketone, nitrate ester, phosphate ester, thiophosphate ester, ester, thioester, sulfate ester, carboxylic acid, phosphonic acid, phosphinic acid, sulfonic acid, amide, primary amine, secondary amine, ammonia, tertiary amine, imine, thiocyanate, cyanamide, oxime, nitrile, diazo, organohalide, nitro, S-heterocyclic ring, thiophene, N-heterocyclic ring, pyrrole, O-heterocyclic ring, furan, epoxide, peroxide, hydroxamic acid, imidazole, and pyridine;

(g) the co-crystal former has at least one functional group selected from the group consisting of: ether, thioether, alcohol, thiol, aldehyde, ketone, thioketone, nitrate ester, phosphate ester, thiophosphate ester, ester, thioester, sulfate ester, carboxylic acid, phosphonic acid, phosphinic acid, sulfonic acid, amide, primary amine, secondary amine, ammonia, tertiary amine, imine, thiocyanate, cyanamide, oxime, nitrile, diazo, organohalide, nitro, S-heterocyclic ring, thiophene, N-heterocyclic ring, pyrrole, O-heterocyclic ring, furan, epoxide, peroxide, hydroxamic acid, imidazole, and pyridine; or

(h) the difference in pK_a between the API and the co-crystal former does not exceed 2.

14. A process for preparing a pharmaceutical co-crystal composition comprising an API, a co-crystal former, and a third molecule, comprising:

(a) providing an API and a co-crystal former, wherein the API is a liquid or a solid at room temperature and the co-crystal former is a solid at room temperature;

(b) grinding, heating, co-subliming, co-melting, or contacting in solution the API with the co-crystal former under crystallization conditions, so as to form a solid phase, wherein the API and the third molecule are bonded to each other, and further wherein the co-crystal former and the third molecule are hydrogen bonded to each other;

(c) isolating co-crystals formed thereby; and

(d) incorporating the co-crystals into a pharmaceutical composition.

15. The process of claim 14, wherein:

(a) the co-crystal former is selected from a co-crystal former of Table I or Table II;

(b) the API is selected from an API of Table IV;

(c) the API is selected from an API of Table IV and the co-crystal former is selected from a co-crystal former of Table I or Table II;

(d) the API is a liquid at room temperature;

(e) the API is a solid at room temperature;

(f) the API has at least one functional group selected from the group consisting of: ether, thioether, alcohol, thiol, aldehyde, ketone, thioketone, nitrate ester, phosphate ester, thiophosphate ester, ester, thioester, sulfate ester, carboxylic acid, phosphonic acid, phosphinic acid, sulfonic acid, amide, primary amine, secondary amine, ammonia, tertiary amine, imine, thiocyanate, cyanamide, oxime, nitrile, diazo, organohalide, nitro, S-heterocyclic ring, thiophene, N-heterocyclic ring, pyrrole, O-heterocyclic ring, furan, epoxide, peroxide, hydroxamic acid, imidazole, and pyridine;

(g) the co-crystal former has at least one functional group selected from the group consisting of: ether, thioether, alcohol, thiol, aldehyde, ketone, thioketone, nitrate ester, phosphate ester, thiophosphate ester, ester, thioester, sulfate ester, carboxylic acid, phosphonic acid, phosphinic acid, sulfonic acid, amide, primary amine, secondary amine, ammonia, tertiary amine, imine, thiocyanate, cyanamide, oxime, nitrile, diazo, organohalide, nitro, S-heterocyclic ring, thiophene, N-heterocyclic ring, pyrrole, O-heterocyclic ring, furan, epoxide, peroxide, hydroxamic acid, imidazole, and pyridine; or

(h) the difference in pK_a between the API and the co-crystal former does not exceed 2.

16. A process for preparing a pharmaceutical co-crystal composition comprising a first and a second API, comprising:

(a) providing a first and a second API, wherein each API is either a liquid or a solid at room temperature;

(b) grinding, heating, co-subliming, co-melting, or contacting in solution the APIs under crystallization conditions, so as to form a solid phase, wherein the APIs are hydrogen bonded to a molecule;

(c) isolating co-crystals formed thereby; and

(d) incorporating the co-crystals into a pharmaceutical composition.

17. The process of claim 16, wherein:

(a) the first API is hydrogen bonded to the second API;

(b) an API is selected from an API of Table IV;

(c) each API is selected from an API of Table IV;

(d) an API is a liquid at room temperature and the other API is a solid at room temperature;

(e) each API is a solid at room temperature;

(f) an API has at least one functional group selected from the group consisting of: ether, thioether, alcohol, thiol, aldehyde, ketone,

thioketone, nitrate ester, phosphate ester, thiophosphate ester, ester, thioester, sulfate ester, carboxylic acid, phosphonic acid, phosphinic acid, sulfonic acid, amide, primary amine, secondary amine, ammonia, tertiary amine, imine, thiocyanate, cyanamide, oxime, nitrile, diazo, organohalide, nitro, S-heterocyclic ring, thiophene, N-heterocyclic ring, pyrrole, O-heterocyclic ring, furan, epoxide, peroxide, hydroxamic acid, imidazole, and pyridine;

(g) each API has at least one functional group selected from the group consisting of: ether, thioether, alcohol, thiol, aldehyde, ketone, thioketone, nitrate ester, phosphate ester, thiophosphate ester, ester, thioester, sulfate ester, carboxylic acid, phosphonic acid, phosphinic acid, sulfonic acid, amide, primary amine, secondary amine, ammonia, tertiary amine, imine, thiocyanate, cyanamide, oxime, nitrile, diazo, organohalide, nitro, S-heterocyclic ring, thiophene, N-heterocyclic ring, pyrrole, O-heterocyclic ring, furan, epoxide, peroxide, hydroxamic acid, imidazole, and pyridine; or

(h) the difference in pK_a between the first API and the second API does not exceed 2.

18. A process for preparing a pharmaceutical co-crystal composition comprising a first and a second co-crystal former, comprising:

(a) providing a first and a second co-crystal former, wherein each co-crystal former is a solid at room temperature;

(b) grinding, heating, co-subliming, co-melting, or contacting in solution the co-crystal formers under crystallization conditions, so as to form a solid phase, wherein both co-crystal formers are hydrogen bonded to a molecule;

(c) isolating co-crystals formed thereby; and

(d) incorporating the co-crystals into a pharmaceutical composition.

19. The process of claim 18, wherein:

(a) the first co-crystal former is hydrogen bonded to the second co-crystal former;

(b) a co-crystal former is selected from a co-crystal former of Table I or Table II;

(c) each co-crystal former is selected from a co-crystal former of Table I or Table II;

(d) a co-crystal former has at least one functional group selected from the group consisting of: ether, thioether, alcohol, thiol, aldehyde, ketone, thioketone, nitrate ester, phosphate ester, thiophosphate ester, ester, thioester, sulfate ester, carboxylic acid, phosphonic acid, phosphinic acid, sulfonic acid, amide, primary amine, secondary amine, ammonia, tertiary amine, imine, thiocyanate, cyanamide, oxime, nitrile, diazo, organohalide, nitro, S-heterocyclic ring, thiophene, N-heterocyclic ring, pyrrole, O-heterocyclic ring, furan, epoxide, peroxide, hydroxamic acid, imidazole, and pyridine;

(e) each co-crystal former has at least one functional group selected from the group consisting of: ether, thioether, alcohol, thiol, aldehyde, ketone, thioketone, nitrate ester, phosphate ester, thiophosphate ester, ester, thioester, sulfate ester, carboxylic acid, phosphonic acid, phosphinic acid, sulfonic acid, amide, primary amine, secondary amine, ammonia, tertiary amine, imine, thiocyanate, cyanamide, oxime, nitrile, diazo, organohalide, nitro, S-heterocyclic ring, thiophene, N-heterocyclic ring, pyrrole, O-heterocyclic ring, furan, epoxide, peroxide, hydroxamic acid, imidazole, and pyridine; or

(f) the difference in pK_a between the first co-crystal former and the second co-crystal former does not exceed 2.

20. The process of claim 12, wherein the API is selected from celecoxib, carbamazepine, itraconazole, olanzapine, topiramate, modafinil, 5-fluorouracil, hydrochlorothiazide, acetaminophen, aspirin, flurbiprofen, phenytoin, or ibuprofen.

21. The process of claim 12, further comprising: incorporating a pharmaceutically acceptable diluent, excipient, or carrier.

22. A process of preparing a co-crystal comprising an API and a co-crystal former, comprising:

(a) providing an API and a co-crystal former;

(b) grinding, heating, co-subliming, co-melting, or contacting in solution the API with the co-crystal former under crystallization conditions, so as to form a solid phase; and

(c) isolating co-crystals formed thereby;

wherein the API and the co-crystal former, respectively, are selected from the group consisting of: carbamazepine and saccharin, carbamazepine and nicotinamide, carbamazepine and trimesic acid, celecoxib and nicotinamide, olanzapine and nicotinamide, celecoxib and 18-crown-6, itraconazole and succinic acid, itraconazole and fumaric acid, itraconazole and tartaric acid, itraconazole and malic acid, itraconazoleHCl and tartaric acid, modafinil and malonic acid, modafinil and glycolic acid, modafinil and maleic acid, topiramate and 18-crown-6, 5-fluorouracil and urea, hydrochlorothiazide and nicotinic acid, hydrochlorothiazide and 18-crown-6, hydrochlorothiazide and piperazine, acetaminophen and 4,4'-bipyridine, phenytoin and pyridone, aspirin and 4,4'-bipyridine, ibuprofen and 4,4'-bipyridine, flurbiprofen and 4,4'-bipyridine, flurbiprofen and trans-1,2-bis(4-pyridyl) ethylene, carbamazepine and p-phthalaldehyde, carbamazepine and 2,6-pyridinecarboxylic acid, carbamazepine and 5-nitroisophthalic acid, carbamazepine and 1,3,5,7-adamantane tetracarboxylic acid, and carbamazepine and benzoquinone.

23. A process for modulating the solubility of an API for use in a pharmaceutical composition, which process comprises:

(a) grinding, heating, co-subliming, co-melting, or contacting in solution the API with a co-crystal forming compound under crystallization conditions, so as to form a co-crystal of the API and the co-crystal forming compound;

(b) isolating the co-crystal, wherein the co-crystal has a modulated solubility as compared to the API; and

(c) incorporating the co-crystal having modulated solubility into a pharmaceutical composition.

24. The process of claim 23, wherein the solubility of the co-crystal is increased as compared to the API.

25. A process for modulating the dose response of an API for use in a pharmaceutical composition, which process comprises:

(a) grinding, heating, co-subliming, co-melting, or contacting in solution the API with a co-crystal forming compound under crystallization conditions, so as to form a co-crystal of the API and the co-crystal forming compound;

(b) isolating the co-crystal, wherein the co-crystal has a modulated dose response as compared to the API; and

(c) incorporating the co-crystal having modulated dose response into a pharmaceutical composition.

26. The process of claim 25, wherein the dose response of the co-crystal is increased as compared to the API.

27. A process for modulating the dissolution of an API for use in a pharmaceutical composition, which process comprises:

(a) grinding, heating, co-subliming, co-melting, or contacting in solution the API with a co-crystal forming compound under crystallization conditions, so as to form a co-crystal of the API and the co-crystal forming compound;

(b) isolating the co-crystal, wherein the co-crystal has a modulated dissolution as compared to the API; and

(c) incorporating the co-crystal having modulated dissolution into a pharmaceutical composition.

28. The process of claim 27, wherein the dissolution of the co-crystal is increased as compared to the API.

29. A process for modulating the bioavailability of an API for use in a pharmaceutical composition, which process comprises:

(a) grinding, heating, co-subliming, co-melting, or contacting in solution the API with a co-crystal forming compound under crystallization conditions, so as to form a co-crystal of the API and the co-crystal forming compound;

(b) isolating the co-crystal, wherein the co-crystal has a modulated bioavailability as compared to the API; and

(c) incorporating the co-crystal having modulated bioavailability into a pharmaceutical composition.

30. The process of claim 29, wherein the bioavailability of the co-crystal is increased as compared to the API.

31. A process for increasing the stability of an API for use in a pharmaceutical composition, which process comprises:

(a) grinding, heating, co-subliming, co-melting, or contacting in solution the API with a co-crystal forming compound under crystallization conditions, so as to form a co-crystal of the API and the co-crystal forming compound;

(b) isolating the co-crystal, wherein the co-crystal has increased stability as compared to the API; and

(c) incorporating the co-crystal having increased stability into a pharmaceutical composition.

32. A process for the incorporation of a difficult to salt or unsaltable API for use in a pharmaceutical composition, which process comprises:

(a) grinding, heating, co-subliming, co-melting, or contacting in solution the API with a co-crystal forming compound under crystallization conditions, so as to form a co-crystal of the API and the co-crystal forming compound;

(b) isolating the co-crystal;

(c) incorporating the co-crystal having a difficult to salt or unsaltable API into a pharmaceutical composition.

33. A process for decreasing the hygroscopicity of an API for use in a pharmaceutical composition, which process comprises:

(a) grinding, heating, co-subliming, co-melting, or contacting in solution the API with a co-crystal forming compound under crystallization conditions, so as to form a co-crystal of the API and the co-crystal forming compound;

(b) isolating the co-crystal, wherein the co-crystal has decreased hygroscopicity as compared to the API; and

(c) incorporating the co-crystal having decreased hygroscopicity into a pharmaceutical composition.

34. A process for crystallizing an amorphous API for use in a pharmaceutical composition, which process comprises:

(a) grinding, heating, co-subliming, co-melting, or contacting in solution the API with a co-crystal forming compound under crystallization conditions, so as to form a co-crystal of the API and the co-crystal forming compound;

(b) isolating the co-crystal;

(c) incorporating the co-crystal into a pharmaceutical composition.

35. A process for decreasing the form diversity of an API for use in a pharmaceutical composition, which process includes:

(a) grinding, heating, co-subliming, co-melting, or contacting in solution the API with a co-crystal forming compound under crystallization conditions, so as to form a co-crystal of the API and the co-crystal forming compound;

(b) isolating the co-crystal, wherein the co-crystal has decreased form diversity as compared to the API; and

(c) incorporating the co-crystal having decreased form diversity into a pharmaceutical composition.

36. A process for modulating the morphology of an API for use in a pharmaceutical composition, which process includes:

(a) grinding, heating, co-subliming, co-melting, or contacting in solution the API with a co-crystal forming compound under crystallization conditions, so as to form a co-crystal of the API and the co-crystal forming compound;

(b) isolating the co-crystal, wherein the co-crystal has a different morphology as compared to the API; and

(c) incorporating the co-crystal having modulated morphology into a pharmaceutical composition.

37. The pharmaceutical co-crystal composition according to claims 1, 3, 5, or 7, wherein the API or co-crystal former comprises an amino-pyridine functional group as a hydrogen bonded moiety and another hydrogen bonded moiety comprises:

(a) a primary amide;

(b) a secondary amide;

(c) a carboxylic acid;

(d) water;

(e) an alcohol;

(f) a primary amine;

(g) a secondary amine;

(h) a carbonyl;

(i) a sulfoxo moiety;

(j) an ether;

(k) an ester;

(l) an aromatic N;

(m) a cyano moiety;

(n) a nitro moiety;

(o) a chloride moiety;

(p) a bromide moiety;

(q) a primary amide where the interaction distance is between about 2.97 and about 3.07 angstroms;

(r) a secondary amide where the interaction distance is between about 2.70 and about 3.20 angstroms;

(s) a secondary amide where the interaction distance is between about 2.75 and about 3.17 angstroms;

(t) a carboxylic acid where the interaction distance is between about 2.72 and about 3.07 angstroms;

(u) a carboxylic acid where the interaction distance is between about 2.54 and about 2.82 angstroms;

(v) water where the interaction distance is between about 2.72 and about 3.15 angstroms;

(w) water where the interaction distance is between about 2.65 and about 3.15 angstroms;

(x) an alcohol where the interaction distance is between about 2.78 and about 3.14 angstroms;

(y) an alcohol where the interaction distance is between about 2.63 and about 3.06 angstroms;

(z) a primary amine where the interaction distance is between about 2.85 and about 3.25 angstroms;

(aa) a secondary amine where the interaction distance is between about 2.83 and about 3.25 angstroms;

(bb) a carbonyl where the interaction distance is between about 2.87 and about 3.10 angstroms;

(cc) a sulfoxo moiety where the interaction distance is between about 2.70 and about 3.10 angstroms;

(dd) an ether where the interaction distance is between about 2.84 and about 3.20 angstroms;

(ee) an ester where the interaction distance is about 3.09 angstroms;

(ff) an ester where the interaction distance is between about 2.85 and about 3.16 angstroms;

(gg) an aromatic N where the interaction distance is between about 2.78 and about 3.25 angstroms;

(hh) a cyano moiety where the interaction distance is between about 2.83 and about 3.30 angstroms;

(ii) a nitro moiety where the interaction distance is between about 2.85 and about 3.28 angstroms;

(jj) a chloride moiety where the interaction distance is between about 3.10 and about 3.45 angstroms; or

(kk) a bromide moiety where the interaction distance is between about 3.27 and about 3.48 angstroms.

38. The pharmaceutical co-crystal composition according to claims 1, 3, 5, or 7, wherein the API or co-crystal former comprises a primary amine functional group as a hydrogen bonded moiety and another hydrogen bonded moiety comprises:

(a) a primary amide;

(b) a secondary amide;

(c) a carboxylic acid;

(d) an amino-pyridine;

(e) a sulfonamide;

(f) water;

(g) an alcohol;

(h) a carbonyl;

(i) a sulfoxo moiety;

(j) a sulfonyl;

(k) an ether;

(l) an ester;

(m) an aromatic N;

(n) a cyano moiety;

(o) a nitro moiety;

(p) a chloride moiety;

(q) a bromide moiety;

(r) a primary amide where the interaction distance is between about 2.73 and about 3.20 angstroms;

(s) a secondary amide where the interaction distance is between about 2.65 and about 3.20 angstroms;

(t) a carboxylic acid where the interaction distance is between about 2.74 and about 3.15 angstroms;

(u) a carboxylic acid where the interaction distance is between about 2.72 and about 3.12 angstroms;

(v) an amino-pyridine where the interaction distance is between about 3.10 and about 3.24 angstroms;

(w) a sulfonamide where the interaction distance is between about 2.86 and about 3.17 angstroms;

(x) water where the interaction distance is between about 2.65 and about 3.17 angstroms;

(y) an alcohol where the interaction distance is between about 2.63 and about 3.26 angstroms;

(z) a carbonyl where the interaction distance is between about 2.64 and about 3.15 angstroms;

(aa) a sulfoxo moiety where the interaction distance is between about 2.70 and about 3.10 angstroms;

(bb) a sulfonyl where the interaction distance is between about 2.93 and about 3.12 angstroms;

(cc) an ether where the interaction distance is between about 2.75 and about 3.25 angstroms;

(dd) an ester where the interaction distance is between about 2.90 and about 3.20 angstroms;

(ee) an ester where the interaction distance is between about 2.74 and about 3.27 angstroms;

(ff) an aromatic N where the interaction distance is between about 2.92 and about 3.26 angstroms;

(gg) a cyano moiety where the interaction distance is between about 2.83 and about 3.30 angstroms;

(hh) a nitro moiety where the interaction distance is between about 2.75 and about 3.17 angstroms;

(ii) a chloride moiety where the interaction distance is between about 3.07 and about 3.50 angstroms; or

(jj) a bromide moiety where the interaction distance is between about 3.23 and about 3.60 angstroms.

39. The pharmaceutical co-crystal composition according to claims 1, 3, 5, or 7, wherein the API or co-crystal former comprises a primary sulfonamide functional group as a hydrogen bonded moiety and another hydrogen bonded moiety comprises:

(a) water;

(b) an alcohol;

(c) a primary amine;

(d) a secondary amine;

(e) a sulfonyl;

(f) an ether;

(g) an ester;

(h) a cyano moiety;

(i) a nitro moiety;

(j) a chloride moiety;

(k) water where the interaction distance is about 2.87 angstroms;

(l) an alcohol where the interaction distance is between about 2.85 and about 3.07 angstroms;

(m) a primary amine where the interaction distance is between about 2.85 and about 3.20 angstroms;

(n) a secondary amine where the interaction distance is between about 2.85 and about 3.20 angstroms;

(o) a sulfonyl where the interaction distance is between about 2.85 and about 3.20 angstroms;

(p) an ether where the interaction distance is between about 2.90 and about 3.20 angstroms;

(q) an ester where the interaction distance is between about 2.85 and about 3.12 angstroms;

(r) a cyano moiety where the interaction distance is about 3.00 angstroms;

(s) a nitro moiety where the interaction distance is between about 3.00 and about 3.20 angstroms; or

(t) a chloride moiety where the interaction distance is between about 3.20 and about 3.32 angstroms.

40. The pharmaceutical co-crystal composition according to claims 1, 3, 5, or 7, wherein the API or co-crystal former comprises a primary amide functional group as a hydrogen bonded moiety and another hydrogen bonded moiety comprises:

(a) a secondary amide;

(b) a carboxylic acid;

(c) an amino-pyridine;

(d) an aromatic N;

(e) water;

(f) an alcohol;

(g) a secondary amine;

(h) a carbonyl;

(i) a sulfonyl;

(j) an ether;

(k) an ester;

(l) a cyano moiety;

(m) a nitro moiety;

(n) a chloride moiety;

(o) a bromide moiety;

(p) a secondary amide where the interaction distance is between about 2.70 and about 3.15 angstroms;

(q) a carboxylic acid where the interaction distance is between about 2.40 and about 2.80 angstroms;

(r) a carboxylic acid where the interaction distance is between about 2.80 and about 3.25 angstroms;

(s) an amino-pyridine where the interaction distance is between about 2.90 and about 3.20 angstroms;

(t) an amino-pyridine where the interaction distance is between about 2.80 and about 3.10 angstroms;

(u) an aromatic N where the interaction distance is between about 2.90 and about 3.21 angstroms;

(v) water where the interaction distance is between about 2.60 and about 3.00 angstroms;

(w) water where the interaction distance is between about 2.70 and about 3.07 angstroms;

(x) an alcohol where the interaction distance is between about 2.50 and about 3.00 angstroms;

(y) an alcohol where the interaction distance is between about 2.70 and about 3.10 angstroms;

(z) a secondary amine where the interaction distance is between about 2.80 and about 3.10 angstroms;

(aa) a secondary amine where the interaction distance is between about 3.00 and about 3.15 angstroms;

(bb) a carbonyl where the interaction distance is between about 2.80 and about 3.15 angstroms;

(cc) a sulfonyl where the interaction distance is between about 2.90 and about 3.00 angstroms;

(dd) an ether where the interaction distance is between about 2.80 and about 3.10 angstroms;

(ee) an ester where the interaction distance is between about 2.70 and about 3.05 angstroms;

(ff) a cyano moiety where the interaction distance is between about 3.00 and about 3.30 angstroms;

(gg) a nitro moiety where the interaction distance is between about 2.90 and about 3.07 angstroms;

(hh) a chloride moiety where the interaction distance is between about 3.10 and about 3.60 angstroms; or

(ii) a bromide moiety where the interaction distance is between about 3.30 and about 3.80 angstroms.

41. The pharmaceutical co-crystal composition according to claims 1, 3, 5, or 7, wherein the API or co-crystal former comprises a secondary amide functional group as a hydrogen bonded moiety and another hydrogen bonded moiety comprises:

(a) a primary amide;

(b) a carboxylic acid;

(c) an amino-pyridine;

(d) a sulfonamide;

(e) an aromatic N;

(f) water;

(g) an alcohol;

(h) a primary amine;

(i) a secondary amine;

(j) a carbonyl;

(k) a sulfonyl;

(l) an ether;

(m) an ester;

(n) a cyano moiety;

(o) a nitro moiety;

(p) a chloride moiety;

(q) a bromide moiety;

(r) a primary amide where the interaction distance is between about 2.70 and about 3.15 angstroms;

(s) a carboxylic acid where the interaction distance is between about 2.70 and about 3.10 angstroms;

(t) a carboxylic acid where the interaction distance is between about 2.40 and about 3.05 angstroms;

(u) an amino-pyridine where the interaction distance is between about 2.70 and about 3.20 angstroms;

(v) an amino-pyridine where the interaction distance is between about 2.75 and about 3.17 angstroms;

(w) a sulfonamide where the interaction distance is between about 2.70 and about 3.00 angstroms;

(x) an aromatic N where the interaction distance is between about 2.60 and about 3.15 angstroms;

(y) water where the interaction distance is between about 2.40 and about 3.10 angstroms;

(z) water where the interaction distance is between about 2.60 and about 3.10 angstroms;

(aa) an alcohol where the interaction distance is between about 2.50 and about 3.04 angstroms;

(bb) an alcohol where the interaction distance is between about 2.50 and about 3.20 angstroms;

(cc) a primary amine where the interaction distance is between about 2.65 and about 3.20 angstroms;

(dd) a secondary amine where the interaction distance is between about 2.60 and about 3.15 angstroms;

(ee) a carbonyl where the interaction distance is between about 2.70 and about 3.07 angstroms;

(ff) a sulfonyl where the interaction distance is between about 2.60 and about 3.25 angstroms;

(gg) an ether where the interaction distance is between about 2.70 and about 3.16 angstroms;

(hh) an ester where the interaction distance is between about 2.80 and about 3.16 angstroms;

(ii) a cyano moiety where the interaction distance is between about 2.90 and about 3.30 angstroms;

(jj) a nitro moiety where the interaction distance is between about 2.80 and about 3.10 angstroms;

(kk) a chloride moiety where the interaction distance is between about 2.90 and about 3.40 angstroms; or

(ll) a bromide moiety where the interaction distance is between about 3.10 and about 3.50 angstroms.

42. The pharmaceutical co-crystal composition according to claims 1, 3, 5, or 7, wherein the API or co-crystal former comprises an alcohol functional group as a hydrogen bonded moiety and another hydrogen bonded moiety comprises:

(a) a primary amide;

(b) a secondary amide;

(c) a carboxylic acid;

(d) an amino-pyridine;

(e) a sulfonamide;

(f) an aromatic N;

(g) water;

(h) a primary amine;

(i) a secondary amine;

(j) a carbonyl;

(k) a sulfonyl;

(l) an ether;

(m) an ester;

(n) a cyano moiety;

(o) a nitro moiety;

(p) a chloride moiety;

(q) a bromide moiety;

(r) a primary amide where the interaction distance is between about 2.50 and about 3.00 angstroms;

(s) a primary amide where the interaction distance is between about 2.70 and about 3.10 angstroms;

(t) a secondary amide where the interaction distance is between about 2.50 and about 3.04 angstroms;

(u) a secondary amide where the interaction distance is between about 2.50 and about 3.20 angstroms;

(v) a carboxylic acid where the interaction distance is between about 2.50 and about 3.00 angstroms;

(w) a carboxylic acid where the interaction distance is between about 2.40 and about 2.90 angstroms;

(x) an amino-pyridine where the interaction distance is between about 2.60 and about 3.06 angstroms;

(y) an amino-pyridine where the interaction distance is between about 2.75 and about 3.15 angstroms;

(z) a sulfonamide where the interaction distance is between about 2.80 and about 3.07 angstroms;

(aa) an aromatic N where the interaction distance is between about 2.50 and about 3.00 angstroms;

(bb) water where the interaction distance is between about 2.40 and about 3.03 angstroms;

(cc) a primary amine where the interaction distance is between about 2.60 and about 3.15 angstroms;

(dd) a secondary amine where the interaction distance is between about 2.60 and about 3.15 angstroms;

(ee) a carbonyl where the interaction distance is between about 2.40 and about 3.05 angstroms;

(ff) a sulfonyl where the interaction distance is between about 2.40 and about 3.15 angstroms;

(gg) an ether where the interaction distance is between about 2.40 and about 3.00 angstroms;

(hh) an ester where the interaction distance is between about 2.50 and about 3.10 angstroms;

(ii) a cyano moiety where the interaction distance is between about 2.40 and about 3.10 angstroms;

(jj) a nitro moiety where the interaction distance is between about 2.45 and about 3.05 angstroms;

(kk) a chloride moiety where the interaction distance is between about 2.60 and about 3.30 angstroms; or

(ll) a bromide moiety where the interaction distance is between about 3.00 and about 3.50 angstroms.

43. The pharmaceutical co-crystal composition according to claims 1, 3, 5, or 7, wherein the API or co-crystal former comprises a carboxylic acid functional group as a hydrogen bonded moiety and another hydrogen bonded moiety comprises:

(a) a primary amide;

(b) a secondary amide;

(c) an amino-pyridine;

(d) an aromatic N;

(e) water;

(f) an alcohol;

(g) a primary amine;

(h) a secondary amine;

(i) a carbonyl;

(j) an ether;

(k) an ester;

(l) a cyano moiety;

(m) a nitro moiety;

(n) a chloride moiety;

(o) a bromide moiety;

(p) a primary amide where the interaction distance is between about 2.80 and about 3.25 angstroms;

(q) a primary amide where the interaction distance is between about 2.40 and about 2.80 angstroms;

(r) a secondary amide where the interaction distance is between about 2.70 and about 3.10 angstroms;

(s) a secondary amide where the interaction distance is between about 2.40 and about 3.05 angstroms;

(t) an amino-pyridine where the interaction distance is between about 2.50 and about 2.80 angstroms;

(u) an amino-pyridine where the interaction distance is between about 2.70 and about 3.00 angstroms;

(v) an aromatic N where the interaction distance is between about 2.54 and about 2.94 angstroms;

(w) water where the interaction distance is between about 2.50 and about 3.00 angstroms;

(x) water where the interaction distance is between about 2.40 and about 3.00 angstroms;

(y) an alcohol where the interaction distance is between about 2.50 and about 3.00 angstroms;

(z) an alcohol where the interaction distance is between about 2.50 and about 2.90 angstroms;

(aa) a primary amine where the interaction distance is between about 2.70 and about 3.10 angstroms;

(bb) a secondary amine where the interaction distance is between about 2.70 and about 3.10 angstroms;

(cc) a carbonyl where the interaction distance is between about 2.40 and about 3.00 angstroms;

(dd) an ether where the interaction distance is between about 2.50 and about 3.00 angstroms;

(ee) an ester where the interaction distance is between about 2.40 and about 3.05 angstroms;

(ff) an ester where the interaction distance is between about 2.40 and about 3.10 angstroms;

(gg) a cyano moiety where the interaction distance is between about 2.50 and about 2.80 angstroms;

(hh) a nitro moiety where the interaction distance is between about 2.70 and about 3.05 angstroms;

(ii) a chloride moiety where the interaction distance is between about 2.80 and about 3.20 angstroms; or

(jj) a bromide moiety where the interaction distance is between about 3.00 and about 3.30 angstroms.

44. The pharmaceutical co-crystal composition according to claims 1, 3, 5, or 7, wherein the API or co-crystal former comprises a carbonyl functional group as a hydrogen bonded moiety and another hydrogen bonded moiety comprises:

(a) a primary amide;

(b) a secondary amide;

(c) a carboxylic acid;

(d) an amino-pyridine;

(e) a secondary sulfonamide;

(f) water;

(g) an alcohol;

(h) a primary amine;

(i) a secondary amine;

(j) a primary amide where the interaction distance is between about 2.83 and about 3.15 angstroms;

(k) a secondary amide where the interaction distance is between about 2.70 and about 3.07 angstroms;

(l) a carboxylic acid where the interaction distance is between about 2.40 and about 3.00 angstroms;

(m) an amino-pyridine where the interaction distance is between about 2.87 and about 3.10 angstroms;

(n) a secondary sulfonamide where the interaction distance is between about 2.76 and about 3.22 angstroms;

(o) water where the interaction distance is between about 2.55 and about 3.05 angstroms;

(p) an alcohol where the interaction distance is between about 2.40 and about 3.05 angstroms;

(q) a primary amine where the interaction distance is between about 2.64 and about 3.15 angstroms; or

(r) a secondary amine where the interaction distance is between about 2.64 and about 3.15 angstroms.

45. The pharmaceutical co-crystal composition according to claims 1, 3, 5, or 7, wherein the API or co-crystal former comprises a cyano group as a hydrogen bonded moiety and another hydrogen bonded moiety comprises:

(a) a primary amide;

(b) a secondary amide;

(c) a carboxylic acid;

(d) an amino-pyridine;

(e) a primary sulfonamide;

(f) a secondary sulfonamide;

(g) water;

(h) an alcohol;

(i) a primary amine;

(j) a secondary amine;

(k) a primary amide where the interaction distance is between about 3.01 and about 3.30 angstroms;

(l) a secondary amide where the interaction distance is between about 2.90 and about 3.30 angstroms;

(m) a carboxylic acid where the interaction distance is between about 2.57 and about 3.00 angstroms;

(n) an amino-pyridine where the interaction distance is between about 2.84 and about 3.33 angstroms;

(o) a primary sulfonamide where the interaction distance is about 2.99 angstroms;

(p) a secondary sulfonamide where the interaction distance is between about 2.83 and about 3.00 angstroms;

(q) water where the interaction distance is between about 2.78 and about 3.20 angstroms;

(r) an alcohol where the interaction distance is between about 2.72 and about 3.13 angstroms;

(s) a primary amine where the interaction distance is between about 2.84 and about 3.27 angstroms; or

(t) a secondary amine where the interaction distance is between about 2.84 and about 3.30 angstroms.

46. The pharmaceutical co-crystal composition according to claims 1, 3, 5, or 7, wherein the API or co-crystal former comprises a sulfonyl group as a hydrogen bonded moiety and another hydrogen bonded moiety comprises:

(a) a primary amide;

(b) a secondary amide;

(c) a primary sulfonamide;

(d) a secondary sulfonamide;

(e) water;

(f) an alcohol;

(g) a primary amine;

(h) a secondary amine;

(i) a primary amide where the interaction distance is about 2.92 angstroms;

(j) a secondary amide where the interaction distance is between about 2.95 and about 3.25 angstroms;

(k) a primary sulfonamide where the interaction distance is between about 2.85 and about 3.10 angstroms;

(l) a secondary sulfonamide where the interaction distance is between about 2.85 and about 3.20 angstroms;

(m) water where the interaction distance is between about 2.84 and about 3.00 angstroms;

(n) an alcohol where the interaction distance is between about 2.65 and about 3.15 angstroms;

(o) a primary amine where the interaction distance is between about 2.93 and about 3.32 angstroms; or

(p) a secondary amide where the interaction distance is between about 2.75 and about 3.32 angstroms.

47. The pharmaceutical co-crystal composition according to claims 1, 3, 5, or 7, wherein the API or co-crystal former comprises an aromatic N as a hydrogen bonded moiety and another hydrogen bonded moiety comprises:

(a) a primary amide;

(b) a secondary amide;

(c) a carboxylic acid;

(d) an amino-pyridine;

(e) water;

(f) an alcohol;

(g) a primary amine;

(h) a secondary amine;

(i) a primary amide where the interaction distance is between about 2.90 and about 3.21 angstroms;

(j) a secondary amide where the interaction distance is between about 2.60 and about 3.15 angstroms;

(k) a carboxylic acid where the interaction distance is between about 2.54 and about 2.94 angstroms;

(l) an amino-pyridine where the interaction distance is between about 2.70 and about 3.20 angstroms;

(m) water where the interaction distance is between about 2.60 and about 3.15 angstroms;

(n) an alcohol where the interaction distance is between about 2.50 and about 3.00 angstroms;

(o) a primary amine where the interaction distance is between about 2.92 and about 3.26 angstroms; or

(p) a secondary amine where the interaction distance is between about 2.73 and about 3.25 angstroms.

48. The pharmaceutical co-crystal composition according to claims 1, 3, 5, or 7, wherein the API or co-crystal former comprises an ether functional group as a hydrogen bonded moiety and another hydrogen bonded moiety comprises:

(a) a primary amide;

(b) a secondary amide;

(c) a carboxylic acid;

(d) an amino-pyridine;

(e) a sulfonamide;

(f) water;

(g) an alcohol;

(h) a primary amine;

(i) a secondary amine;

(j) a primary amide where the interaction distance is between about 2.80 and about 3.10 angstroms;

(k) a secondary amide where the interaction distance is between about 2.70 and about 3.16 angstroms;

(l) a carboxylic acid where the interaction distance is between about 2.50 and about 3.02 angstroms;

(m) an amino-pyridine where the interaction distance is between about 2.80 and about 3.20 angstroms;

(n) a sulfonamide where the interaction distance is less than about 3.20 angstroms;

(o) water where the interaction distance is between about 2.40 and about 3.15 angstroms;

(p) an alcohol where the interaction distance is between about 2.40 and about 3.00 angstroms;

(q) a primary amine where the interaction distance is between about 2.75 and about 3.25 angstroms; or

(r) a secondary amine where the interaction distance is between about 2.60 and about 3.25 angstroms.

49. The pharmaceutical co-crystal composition according to claims 1, 3, 5, or 7, wherein the API or co-crystal former comprises a chloride moiety as a hydrogen bonded moiety and another hydrogen bonded moiety comprises:

(a) a primary amide;

(b) a secondary amide;

(c) a carboxylic acid;

(d) an amino-pyridine;

(e) a sulfonamide;

(f) water;

(g) an alcohol;

(h) a primary amine;

(i) a secondary amine;

(j) a primary amide where the interaction distance is between about 3.10 and about 3.60 angstroms;

(k) a secondary amide where the interaction distance is between about 2.90 and about 3.30 angstroms;

(l) a carboxylic acid where the interaction distance is between about 2.80 and about 3.30 angstroms;

(m) an amino-pyridine where the interaction distance is between about 3.10 and about 3.45 angstroms;

(n) a sulfonamide where the interaction distance is less than about 3.35 angstroms;

(o) water where the interaction distance is between about 2.70 and about 3.30 angstroms;

(p) an alcohol where the interaction distance is between about 2.50 and about 3.30 angstroms;

(q) a primary amine where the interaction distance is between about 3.00 and about 3.50 angstroms; or

(r) a secondary amine where the interaction distance is between about 2.90 and about 3.40 angstroms.

50. The pharmaceutical co-crystal composition according to claims 1, 3, 5, or 7, wherein the API or co-crystal former comprises an organochloride moiety as a hydrogen bonded moiety and another hydrogen bonded moiety comprises:

(a) a primary amide;

(b) a secondary amide;

(c) a carboxylic acid;

(d) an amino-pyridine;

(e) a sulfonamide;

(f) water;

(g) an alcohol;

(h) a primary amine;

(i) a secondary amine;

(j) a primary amide where the interaction distance is between about 3.18 and about 3.21 angstroms;

(k) a secondary amide where the interaction distance is between about 3.20 and about 3.27 angstroms;

(l) a carboxylic acid where the interaction distance is between about 2.90 and about 3.23 angstroms;

(m) an amino-pyridine where the interaction distance is between about 3.28 and about 3.33 angstroms;

(n) a sulfonamide where the interaction distance is less than about 3.50 angstroms;

(o) water where the interaction distance is between about 2.79 and about 3.26 angstroms;

(p) an alcohol where the interaction distance is between about 2.90 and about 3.29 angstroms;

(q) a primary amine where the interaction distance is between about 3.21 and about 3.29 angstroms; or

(r) a secondary amine where the interaction distance is between about 3.26 and about 3.30 angstroms.

51. The pharmaceutical co-crystal composition according to claims 1, 3, 5, or 7, wherein the API or co-crystal former comprises a bromide moiety as a hydrogen bonded moiety and another hydrogen bonded moiety comprises:

(a) a primary amide;

(b) a secondary amide;

(c) a carboxylic acid;

(d) an amino-pyridine;

(e) an alcohol;

(f) a primary amine;

(g) a secondary amine;

(h) a primary amide where the interaction distance is between about 3.30 and about 3.80 angstroms;

(i) a secondary amide where the interaction distance is between about 3.10 and about 3.80 angstroms;

(j) a carboxylic acid where the interaction distance is between about 3.00 and about 3.30 angstroms;

(k) an amino-pyridine where the interaction distance is between about 3.20 and about 3.50 angstroms;

(l) an alcohol where the interaction distance is between about 3.00 and about 3.50 angstroms;

(m) a primary amine where the interaction distance is between about 3.20 and about 3.60 angstroms; or

(n) a secondary amine where the interaction distance is between about 3.10 and about 3.60 angstroms.

52. The pharmaceutical co-crystal composition according to claims 1, 3, 5, or 7, wherein the API or co-crystal former comprises an organobromide moiety as a hydrogen bonded moiety and another hydrogen bonded moiety comprises:

(a) a primary amide;

(b) a secondary amide;

(c) a carboxylic acid;

(d) an amino-pyridine;

(e) a sulfonamide;

(f) water;

(g) an alcohol;

(h) a primary amine;

(i) a secondary amine;

(j) a primary amide where the interaction distance is less than about 3.50 angstroms;

(k) a secondary amide where the interaction distance is less than about 3.50 angstroms;

(l) a carboxylic acid where the interaction distance is between about 3.01 and about 3.31 angstroms;

(m) an amino-pyridine where the interaction distance is less than about 3.50 angstroms;

(n) a sulfonamide where the interaction distance is less than about 3.50 angstroms;

(o) water where the interaction distance is between about 3.14 and about 3.27 angstroms;

(p) an alcohol where the interaction distance is between about 2.90 and about 3.36 angstroms;

(q) a primary amine where the interaction distance is less than about 3.50 angstroms; or

(r) a secondary amine where the interaction distance is between about 3.20 and about 3.39 angstroms.

53. The pharmaceutical co-crystal composition according to claims 1, 3, 5, or 7, wherein the API or co-crystal former comprises an organoiodide moiety as a hydrogen bonded moiety and another hydrogen bonded moiety comprises:

(a) a primary amide;

(b) a secondary amide;

(c) a carboxylic acid;

(d) an amino-pyridine;

(e) an aromatic N;

(f) an alcohol;

(g) a primary amine;

(h) a secondary amine;

(i) a primary amide where the interaction distance is less than about 3.80 angstroms;

(j) a secondary amide where the interaction distance is less than about 3.80 angstroms;

(k) a carboxylic acid where the interaction distance is less than about 3.80 angstroms;

(l) an amino-pyridine where the interaction distance is less than about 3.80 angstroms;

(m) an aromatic N where the interaction distance is between about 2.70 and about 3.23 angstroms;

(n) an alcohol where the interaction distance is between about 2.90 and about 3.48 angstroms;

(o) a primary amine where the interaction distance is between about 3.25 and about 3.42 angstroms; or

(p) a secondary amine where the interaction distance is between about 2.71 and about 2.87 angstroms.

54. The pharmaceutical co-crystal composition according to claims 1 or 3, wherein the API forms a dimeric primary amide structure via hydrogen bonds with an $R^2_2(8)$ motif, and further wherein the composition comprises:

(a) at least one hydrogen bond donor;

(b) at least two hydrogen bond donors;

(c) at least three hydrogen bond donors;

(d) at least four hydrogen bond donors;

(e) at least one hydrogen bond acceptor;

(f) at least two hydrogen bond acceptors;

(g) at least one hydrogen bond donor and one hydrogen bond acceptor;

(h) at least two hydrogen bond donors and one hydrogen bond acceptor;

(i) at least one hydrogen bond donor and two hydrogen bond acceptors;

(j) at least two hydrogen bond donors and two hydrogen bond acceptors; or

(k) at least three hydrogen bond donors and one hydrogen bond acceptor.

55. The co-crystal according to claim 11, wherein:

(a) the co-crystal is characterized by a powder X-ray diffraction pattern comprising peaks expressed in terms of 2-theta angles, wherein:

(i) said co-crystal is a celecoxib:nicotinamide co-crystal and said X-ray diffraction pattern comprises peaks at 3.77, 9.63, and 17.78 degrees;

(ii) said co-crystal is a celecoxib:nicotinamide co-crystal and said X-ray diffraction pattern comprises peaks at 9.63, 20.44, and 22.10 degrees;

(iii) said co-crystal is a celecoxib:nicotinamide co-crystal and said X-ray diffraction pattern comprises peaks at 14.76 and 21.19 degrees;

(iv) said co-crystal is a celecoxib:nicotinamide co-crystal and said X-ray diffraction pattern comprises peaks at 3.77 and 19.31 degrees;

(v) said co-crystal is a celecoxib:nicotinamide co-crystal and said X-ray diffraction pattern comprises peaks at 17.78 and 20.44 degrees;

(vi) said co-crystal is a celecoxib:nicotinamide co-crystal and said X-ray diffraction pattern comprises a peak at 3.77 degrees; or

(vii) said co-crystal is a celecoxib:nicotinamide co-crystal and said X-ray diffraction pattern comprises a peak at 17.78 degrees;

(b) the co-crystal is characterized by a DSC thermogram, wherein said co-crystal is a celecoxib:nicotinamide co-crystal and said DSC thermogram comprises an endothermic transition at about 130 degrees C; or

(c) the co-crystal is characterized by a Raman spectrum comprising peaks expressed in terms of cm^{-1}, wherein:

(i) said co-crystal is a celecoxib:nicotinamide co-crystal and said Raman spectrum comprises peaks at 1599, 1162, and 1044;

(ii) said co-crystal is a celecoxib:nicotinamide co-crystal and said Raman spectrum comprises peaks at 1618, 1044, and 796;

(iii) said co-crystal is a celecoxib:nicotinamide co-crystal and said Raman spectrum comprises peaks at 1599 and 1044;

(iv) said co-crystal is a celecoxib:nicotinamide co-crystal and said Raman spectrum comprises a peak at 1044;

(v) said co-crystal is a celecoxib:nicotinamide co-crystal and said Raman spectrum comprises a peak at 1618; or

(vi) said co-crystal is a celecoxib:nicotinamide co-crystal and said Raman spectrum comprises a peak at 1599.

56. The co-crystal according to claim 11, wherein:

(a) the co-crystal is characterized by a powder X-ray diffraction pattern comprising peaks expressed in terms of 2-theta angles, wherein:

(i) said co-crystal is a celecoxib:18-crown-6 co-crystal and said X-ray diffraction pattern comprises peaks at 8.73, 13.13, and 18.45 degrees;

(ii) said co-crystal is a celecoxib:18-crown-6 co-crystal and said X-ray diffraction pattern comprises peaks at 8.73, 11.89, and 17.75 degrees;

(iii) said co-crystal is a celecoxib:18-crown-6 co-crystal and said X-ray diffraction pattern comprises peaks at 16.37, 18.45, and 23.11 degrees;

(iv) said co-crystal is a celecoxib:18-crown-6 co-crystal and said X-ray diffraction pattern comprises peaks at 17.75 and 20.75 degrees;

(v) said co-crystal is a celecoxib:18-crown-6 co-crystal and said X-ray diffraction pattern comprises peaks at 8.73 and 13.13 degrees;

(vi) said co-crystal is a celecoxib:18-crown-6 co-crystal and said X-ray diffraction pattern comprises peaks at 11.89 and 22.37 degrees;

(vii) said co-crystal is a celecoxib:18-crown-6 co-crystal and said X-ray diffraction pattern comprises a peak at 8.73 degrees;

(viii) said co-crystal is a celecoxib:18-crown-6 co-crystal and said X-ray diffraction pattern comprises a peak at 11.89 degrees; or

(ix) said co-crystal is a celecoxib:18-crown-6 co-crystal and said X-ray diffraction pattern comprises a peak at 17.75 degrees; or

(b) the co-crystal is characterized by a DSC thermogram, wherein said co-crystal is a celecoxib:18-crown-6 co-crystal and said DSC thermogram comprises an endothermic transition at about 190 degrees C.

57. The co-crystal according to claim 11, wherein:

(a) the co-crystal is characterized by a powder X-ray diffraction pattern comprising peaks expressed in terms of 2-theta angles, wherein:

(i) said co-crystal is a topiramate:18-crown-6 co-crystal and said X-ray diffraction pattern comprises peaks at 11.07, 13.83, and 18.03 degrees;

(ii) said co-crystal is a topiramate:18-crown-6 co-crystal and said X-ray diffraction pattern comprises peaks at 10.79, 16.13, and 18.51 degrees;

(iii) said co-crystal is a topiramate:18-crown-6 co-crystal and said X-ray diffraction pattern comprises peaks at 12.17, 18.03, and 21.43 degrees;

(iv) said co-crystal is a topiramate:18-crown-6 co-crystal and said X-ray diffraction pattern comprises peaks at 11.07 and 18.03 degrees;

(v) said co-crystal is a topiramate:18-crown-6 co-crystal and said X-ray diffraction pattern comprises peaks at 12.17 and 18.51 degrees;

(vi) said co-crystal is a topiramate:18-crown-6 co-crystal and said X-ray diffraction pattern comprises peaks at 16.13 and 21.43 degrees;

(vii) said co-crystal is a topiramate:18-crown-6 co-crystal and said X-ray diffraction pattern comprises a peak at 11.07 degrees; or

(viii) said co-crystal is a topiramate:18-crown-6 co-crystal and said X-ray diffraction pattern comprises a peak at 13.83 degrees; or

(b) the co-crystal is characterized by a DSC thermogram, wherein said co-crystal is a topiramate:18-crown-6 co-crystal and said DSC thermogram comprises an endothermic transition at about 135 degrees C.

58. The co-crystal according to claim 11, wherein:

(a) the co-crystal is characterized by a powder X-ray diffraction pattern comprising peaks expressed in terms of 2-theta angles, wherein:

(i) said co-crystal is an olanzapine:nicotinamide form I co-crystal and said X-ray diffraction pattern comprises peaks at 4.89, 8.65, and 17.15 degrees;

(ii) said co-crystal is an olanzapine:nicotinamide form I co-crystal and said X-ray diffraction pattern comprises peaks at 17.15, 23.95, and 25.53 degrees;

(iii) said co-crystal is an olanzapine:nicotinamide form I co-crystal and said X-ray diffraction pattern comprises peaks at 8.65, 19.71, and 26.71 degrees;

(iv) said co-crystal is an olanzapine:nicotinamide form I co-crystal and said X-ray diffraction pattern comprises peaks at 4.89 and 17.15 degrees;

(v) said co-crystal is an olanzapine:nicotinamide form I co-crystal and said X-ray diffraction pattern comprises peaks at 8.65 and 23.95 degrees;

(vi) said co-crystal is an olanzapine:nicotinamide form I co-crystal and said X-ray diffraction pattern comprises peaks at 23.95 and 25.53 degrees;

(vii) said co-crystal is an olanzapine:nicotinamide form I co-crystal and said X-ray diffraction pattern comprises a peak at 4.89 degrees; or

(viii) said co-crystal is an olanzapine:nicotinamide form I co-crystal and said X-ray diffraction pattern comprises a peak at 17.15 degrees; or

(b) the co-crystal is characterized by a DSC thermogram, wherein said co-crystal is an olanzapine:nicotinamide form I co-crystal and said DSC thermogram comprises an endothermic transition at about 126 degrees C.

59. The co-crystal according to claim 11, wherein the co-crystal is characterized by a powder X-ray diffraction pattern comprising peaks expressed in terms of 2-theta angles, wherein:

(a) said co-crystal is an olanzapine:nicotinamide form II co-crystal and said X-ray diffraction pattern comprises peaks at 8.65, 17.53, and 24.19 degrees;

(b) said co-crystal is an olanzapine:nicotinamide form II co-crystal and said X-ray diffraction pattern comprises peaks at 11.87, 14.53, and 19.69 degrees;

(c) said co-crystal is an olanzapine:nicotinamide form II co-crystal and said X-ray diffraction pattern comprises peaks at 8.65, 17.53, and 18.09 degrees;

(d) said co-crystal is an olanzapine:nicotinamide form II co-crystal and said X-ray diffraction pattern comprises peaks at 11.87 and 17.53 degrees;

(e) said co-crystal is an olanzapine:nicotinamide form II co-crystal and said X-ray diffraction pattern comprises peaks at 8.65 and 14.53 degrees;

(f) said co-crystal is an olanzapine:nicotinamide form II co-crystal and said X-ray diffraction pattern comprises peaks at 11.87 and 24.19 degrees;

(g) said co-crystal is an olanzapine:nicotinamide form II co-crystal and said X-ray diffraction pattern comprises a peak at 8.65 degrees;

(h) said co-crystal is an olanzapine:nicotinamide form II co-crystal and said X-ray diffraction pattern comprises a peak at 17.53 degrees; or

(i) said co-crystal is an olanzapine:nicotinamide form II co-crystal and said X-ray diffraction pattern comprises a peak at 11.87 degrees.

60. The co-crystal according to claim 11, wherein the co-crystal is characterized by a powder X-ray diffraction pattern comprising peaks expressed in terms of 2-theta angles, wherein:

(a) said co-crystal is an olanzapine:nicotinamide form III co-crystal and said X-ray diffraction pattern comprises peaks at 6.41, 12.85, and 18.67 degrees;

(b) said co-crystal is an olanzapine:nicotinamide form III co-crystal and said X-ray diffraction pattern comprises peaks at 12.85, 21.85, and 24.37 degrees;

(c) said co-crystal is an olanzapine:nicotinamide form III co-crystal and said X-ray diffraction pattern comprises peaks at 14.91, 18.67, and 21.85 degrees;

(d) said co-crystal is an olanzapine:nicotinamide form III co-crystal and said X-ray diffraction pattern comprises peaks at 6.41 and 12.85 degrees;

(e) said co-crystal is an olanzapine:nicotinamide form III co-crystal and said X-ray diffraction pattern comprises peaks at 6.41 and 18.67 degrees;

(f) said co-crystal is an olanzapine:nicotinamide form III co-crystal and said X-ray diffraction pattern comprises peaks at 12.85 and 18.67 degrees;

(g) said co-crystal is an olanzapine:nicotinamide form III co-crystal and said X-ray diffraction pattern comprises a peak at 6.41 degrees;

(h) said co-crystal is an olanzapine:nicotinamide form III co-crystal and said X-ray diffraction pattern comprises a peak at 12.85 degrees; or

(i) said co-crystal is an olanzapine:nicotinamide form III co-crystal and said X-ray diffraction pattern comprises a peak at 18.67 degrees.

61. The co-crystal according to claim 11, wherein:

(a) the co-crystal is characterized by a powder X-ray diffraction pattern comprising peaks expressed in terms of 2-theta angles, wherein:

(i) said co-crystal is a *cis*-itraconazole:succinic acid co-crystal and said X-ray diffraction pattern comprises peaks at 3.01, 16.17, and 17.29 degrees;

(ii) said co-crystal is a *cis*-itraconazole:succinic acid co-crystal and said X-ray diffraction pattern comprises peaks at 6.01, 15.87, and 24.47 degrees;

(iii) said co-crystal is a *cis*-itraconazole:succinic acid co-crystal and said X-ray diffraction pattern comprises peaks at 9.05, 20.41, and 22.27 degrees;

(iv) said co-crystal is a *cis*-itraconazole:succinic acid co-crystal and said X-ray diffraction pattern comprises peaks at 3.01 and 17.29 degrees;

(v) said co-crystal is a *cis*-itraconazole:succinic acid co-crystal and said X-ray diffraction pattern comprises peaks at 6.01 and 16.17 degrees;

(vi) said co-crystal is a *cis*-itraconazole:succinic acid co-crystal and said X-ray diffraction pattern comprises peaks at 9.05 and 22.27 degrees;

(vii) said co-crystal is a *cis*-itraconazole:succinic acid co-crystal and said X-ray diffraction pattern comprises a peak at 3.01 degrees;

(viii) said co-crystal is a *cis*-itraconazole:succinic acid co-crystal and said X-ray diffraction pattern comprises a peak at 16.17 degrees; or

(ix) said co-crystal is a *cis*-itraconazole:succinic acid co-crystal and said X-ray diffraction pattern comprises a peak at 17.29 degrees; or

(b) the co-crystal is characterized by a DSC thermogram, wherein said co-crystal is a *cis*-itraconazole:succinic acid co-crystal and said DSC thermogram comprises an endothermic transition at about 160 degrees C.

62. The co-crystal according to claim 11, wherein:

(a) the co-crystal is characterized by a powder X-ray diffraction pattern comprising peaks expressed in terms of 2-theta angles, wherein:

(i) said co-crystal is a *cis*-itraconazole:fumaric acid co-crystal and said X-ray diffraction pattern comprises peaks at 4.61, 5.89, and 10.57 degrees;

(ii) said co-crystal is a *cis*-itraconazole:fumaric acid co-crystal and said X-ray diffraction pattern comprises peaks at 9.23, 19.05, and 20.79 degrees;

(iii) said co-crystal is a *cis*-itraconazole:fumaric acid co-crystal and said X-ray diffraction pattern comprises peaks at 15.51, 16.23, and 16.93 degrees;

(iv) said co-crystal is a *cis*-itraconazole:fumaric acid co-crystal and said X-ray diffraction pattern comprises peaks at 4.61 and 20.79 degrees;

(v) said co-crystal is a *cis*-itraconazole:fumaric acid co-crystal and said X-ray diffraction pattern comprises peaks at 5.89 and 19.05 degrees;

(vi) said co-crystal is a *cis*-itraconazole:fumaric acid co-crystal and said X-ray diffraction pattern comprises peaks at 10.57 and 16.23 degrees;

(vii) said co-crystal is a *cis*-itraconazole:fumaric acid co-crystal and said X-ray diffraction pattern comprises a peak at 4.61 degrees;

(viii) said co-crystal is a *cis*-itraconazole:fumaric acid co-crystal and said X-ray diffraction pattern comprises a peak at 5.89 degrees;

(ix) said co-crystal is a *cis*-itraconazole:fumaric acid co-crystal and said X-ray diffraction pattern comprises a peak at 10.57 degrees; or

(x) said co-crystal is a *cis*-itraconazole:fumaric acid co-crystal and said X-ray diffraction pattern comprises a peak at 19.05 degrees; or

(b) the co-crystal is characterized by a DSC thermogram, wherein said co-crystal is a *cis*-itraconazole:fumaric acid co-crystal and said DSC thermogram comprises an endothermic transition at about 180 degrees C.

63. The co-crystal according to claim 11, wherein:

(a) the co-crystal is characterized by a powder X-ray diffraction pattern comprising peaks expressed in terms of 2-theta angles, wherein:

(i) said co-crystal is a *cis*-itraconazole:L-tartaric acid co-crystal and said X-ray diffraction pattern comprises peaks at 4.13, 6.19, and 8.49 degrees;

(ii) said co-crystal is a *cis*-itraconazole:L-tartaric acid co-crystal and said X-ray diffraction pattern comprises peaks at 6.19, 16.13, and 17.23 degrees;

(iii) said co-crystal is a *cis*-itraconazole:L-tartaric acid co-crystal and said X-ray diffraction pattern comprises peaks at 8.49, 18.07, and 20.79 degrees;

(iv) said co-crystal is a *cis*-itraconazole:L-tartaric acid co-crystal and said X-ray diffraction pattern comprises peaks at 4.13 and 8.49 degrees;

(v) said co-crystal is a *cis*-itraconazole:L-tartaric acid co-crystal and said X-ray diffraction pattern comprises peaks at 6.19 and 20.79 degrees;

(vi) said co-crystal is a *cis*-itraconazole:L-tartaric acid co-crystal and said X-ray diffraction pattern comprises peaks at 16.13 and 17.23 degrees;

(vii) said co-crystal is a *cis*-itraconazole:L-tartaric acid co-crystal and said X-ray diffraction pattern comprises a peak at 4.13 degrees;

(viii) said co-crystal is a *cis*-itraconazole:L-tartaric acid co-crystal and said X-ray diffraction pattern comprises a peak at 6.19 degrees; or

(ix) said co-crystal is a *cis*-itraconazole:L-tartaric acid co-crystal and said X-ray diffraction pattern comprises a peak at 8.49 degrees; or

(b) the co-crystal is characterized by a DSC thermogram, wherein said co-crystal is a *cis*-itraconazole:L-tartaric acid co-crystal and said DSC thermogram comprises an endothermic transition at about 181 degrees C.

64. The co-crystal according to claim 11, wherein:

(a) the co-crystal is characterized by a powder X-ray diffraction pattern comprising peaks expressed in terms of 2-theta angles, wherein:

(i) said co-crystal is a *cis*-itraconazole:L-malic acid co-crystal and said X-ray diffraction pattern comprises peaks at 6.07, 8.85, and 17.05 degrees;

(ii) said co-crystal is a *cis*-itraconazole:L-malic acid co-crystal and said X-ray diffraction pattern comprises peaks at 15.93, 20.49, and 22.85 degrees;

(iii) said co-crystal is a *cis*-itraconazole:L-malic acid co-crystal and said X-ray diffraction pattern comprises peaks at 8.85, 15.93 and 26.17 degrees;

(iv) said co-crystal is a *cis*-itraconazole:L-malic acid co-crystal and said X-ray diffraction pattern comprises peaks at 6.07 and 17.05 degrees;

(v) said co-crystal is a *cis*-itraconazole:L-malic acid co-crystal and said X-ray diffraction pattern comprises peaks at 8.85 and 21.27 degrees;

(vi) said co-crystal is a *cis*-itraconazole:L-malic acid co-crystal and said X-ray diffraction pattern comprises peaks at 6.07 and 8.85 degrees;

(vii) said co-crystal is a *cis*-itraconazole:L-malic acid co-crystal and said X-ray diffraction pattern comprises a peak at 6.07 degrees;

(viii) said co-crystal is a *cis*-itraconazole:L-malic acid co-crystal and said X-ray diffraction pattern comprises a peak at 8.85 degrees; or

(ix) said co-crystal is a *cis*-itraconazole:L-malic acid co-crystal and said X-ray diffraction pattern comprises a peak at 17.05 degrees; or

(b) the co-crystal is characterized by a DSC thermogram, wherein said co-crystal is a *cis*-itraconazole:L-malic acid co-crystal and said DSC thermogram comprises an endothermic transition at about 154 degrees C.

65. The co-crystal according to claim 11, wherein:

(a) the co-crystal is characterized by a powder X-ray diffraction pattern comprising peaks expressed in terms of 2-theta angles, wherein:

(i) said co-crystal is a *cis*-itraconazoleHCl:DL-tartaric acid co-crystal and said X-ray diffraction pattern comprises peaks at 3.73, 10.95, and 13.83 degrees;

(ii) said co-crystal is a *cis*-itraconazoleHCl:DL-tartaric acid co-crystal and said X-ray diffraction pattern comprises peaks at 16.53, 17.75, and 19.65 degrees;

(iii) said co-crystal is a *cis*-itraconazoleHCl:DL-tartaric acid co-crystal and said X-ray diffraction pattern comprises peaks at 10.95, 16.53, and 21.11 degrees;

(iv) said co-crystal is a *cis*-itraconazoleHCl:DL-tartaric acid co-crystal and said X-ray diffraction pattern comprises peaks at 3.73 and 10.95 degrees;

(v) said co-crystal is a *cis*-itraconazoleHCl:DL-tartaric acid co-crystal and said X-ray diffraction pattern comprises peaks at 13.83 and 17.75 degrees;

(vi) said co-crystal is a *cis*-itraconazoleHCl:DL-tartaric acid co-crystal and said X-ray diffraction pattern comprises peaks at 16.53 and 19.65 degrees;

(vii) said co-crystal is a *cis*-itraconazoleHCl:DL-tartaric acid co-crystal and said X-ray diffraction pattern comprises a peak at 3.73 degrees;

(viii) said co-crystal is a *cis*-itraconazoleHCl:DL-tartaric acid co-crystal and said X-ray diffraction pattern comprises a peak at 10.95 degrees; or

(ix) said co-crystal is a *cis*-itraconazoleHCl:DL-tartaric acid co-crystal and said X-ray diffraction pattern comprises a peak at 17.75 degrees; or

(b) the co-crystal is characterized by a DSC thermogram, wherein said co-crystal is a *cis*-itraconazoleHCl:DL-tartaric acid co-crystal and said DSC thermogram comprises an endothermic transition at about 162 degrees C.

66. The co-crystal according to claim 11, wherein:

(a) the co-crystal is characterized by a powder X-ray diffraction pattern comprising peaks expressed in terms of 2-theta angles, wherein:

(i) said co-crystal is a modafinil:malonic acid form I co-crystal and said X-ray diffraction pattern comprises peaks at 5.11, 9.35, and 16.87 degrees;

(ii) said co-crystal is a modafinil:malonic acid form I co-crystal and said X-ray diffraction pattern comprises peaks at 16.87, 18.33, and 19.53 degrees;

(iii) said co-crystal is a modafinil:malonic acid form I co-crystal and said X-ray diffraction pattern comprises peaks at 9.35, 19.53, and 22.89 degrees;

(iv) said co-crystal is a modafinil:malonic acid form I co-crystal and said X-ray diffraction pattern comprises peaks at 5.11 and 9.35 degrees;

(v) said co-crystal is a modafinil:malonic acid form I co-crystal and said X-ray diffraction pattern comprises peaks at 16.87 and 19.53 degrees;

(vi) said co-crystal is a modafinil:malonic acid form I co-crystal and said X-ray diffraction pattern comprises peaks at 18.33 and 22.89 degrees;

(vii) said co-crystal is a modafinil:malonic acid form I co-crystal and said X-ray diffraction pattern comprises a peak at 5.11 degrees;

(viii) said co-crystal is a modafinil:malonic acid form I co-crystal and said X-ray diffraction pattern comprises a peak at 9.35 degrees; or

(ix) said co-crystal is a modafinil:malonic acid form I co-crystal and said X-ray diffraction pattern comprises a peak at 16.87 degrees;

(b) the co-crystal is characterized by a DSC thermogram, wherein said co-crystal is a modafinil:malonic acid form I co-crystal and said DSC thermogram comprises an endothermic transition at about 106 degrees C; or

(c) the co-crystal is characterized by a Raman spectrum comprising peaks expressed in terms of cm^{-1}, wherein:

(i) said co-crystal is a modafinil:malonic acid form I co-crystal and said Raman spectrum comprises peaks at 1004, 633, and 265;

(ii) said co-crystal is a modafinil:malonic acid form I co-crystal and said Raman spectrum comprises peaks at 1032, 1601, and 767;

(iii) said co-crystal is a modafinil:malonic acid form I co-crystal and said Raman spectrum comprises peaks at 1004 and 633;

(iv) said co-crystal is a modafinil:malonic acid form I co-crystal and said Raman spectrum comprises peaks at 1183 and 767; or

(v) said co-crystal is a modafinil:malonic acid form I co-crystal and said Raman spectrum comprises peaks at 1601 and 718.

67. The co-crystal according to claim 11, wherein the co-crystal is characterized by a powder X-ray diffraction pattern comprising peaks expressed in terms of 2-theta angles, wherein:

(a) said co-crystal is a modafinil:malonic acid form II co-crystal and said X-ray diffraction pattern comprises peaks at 5.90, 9.54, and 20.01 degrees;

(b) said co-crystal is a modafinil:malonic acid form II co-crystal and said X-ray diffraction pattern comprises peaks at 15.79, 18.02, and 21.66 degrees;

(c) said co-crystal is a modafinil:malonic acid form II co-crystal and said X-ray diffraction pattern comprises peaks at 9.54, 20.01, and 25.30 degrees;

(d) said co-crystal is a modafinil:malonic acid form II co-crystal and said X-ray diffraction pattern comprises peaks at 5.90 and 9.54 degrees;

(e) said co-crystal is a modafinil:malonic acid form II co-crystal and said X-ray diffraction pattern comprises peaks at 5.90 and 20.01 degrees;

(f) said co-crystal is a modafinil:malonic acid form II co-crystal and said X-ray diffraction pattern comprises peaks at 9.54 and 20.01 degrees;

(g) said co-crystal is a modafinil:malonic acid form II co-crystal and said X-ray diffraction pattern comprises peaks at 5.90 degrees; or

(h) said co-crystal is a modafinil:malonic acid form II co-crystal and said X-ray diffraction pattern comprises peaks at 9.54 degrees.

68. The co-crystal according to claim 11, wherein the co-crystal is characterized by a powder X-ray diffraction pattern comprising peaks expressed in terms of 2-theta angles, wherein:

(a) said co-crystal is a modafinil:glycolic acid co-crystal and said X-ray diffraction pattern comprises peaks at 9.51, 15.97, and 20.03 degrees;

(b) said co-crystal is a modafinil:glycolic acid co-crystal and said X-ray diffraction pattern comprises peaks at 14.91, 19.01, and 22.75 degrees;

(c) said co-crystal is a modafinil:glycolic acid co-crystal and said X-ray diffraction pattern comprises peaks at 15.97, 25.03, and 25.71 degrees;

(d) said co-crystal is a modafinil:glycolic acid co-crystal and said X-ray diffraction pattern comprises peaks at 9.51 and 15.97 degrees;

(e) said co-crystal is a modafinil:glycolic acid co-crystal and said X-ray diffraction pattern comprises peaks at 20.03 and 25.03 degrees;

(f) said co-crystal is a modafinil:glycolic acid co-crystal and said X-ray diffraction pattern comprises peaks at 15.97 and 25.03 degrees;

(g) said co-crystal is a modafinil:glycolic acid co-crystal and said X-ray diffraction pattern comprises a peak at 9.51 degrees;

(h) said co-crystal is a modafinil:glycolic acid co-crystal and said X-ray diffraction pattern comprises a peak at 15.97 degrees; or

(i) said co-crystal is a modafinil:glycolic acid co-crystal and said X-ray diffraction pattern comprises a peak at 20.03 degrees.

69. The co-crystal according to claim 11, wherein the co-crystal is characterized by a powder X-ray diffraction pattern comprising peaks expressed in terms of 2-theta angles, wherein:

(a) said co-crystal is a modafinil:maleic acid co-crystal and said X-ray diffraction pattern comprises peaks at 4.69, 6.15, and 9.61 degrees;

(b) said co-crystal is a modafinil:maleic acid co-crystal and said X-ray diffraction pattern comprises peaks at 10.23, 19.97, and 21.83 degrees;

(c) said co-crystal is a modafinil:maleic acid co-crystal and said X-ray diffraction pattern comprises peaks at 4.69, 10.23, and 21.83 degrees;

(d) said co-crystal is a modafinil:maleic acid co-crystal and said X-ray diffraction pattern comprises peaks at 4.69 and 19.97 degrees;

(e) said co-crystal is a modafinil:maleic acid co-crystal and said X-ray diffraction pattern comprises peaks at 6.15 and 9.61 degrees;

(f) said co-crystal is a modafinil:maleic acid co-crystal and said X-ray diffraction pattern comprises peaks at 4.69 and 6.15 degrees;

(g) said co-crystal is a modafinil:maleic acid co-crystal and said X-ray diffraction pattern comprises a peak at 4.69 degrees;

(h) said co-crystal is a modafinil:maleic acid co-crystal and said X-ray diffraction pattern comprises a peak at 9.61 degrees; or

(i) said co-crystal is a modafinil:maleic acid co-crystal and said X-ray diffraction pattern comprises a peak at 19.97 degrees.

70. The co-crystal according to claim 11, wherein:

(a) the co-crystal is characterized by a powder X-ray diffraction pattern comprising peaks expressed in terms of 2-theta angles, wherein:

(i) said co-crystal is a 5-fluorouracil:urea co-crystal and said X-ray diffraction pattern comprises peaks at 11.23, 13.27, and 16.93 degrees;

(ii) said co-crystal is a 5-fluorouracil:urea co-crystal and said X-ray diffraction pattern comprises peaks at 12.69, 20.37, and 25.55 degrees;

(iii) said co-crystal is a 5-fluorouracil:urea co-crystal and said X-ray diffraction pattern comprises peaks at 17.93, 23.65, and 26.87 degrees;

(iv) said co-crystal is a 5-fluorouracil:urea co-crystal and said X-ray diffraction pattern comprises peaks at 11.23 and 16.93 degrees;

(v) said co-crystal is a 5-fluorouracil:urea co-crystal and said X-ray diffraction pattern comprises peaks at 23.65 and 32.49 degrees;

(vi) said co-crystal is a 5-fluorouracil:urea co-crystal and said X-ray diffraction pattern comprises peaks at 13.27 and 25.55 degrees;

(vii) said co-crystal is a 5-fluorouracil:urea co-crystal and said X-ray diffraction pattern comprises a peak at 11.23 degrees;

(viii) said co-crystal is a 5-fluorouracil:urea co-crystal and said X-ray diffraction pattern comprises a peak at 16.93 degrees; or

(ix) said co-crystal is a 5-fluorouracil:urea co-crystal and said X-ray diffraction pattern comprises a peak at 25.55 degrees;

(b) the co-crystal is characterized by a DSC thermogram, wherein said co-crystal is a 5-fluorouracil:urea co-crystal and said DSC thermogram comprises an endothermic transition at about 208 degrees C; or

(c) the co-crystal is characterized by a Raman spectrum comprising peaks expressed in terms of cm^{-1}, wherein:

(i) said co-crystal is a 5-fluorouracil:urea co-crystal and said Raman spectrum comprises peaks at 1347, 1024, and 757;

(ii) said co-crystal is a 5-fluorouracil:urea co-crystal and said Raman spectrum comprises peaks at 644, 545, and 472;

(iii) said co-crystal is a 5-fluorouracil:urea co-crystal and said Raman spectrum comprises peaks at 1680 and 1347;

(iv) said co-crystal is a 5-fluorouracil:urea co-crystal and said Raman spectrum comprises peaks at 1347 and 757; or

(v) said co-crystal is a 5-fluorouracil:urea co-crystal and said Raman spectrum comprises peaks at 1024 and 757.

71. The co-crystal according to claim 11, wherein the co-crystal is characterized by a powder X-ray diffraction pattern comprising peaks expressed in terms of 2-theta angles, wherein:

(a) said co-crystal is a hydrochlorothiazide:nicotinic acid co-crystal and said X-ray diffraction pattern comprises peaks at 8.57, 13.23, and 21.13 degrees;

(b) said co-crystal is a hydrochlorothiazide:nicotinic acid co-crystal and said X-ray diffraction pattern comprises peaks at 14.31, 17.89, and 26.57 degrees;

(c) said co-crystal is a hydrochlorothiazide:nicotinic acid co-crystal and said X-ray diffraction pattern comprises peaks at 8.57, 21.13, and 25.73 degrees;

(d) said co-crystal is a hydrochlorothiazide:nicotinic acid co-crystal and said X-ray diffraction pattern comprises peaks at 8.57 and 21.13 degrees;

(e) said co-crystal is a hydrochlorothiazide:nicotinic acid co-crystal and said X-ray diffraction pattern comprises peaks at 13.23 and 26.57 degrees;

(f) said co-crystal is a hydrochlorothiazide:nicotinic acid co-crystal and said X-ray diffraction pattern comprises peaks at 17.89 and 24.41 degrees;

(g) said co-crystal is a hydrochlorothiazide:nicotinic acid co-crystal and said X-ray diffraction pattern comprises a peak at 8.57 degrees;

(h) said co-crystal is a hydrochlorothiazide:nicotinic acid co-crystal and said X-ray diffraction pattern comprises a peak at 13.23 degrees; or

(i) said co-crystal is a hydrochlorothiazide:nicotinic acid co-crystal and said X-ray diffraction pattern comprises a peak at 21.13 degrees.

72. The co-crystal according to claim 11, wherein the co-crystal is characterized by a powder X-ray diffraction pattern comprising peaks expressed in terms of 2-theta angles, wherein:

(a) said co-crystal is a hydrochlorothiazide:18-crown-6 co-crystal and said X-ray diffraction pattern comprises peaks at 9.97, 11.57, and 15.67 degrees;

(b) said co-crystal is a hydrochlorothiazide:18-crown-6 co-crystal and said X-ray diffraction pattern comprises peaks at 14.53, 19.05, and 20.31 degrees;

(c) said co-crystal is a hydrochlorothiazide:18-crown-6 co-crystal and said X-ray diffraction pattern comprises peaks at 16.61, 20.65, and 23.63 degrees;

(d) said co-crystal is a hydrochlorothiazide:18-crown-6 co-crystal and said X-ray diffraction pattern comprises peaks at 9.97 and 10.43 degrees;

(e) said co-crystal is a hydrochlorothiazide:18-crown-6 co-crystal and said X-ray diffraction pattern comprises peaks at 12.83 and 15.67 degrees;

(f) said co-crystal is a hydrochlorothiazide:18-crown-6 co-crystal and said X-ray diffraction pattern comprises peaks at 14.53 and 20.31 degrees;

(g) said co-crystal is a hydrochlorothiazide:18-crown-6 co-crystal and said X-ray diffraction pattern comprises a peak at 10.43 degrees;

(h) said co-crystal is a hydrochlorothiazide:18-crown-6 co-crystal and said X-ray diffraction pattern comprises a peak at 12.83 degrees; or

(i) said co-crystal is a hydrochlorothiazide:18-crown-6 co-crystal and said X-ray diffraction pattern comprises a peak at 20.31 degrees.

73. The co-crystal according to claim 11, wherein the co-crystal is characterized by a powder X-ray diffraction pattern comprising peaks expressed in terms of 2-theta angles, wherein:

(a) said co-crystal is a hydrochlorothiazide:piperazine co-crystal and said X-ray diffraction pattern comprises peaks at 6.85, 13.75, and 18.71 degrees;

(b) said co-crystal is a hydrochlorothiazide:piperazine co-crystal and said X-ray diffraction pattern comprises peaks at 15.93, 23.27, and 24.17 degrees;

(c) said co-crystal is a hydrochlorothiazide:piperazine co-crystal and said X-ray diffraction pattern comprises peaks at 18.17, 20.93, and 27.75 degrees;

(d) said co-crystal is a hydrochlorothiazide:piperazine co-crystal and said X-ray diffraction pattern comprises peaks at 6.85 and 18.71 degrees;

(e) said co-crystal is a hydrochlorothiazide:piperazine co-crystal and said X-ray diffraction pattern comprises peaks at 13.75 and 23.27 degrees;

(f) said co-crystal is a hydrochlorothiazide:piperazine co-crystal and said X-ray diffraction pattern comprises peaks at 15.93 and 24.17 degrees;

(g) said co-crystal is a hydrochlorothiazide:piperazine co-crystal and said X-ray diffraction pattern comprises a peak at 6.85 degrees;

(h) said co-crystal is a hydrochlorothiazide:piperazine co-crystal and said X-ray diffraction pattern comprises a peak at 13.75 degrees; or

(i) said co-crystal is a hydrochlorothiazide:piperazine co-crystal and said X-ray diffraction pattern comprises a peak at 18.71 degrees.

74. The co-crystal according to claim 11, wherein the co-crystal is characterized by a DSC thermogram, wherein said co-crystal is an acetaminophen:4,4-bipyridine:water co-crystal and said DSC thermogram comprises an endothermic transition at about 58 degrees C.

75. The co-crystal according to claim 11, wherein:

(a) the co-crystal is characterized by a powder X-ray diffraction pattern comprising peaks expressed in terms of 2-theta angles, wherein:

(i) said co-crystal is a phenytoin:pyridone co-crystal and said X-ray diffraction pattern comprises peaks at 5.2, 15.1, and 16.7 degrees;

(ii) said co-crystal is a phenytoin:pyridone co-crystal and said X-ray diffraction pattern comprises peaks at 11.1, 16.2, and 17.8 degrees;

(iii) said co-crystal is a phenytoin:pyridone co-crystal and said X-ray diffraction pattern comprises peaks at 5.2 and 15.1 degrees;

(iv) said co-crystal is a phenytoin:pyridone co-crystal and said X-ray diffraction pattern comprises peaks at 15.1 and 19.4 degrees;

(v) said co-crystal is a phenytoin:pyridone co-crystal and said X-ray diffraction pattern comprises a peak at 5.2 degrees; or

(vi) said co-crystal is a phenytoin:pyridone co-crystal and said X-ray diffraction pattern comprises a peak at 15.1 degrees; or

(b) the co-crystal is characterized by a DSC thermogram, wherein said co-crystal is a phenytoin:pyridone co-crystal and said DSC thermogram comprises an endothermic transition at about 233 degrees C.

76. The co-crystal according to claim 11, wherein the co-crystal is characterized by a DSC thermogram, wherein said co-crystal is an aspirin:4,4-bipyridine co-crystal and said DSC thermogram comprises an endothermic transition at about 95 degrees C.

77. The co-crystal according to claim 11, wherein:

(a) the co-crystal is characterized by a powder X-ray diffraction pattern comprising peaks expressed in terms of 2-theta angles, wherein:

(i) said co-crystal is an ibuprofen:4,4-bipyridine co-crystal and said X-ray diffraction pattern comprises peaks at 3.4 and 6.9 degrees;

(ii) said co-crystal is an ibuprofen:4,4-bipyridine co-crystal and said X-ray diffraction pattern comprises peaks at 3.4 and 10.4 degrees;

(iii) said co-crystal is an ibuprofen:4,4-bipyridine co-crystal and said X-ray diffraction pattern comprises peaks at 10.4 and 17.3 degrees;

(iv) said co-crystal is an ibuprofen:4,4-bipyridine co-crystal and said X-ray diffraction pattern comprises a peak at 3.4 degrees; or

(v) said co-crystal is an ibuprofen:4,4-bipyridine co-crystal and said X-ray diffraction pattern comprises a peak at 10.4 degrees; or

(b) the co-crystal is characterized by a DSC thermogram, wherein said co-crystal is an ibuprofen:4,4-bipyridine co-crystal and said DSC thermogram comprises an endothermic transition at about 119 degrees C.

78. The co-crystal according to claim 11, wherein:

(a) the co-crystal is characterized by a powder X-ray diffraction pattern comprising peaks expressed in terms of 2-theta angles, wherein:

(i) said co-crystal is a flurbiprofen:4,4-bipyridine co-crystal and said X-ray diffraction pattern comprises peaks at 16.8, 18.1, and 20.0 degrees;

(ii) said co-crystal is a flurbiprofen:4,4-bipyridine co-crystal and said X-ray diffraction pattern comprises peaks at 18.1, 21.3, and 25.0 degrees;

(iii) said co-crystal is a flurbiprofen:4,4-bipyridine co-crystal and said X-ray diffraction pattern comprises peaks at 16.8 and 19.0 degrees;

(iv) said co-crystal is a flurbiprofen:4,4-bipyridine co-crystal and said X-ray diffraction pattern comprises peaks at 17.1 and 21.3 degrees;

(v) said co-crystal is a flurbiprofen:4,4-bipyridine co-crystal and said X-ray diffraction pattern comprises a peak at 16.8 degrees; or

(vi) said co-crystal is a flurbiprofen:4,4-bipyridine co-crystal and said X-ray diffraction pattern comprises a peak at 19.0 degrees; or

(b) the co-crystal is characterized by a DSC thermogram, wherein said co-crystal is a flurbiprofen:4,4-bipyridine co-crystal and said DSC thermogram comprises an endothermic transition at about 163 degrees C.

79. The co-crystal according to claim 11, wherein:

(a) the co-crystal is characterized by a powder X-ray diffraction pattern comprising peaks expressed in terms of 2-theta angles, wherein:

(i) said co-crystal is a flurbiprofen:trans-1,2-bis-(4-pyridyl) ethylene co-crystal and said X-ray diffraction pattern comprises peaks at 3.6, 17.3, and 18.4 degrees;

(ii) said co-crystal is a flurbiprofen:trans-1,2-bis-(4-pyridyl) ethylene co-crystal and said X-ray diffraction pattern comprises peaks at 17.3, 19.1, and 23.8 degrees;

(iii) said co-crystal is a flurbiprofen:trans-1,2-bis-(4-pyridyl) ethylene co-crystal and said X-ray diffraction pattern comprises peaks at 18.1 and 22.3 degrees;

(iv) said co-crystal is a flurbiprofen:trans-1,2-bis-(4-pyridyl) ethylene co-crystal and said X-ray diffraction pattern comprises peaks at 3.6 and 18.4 degrees;

(v) said co-crystal is a flurbiprofen:trans-1,2-bis-(4-pyridyl) ethylene co-crystal and said X-ray diffraction pattern comprises a peak at 3.6 degrees; or

(vi) said co-crystal is a flurbiprofen:trans-1,2-bis-(4-pyridyl) ethylene co-crystal and said X-ray diffraction pattern comprises a peak at 19.1 degrees; or

(b) the co-crystal is characterized by a DSC thermogram, wherein said co-crystal is a flurbiprofen:trans-1,2-bis-(4-pyridyl) ethylene co-crystal and said DSC thermogram comprises an endothermic transition at about 164 degrees C.

80. The co-crystal according to claim 11, wherein:

(a) the co-crystal is characterized by a powder X-ray diffraction pattern comprising peaks expressed in terms of 2-theta angles, wherein:

(i) said co-crystal is a carbamazepine:p-phthalaldehyde co-crystal and said X-ray diffraction pattern comprises peaks at 8.5, 11.9, and 15.1 degrees;

(ii) said co-crystal is a carbamazepine:p-phthalaldehyde co-crystal and said X-ray diffraction pattern comprises peaks at 10.6, 14.4, and 18.0 degrees;

(iii) said co-crystal is a carbamazepine:p-phthalaldehyde co-crystal and said X-ray diffraction pattern comprises peaks at 11.9 and 23.7 degrees;

(iv) said co-crystal is a carbamazepine:p-phthalaldehyde co-crystal and said X-ray diffraction pattern comprises peaks at 8.5 and 14.4 degrees;

(v) said co-crystal is a carbamazepine:p-phthalaldehyde co-crystal and said X-ray diffraction pattern comprises a peak at 8.5 degrees; or

(vi) said co-crystal is a carbamazepine:p-phthalaldehyde co-crystal and said X-ray diffraction pattern comprises a peak at 11.9 degrees; or

(b) the co-crystal is characterized by a DSC thermogram, wherein said co-crystal is a carbamazepine:p-phthalaldehyde co-crystal and said DSC thermogram comprises an endothermic transition at about 128 degrees C.

81. The co-crystal according to claim 11, wherein:

(a) the co-crystal is characterized by a powder X-ray diffraction pattern comprising peaks expressed in terms of 2-theta angles, wherein:

(i) said co-crystal is a carbamazepine:nicotinamide co-crystal and said X-ray diffraction pattern comprises peaks at 8.8, 13.2, and 15.6 degrees;

(ii) said co-crystal is a carbamazepine:nicotinamide co-crystal and said X-ray diffraction pattern comprises peaks at 13.2, 15.6, and 20.4 degrees;

(iii) said co-crystal is a carbamazepine:nicotinamide co-crystal and said X-ray diffraction pattern comprises peaks at 8.8 and 26.4 degrees;

(iv) said co-crystal is a carbamazepine:nicotinamide co-crystal and said X-ray diffraction pattern comprises peaks at 13.2 and 15.6 degrees;

(v) said co-crystal is a carbamazepine:nicotinamide co-crystal and said X-ray diffraction pattern comprises a peak at 8.8 degrees; or

(vi) said co-crystal is a carbamazepine:nicotinamide co-crystal and said X-ray diffraction pattern comprises a peak at 15.6 degrees; or

(b) the co-crystal is characterized by a DSC thermogram, wherein said co-crystal is a carbamazepine:nicotinamide co-crystal and said DSC thermogram comprises an endothermic transition at about 157 degrees C.

82. The co-crystal according to claim 11, wherein:

(a) the co-crystal is characterized by a powder X-ray diffraction pattern comprising peaks expressed in terms of 2-theta angles, wherein:

(i) said co-crystal is a carbamazepine:saccharin co-crystal and said X-ray diffraction pattern comprises peaks at 6.9, 13.6, and 15.3 degrees;

(ii) said co-crystal is a carbamazepine:saccharin co-crystal and said X-ray diffraction pattern comprises peaks at 14.0, 20.2, and 28.3 degrees;

(iii) said co-crystal is a carbamazepine:saccharin co-crystal and said X-ray diffraction pattern comprises peaks at 12.2 and 21.3 degrees;

(iv) said co-crystal is a carbamazepine:saccharin co-crystal and said X-ray diffraction pattern comprises peaks at 14.0 and 20.2 degrees;

(v) said co-crystal is a carbamazepine:saccharin co-crystal and said X-ray diffraction pattern comprises a peak at 14.0 degrees; or

(vi) said co-crystal is a carbamazepine:saccharin co-crystal and said X-ray diffraction pattern comprises a peak at 21.3 degrees; or

(b) the co-crystal is characterized by a DSC thermogram, wherein said co-crystal is a carbamazepine:saccharin co-crystal and said DSC thermogram comprises an endothermic transition at about 177 degrees C.

83. The co-crystal according to claim 11, wherein:

(a) the co-crystal is characterized by a powder X-ray diffraction pattern comprising peaks expressed in terms of 2-theta angles, wherein:

(i) said co-crystal is a carbamazepine:5-nitroisophthalic acid co-crystal and said X-ray diffraction pattern comprises peaks at 10.14 and 17.44 degrees;

(ii) said co-crystal is a carbamazepine:5-nitroisophthalic acid co-crystal and said X-ray diffraction pattern comprises peaks at 15.29 and 21.17 degrees;

(iii) said co-crystal is a carbamazepine:5-nitroisophthalic acid co-crystal and said X-ray diffraction pattern comprises peaks at 10.14 and 15.29 degrees;

(iv) said co-crystal is a carbamazepine:5-nitroisophthalic acid co-crystal and said X-ray diffraction pattern comprises peaks at 21.17 and 31.41 degrees;

(v) said co-crystal is a carbamazepine:5-nitroisophthalic acid co-crystal and said X-ray diffraction pattern comprises a peak at 10.14 degrees; or

(vi) said co-crystal is a carbamazepine:5-nitroisophthalic acid co-crystal and said X-ray diffraction pattern comprises a peak at 17.44 degrees; or

(b) the co-crystal is characterized by a DSC thermogram, wherein said co-crystal is a carbamazepine:5-nitroisophthalic acid co-crystal and said DSC thermogram comprises an endothermic transition at about 191 degrees C.

84. The co-crystal according to claim 11, wherein:

(a) the co-crystal is characterized by a powder X-ray diffraction pattern comprising peaks expressed in terms of 2-theta angles, wherein:

(i) said co-crystal is a carbamazepine:trimesic acid co-crystal and said X-ray diffraction pattern comprises peaks at 10.89, 12.23, and 16.25 degrees;

(ii) said co-crystal is a carbamazepine:trimesic acid co-crystal and said X-ray diffraction pattern comprises peaks at 10.89, 17.05, and 18.47 degrees;

(iii) said co-crystal is a carbamazepine:trimesic acid co-crystal and said X-ray diffraction pattern comprises peaks at 12.23 and 17.05 degrees;

(iv) said co-crystal is a carbamazepine:trimesic acid co-crystal and said X-ray diffraction pattern comprises peaks at 10.89 and 21.95 degrees;

(v) said co-crystal is a carbamazepine:trimesic acid co-crystal and said X-ray diffraction pattern comprises a peak at 10.89 degrees; or

(vi) said co-crystal is a carbamazepine:trimesic acid co-crystal and said X-ray diffraction pattern comprises a peak at 16.25 degrees; or

(b) the co-crystal is characterized by a DSC thermogram, wherein said co-crystal is a carbamazepine:trimesic acid co-crystal and said DSC thermogram comprises an endothermic transition at about 273 degrees C.

85. The co-crystal of claim 1, specifically excluding a co-crystal selected from the group consisting of: nabumetone:2,3-naphthalenediol, fluoxetine HCl:benzoic acid, fluoxetine HCl:succinic acid, acetaminophen:piperazine, acetaminophen:theophylline, theophylline:salicylic acid, theophylline:p-hydroxybenzoic acid, theophylline:sorbic acid, theophylline:1-hydroxy-2-naphthoic acid, theophylline:glycolic acid, theophylline:2,5-dihydroxybenzoic acid, theophylline:chloroacetic acid, bis(diphenylhydantoin):9-ethyladenine acetylacetone solvate, bis(diphenylhydantoin):9-ethyladenine 2,4-pentanedione solvate, 5,5-diphenylbarbituric acid:9-ethyladenine, bis(diphenylhydantoin):9-ethyladenine, 4-aminobenzoic acid:4-aminobenzonitrile, sulfadimidine:salicylic acid, 8-hydroxyquinolinium 4-nitrobenzoate:4-nitrobenzoic acid, sulfaproxyline:caffeine, retro-inverso-isopropyl (2R,3S)-4-cyclohexyl-2-hydroxy-3-(N-((2R)-2-morpholinocarbonylmethyl-3-(1-naphthyl)propionyl)-L-histidylamino)butyrate:cinnamic acid monohydrate, benzoic acid:isonicotinamide, 3-(2-N',N'-(dimethylhydrazino)-4-thiazolylmethylthio)-N''-sulfamoylpropionamidine:maleic acid, diglycine hydrochloride ($C_2H_5NO_2$:$C_2H_6NO_2^+Cl^-$), octadecanoic acid:3-pyridinecarboxamide, cis-N-(3-methyl-1-(2-(1,2,3,4-tetrahydro)naphthyl)-piperidin-4-yl)-N-phenylpropanamide hydrochloride:oxalic acid, trans-N-(3-methyl-1-(2-(1,2,3,4-tetrahydro)naphthyl)-piperidin-4-ylium)-N-phenylpropanamide oxalate:oxalic acid dihydrate, bis(1-(3-((4-(2-isopropoxyphenyl)-1-piperazinyl)methyl)benzoyl)piperidine) succinate:succinic acid, bis(p-cyanophenyl)imidazolylmethane:succinic acid, cis-1-((4-(1-imidazolylmethyl)cyclohexyl)methyl)imidazole:succinic acid, (+)-2-(5,6-dimethoxy-1,2,3,4-tetrahydro-1-naphthyl)imidazoline:(+)-dibenzoyl-D-tartaric acid, raclopride:tartaric acid, 2,6-diamino-9-ethylpurine:5,5-diethylbarbituric acid, 5,5-diethylbarbituric acid:bis(2-aminopyridine), 5,5-diethylbarbituric acid:acetamide, 5,5-diethylbarbituric acid:KI_3, 5,5-diethylbarbituric acid:urea, bis(barbital):hexamethylphosphoramide, 5,5-diethylbarbituric acid:imidazole, barbital:1-methylimidazole, 5,5-diethylbarbituric acid:N-methyl-2-pyridone, 2,4-diamino-5-(3,4,5-trimethoxybenzyl)-pyrimidine:5,5-diethylbarbituric acid, bis(barbital):caffeine, bis(barbital):1-methylimidazole, bis(beta-cyclodextrin):bis(barbital) hydrate, tetrakis(beta-cyclodextrin):tetrakis(barbital), 9-ethyladenine:5,5-diethylbarbituric acid,

barbital:N'-(*p*-cyanophenyl)-N-(*p*-iodophenyl)melamine, barbital:2-amino-4-(*m*-bromophenylamino)-6-chloro-1,3,5-triazine, 5,5-diethylbarbituric acid:N,N'-diphenylmelamine, 5,5-diethylbarbituric acid:N,N'-bis(*p*-chlorophenyl)melamine, N,N'-bis(*p*-bromophenyl)melamine:5,5-diethylbarbituric acid, 5,5-diethylbarbituric acid:N,N'-bis(*p*-iodophenyl)melamine, 5,5-diethylbarbituric acid:N,N'-bis(*p*-tolyl)melamine, 5,5-diethylbarbituric acid:N,N'-bis(*m*-tolyl)melamine, 5,5-diethylbarbituric acid:N,N'-bis(*m*-chlorophenyl)melamine, N,N'-Bis(*m*-methylphenyl)melamine:barbital, N,N'-bis(*m*-chlorophenyl)melamine:barbital tetrahydrofuran solvate, 5,5-diethylbarbituric acid:N,N'-bis(*tert*-butyl)melamine, 5,5-diethylbarbituric acid:N,N'-di(*tert*-butyl)melamine, 6,6'-diquinolyl ether:5,5-diethylbarbituric acid, 5-*tert*-butyl-2,4,6-triaminopyrimidine:diethylbarbituric acid, N,N'-bis(4-carboxymethylphenyl)melamine:barbital ethanol solvate, N,N'-bis(4-*tert*-butylphenyl)melamine:barbital, tris(5,17-N,N'-bis(4-amino-6-(butylamino)-1,3,5-triazin-2-yl)diamino-11,23-dinitro-25,26,27,28-tetrapropoxycalix(4)arene):hexakis(diethylbarbituric acid) toluene solvate, N,N'-bis(*m*-fluorophenyl)melamine:barbital, N,N'-bis(*m*-bromophenyl)melamine:barbital acetone solvate, N,N'-bis(*m*-iodophenyl)melamine:barbital acetonitrile solvate, N,N'-bis(*m*-trifluoromethylphenyl)melamine:barbital acetonitrile solvate, aminopyrine:barbital, N,N'-bis(4-fluorophenyl)melamine:barbital, N,N'-bis(4-trifluoromethylphenyl)melamine:barbital, 2,4-diamino-5-(3,4,5-trimethoxybenzyl)pyrimidine:barbital, hydroxybutyrate:hydroxyvalerate, 2-aminopyrimidine:succinic acid, 1,3-bis(((6-methylpyrid-2-yl)amino)carbonyl)benzene:glutaric acid, 5-*tert*-butyl-2,4,6-triaminopyrimidine:diethylbarbituric acid, bis(dithiobiuret-S,S')nickel(II):diuracil, platinum 3,3'-dihydroxymethyl-2,2'-bipyridine dichloride:AgF_3CSO_3, 4,4'-bipyridyl:isophthalic acid, 4,4'-bipyridyl:1,4-naphthalenedicarboxylic acid, 4,4'-bipyridyl:1,3,5-cyclohexane-tricarboxylic acid, 4,4'-bipyridyl:tricaballylic acid, urotropin:azelaic acid, insulin:C8-HI (octanoyl-N^{ε}-LysB29-human insulin), isonicotinamide:cinnamic acid, isonicotinamide:3-hydroxybenzoic acid, isonicotinamide:3-N,N-dimethylaminobenzoic acid, isonicotinamide:3,5-bis(trifluoromethyl)-benzoic acid, isonicotinamide:d,l-mandelic acid,

isonicotinamide:chloroacetic acid, isonicotinamide:fumaric acid monoethyl ester, isonicotinamide:12-bromododecanoic acid, isonicotinamide:fumaric acid, isonicotinamide:succinic acid, isonicotinamide:4-ketopimelic acid, isonicotinamide:thiodiglycolic acid, 1,3,5-cyclohexane-tricarboxylic acid:hexamethyltetramine, 1,3,5-cyclohexane-tricarboxylic acid:4,7-phenanthroline, 4,7-phenanthroline:oxalic acid, 4,7-phenanthroline:terephthalic acid, 4,7-phenanthroline: 1,3,5-cyclohexane-tricarboxylic acid, 4,7-phenanthroline:1,4-naphthalenedicarboxylic acid, pyrazine:methanoic acid, pyrazine:ethanoic acid, pyrazine:propanoic acid, pyrazine:butanoic acid, pyrazine:pentanoic acid, pyrazine:hexanoic acid, pyrazine:heptanoic acid, pyrazine:octanoic acid, pyrazine:nonanoic acid, pyrazine:decanoic acid, diammine-(deoxy-quanyl-quanyl-N^7,N^7)-platinum:tris(glycine) hydrate, 2-aminopyrimidine:p-phenylenediacetic acid, bis(2-aminopyrimidin-1-ium)fumarate:fumaric acid, 2-aminopyrimidine:indole-3-acetic acid, 2-aminopyrimidine:N-methylpyrrole-2-carboxylic acid, 2-aminopyrimidine:thiophen-2-carboxylic acid, 2-aminopyrimidine:(+)-camphoric acid, 2,4,6-Trinitrobenzoic acid:2-aminopyrimidine, 2-aminopyrimidine:4-aminobenzoic acid, 2-aminopyrimidine:bis(phenoxyacetic acid), 2-aminopyrimidine:(2,4-dichlorophenoxy)acetic acid, 2-aminopyrimidine:(3,4-dichlorophenoxy)acetic acid, 2-aminopyrimidine:indole-2-carboxylic acid, 2-aminopyrimidine:terephthalic acid, 2-aminopyrimidine:bis(2-nitrobenzoic acid), 2-aminopyrimidine:bis(2-aminobenzoic acid), 2-aminopyrimidine:3-aminobenzoic acid, 2-hexeneoic acid:isonicotinamide, 4-nitrobenzoic acid:isonicotinamide, 3,5-dinitrobenzoic acid:isonicotinamide:4-methylbenzoic acid, 2-amino-5-nitropyrimidine:2-amino-3-nitropyridine, 3,5-dinitrobenzoic acid:4-chlorobenzamide, 3-dimethylaminobenzoic acid:4-chlorobenzamide, fumaric acid:4-chlorobenzamide, oxine:4-nitrobenzoic acid, oxine:3,5-dinitrobenzoic acid, oxine:3,5-dinitrosalicylic acid, 3-[2-(N',N'-dimethylhydrazino)-4-thiazolylmethylthio]-N^2-sulfamoylpropionamidine:maleic acid, 5-fluorouracil:9-ethylhypoxanthine, 5-fluorouracil:cytosine dihydrate, 5-fluorouracil:theophylline monohydrate, stearic acid:nicotinamide, cis-1-{[4-(1-imidazolylmethyl)cyclohexyl]methyl}imidazole:succinic acid, CGS18320B:succinic acid, sulfaproxyline:caffeine, 4-aminobenzoic acid:4-aminobenzonitrile, 3,5-

dinitrobenzoic acid:isonicotinamide:3-methylbenzoic acid, 3,5-dinitrobenzoic acid:isonicotinamide:4-(dimethylamino)benzoic acid, 3,5-dinitrobenzoic acid:isonicotinamide:4-hydroxy-3-methoxycinnamic acid, isonicotinamide:oxalic acid, isonicotinamide:malonic acid, isonicotinamide:succinic acid, isonicotinamide:glutaric acid, isonicotinamide:adipic acid, benzoic acid:isonicotinamide, mazapertine:succinate, betaine:dichloronitrophenol, betainepyridine:dichloronitrophenol, betainepyridine:pentachlorophenol, 4-{2-[1-(2-hydroxyethyl)-4-pyridylidene]-ethylidene}-cyclo-hexa-2,5-dien-1-one:methyl 2,4-dihydroxybenzoate, 4-{2-[1-(2-hydroxyethyl)-4-pyridylidene]-ethylidene}-cyclo-hexa-2,5-dien-1-one:2,4-dihydroxypropiophenone, 4-{2-[1-(2-hydroxyethyl)-4-pyridylidene]-ethylidene}-cyclo-hexa-2,5-dien-1-one:2,4-dihydroxyacetophenone, squaric acid:4,4'-dipyridylacetylene, squaric acid:1,2-bis(4-pyridyl)ethylene, chloranilic acid:1,4-bis[(4-pyridyl)ethynyl]benzene, 4,4'-bipyridine:phthalic acid, 4,4'-dipyridylacetylene:phthalic acid, bis(pentamethylcyclopentadienyl)iron:bromanilic acid, bis(pentamethylcyclopentadienyl)iron:chloranilic acid, bis(pentamethylcyclopentadienyl)iron:cyananilic acid, pyrazinotetrathiafulvalene:chloranilic acid, phenol:pentafluorophenol, co-crystals of itraconazole, and co-crystals of topiramate.

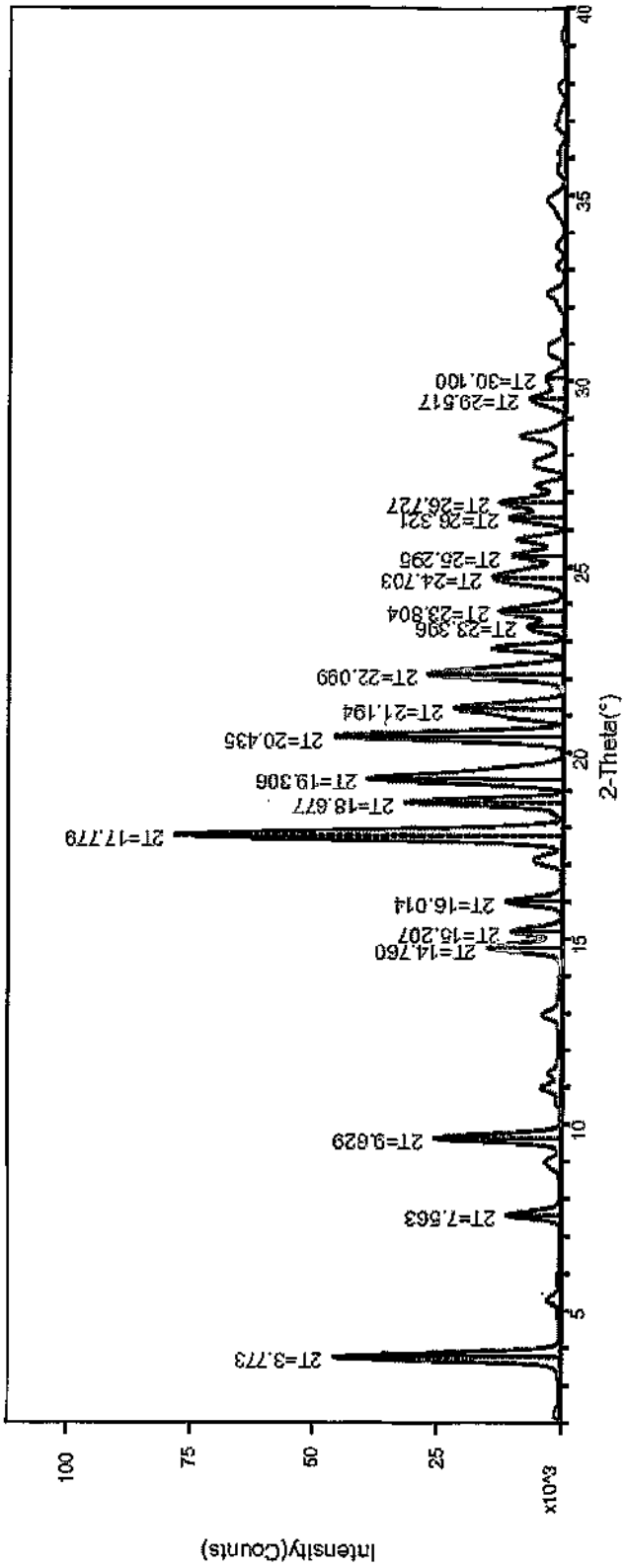

Intensity(Counts)
x10^3
100
75
50
25
5
10
15
20
25
30
35
40
2-Theta(°)
2T=3.773
2T=7.563
2T=9.829
2T=14.760
2T=15.207
2T=16.014
2T=17.779
2T=18.677
2T=19.306
2T=20.435
2T=21.194
2T=22.099
2T=23.396
2T=23.804
2T=24.703
2T=25.295
2T=26.321
2T=26.727
2T=29.517
2T=30.100

FIG. 1A

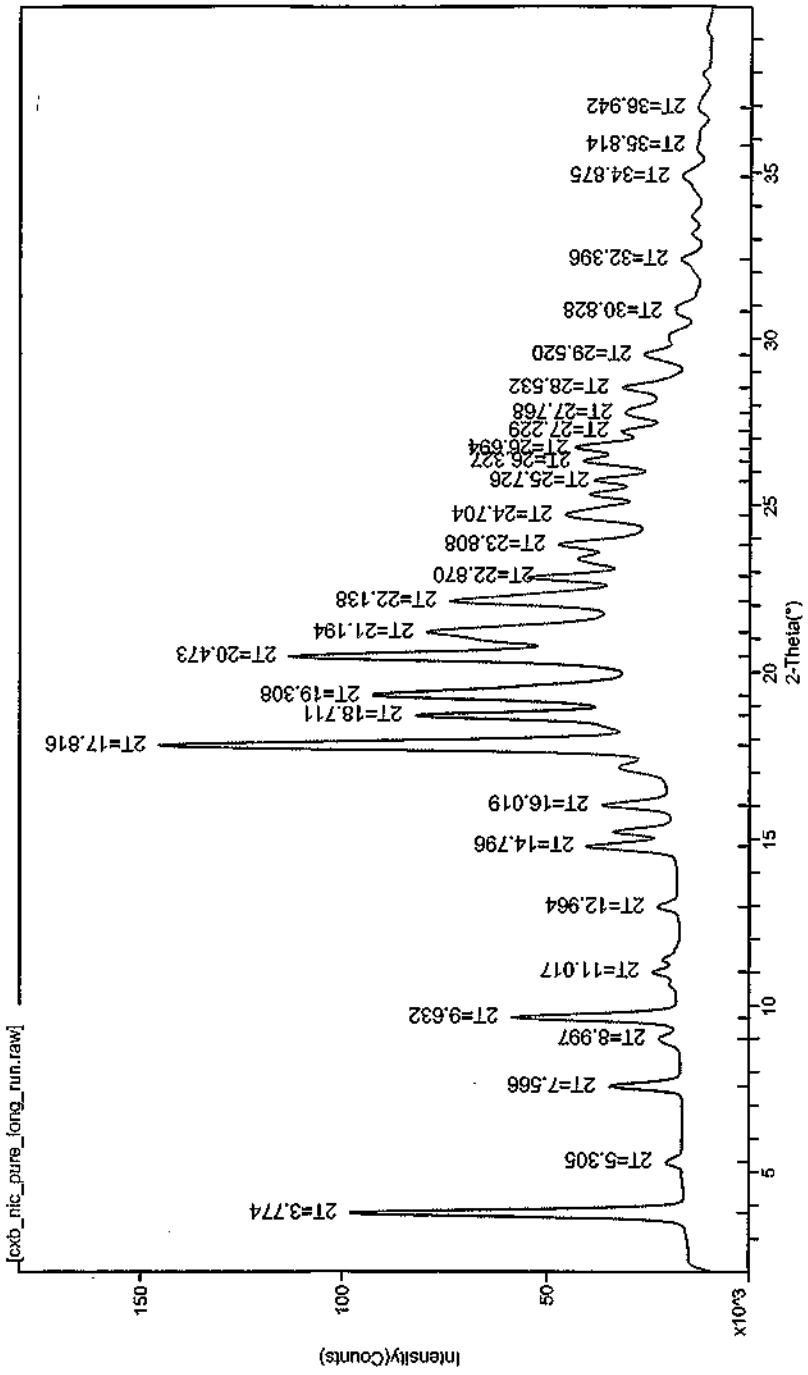

[cxb_nic_pure_long_run.raw]
Intensity(Counts)
x10^3
2-Theta(°)
2T=3.774
2T=5.305
2T=7.566
2T=8.997
2T=9.632
2T=11.017
2T=12.964
2T=14.796
2T=16.019
2T=17.816
2T=18.711
2T=19.308
2T=20.473
2T=21.194
2T=22.138
2T=22.870
2T=23.808
2T=24.704
2T=25.726
2T=26.327
2T=26.694
2T=27.229
2T=27.768
2T=28.532
2T=29.520
2T=30.828
2T=32.396
2T=34.875
2T=35.814
2T=36.942

FIG. 1B

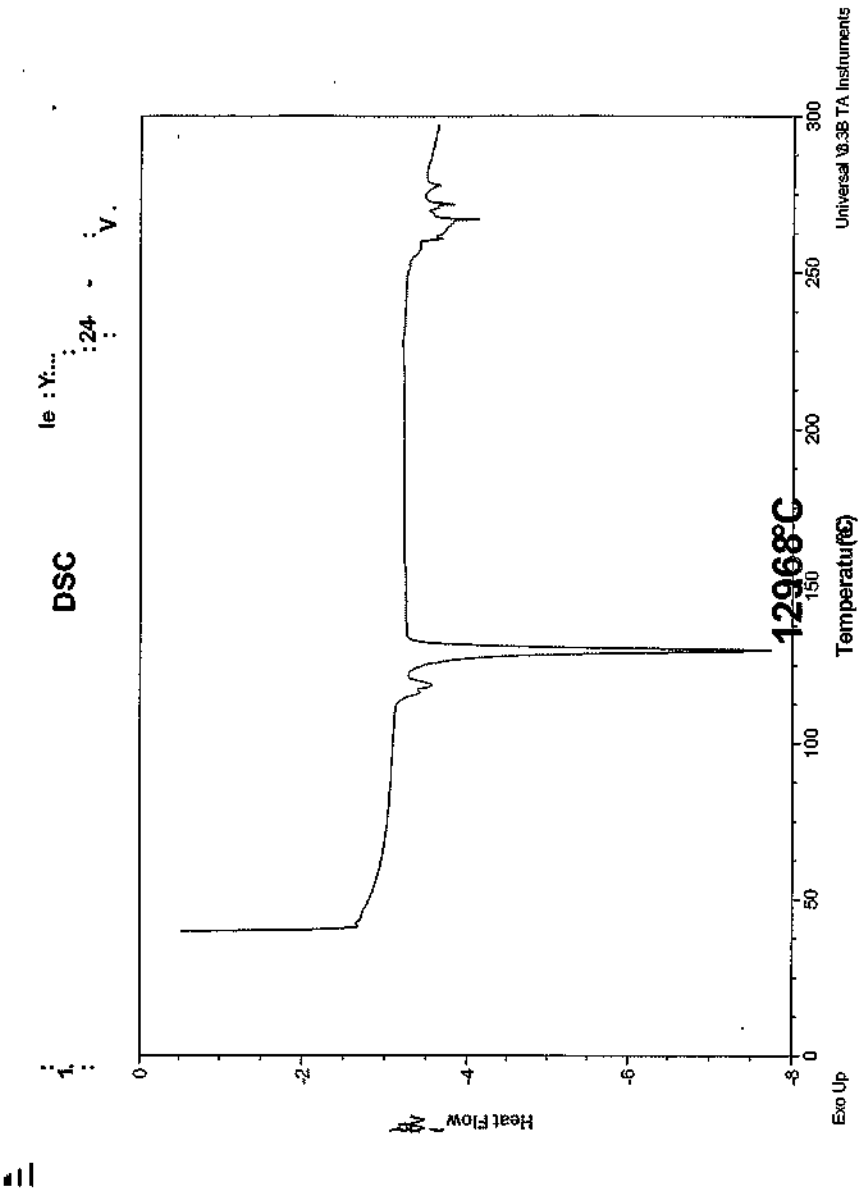

DSC
129.68°C
Heat Flow
Exo Up
Temperature(°C)
Universal V3.3B TA Instruments

FIG. 2

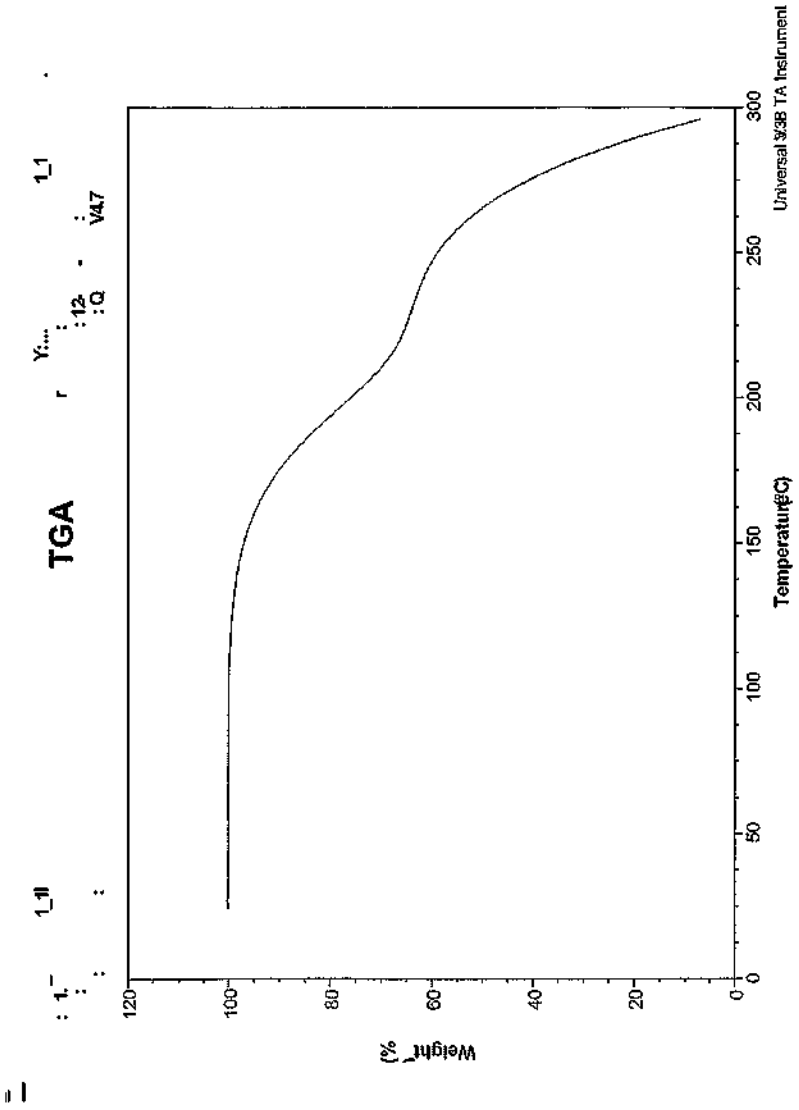

TGA
Weight (%)
Temperature(°C)
Universal V3B TA Instrument
0
20
40
60
80
100
120
0
50
100
150
200
250
300

FIG. 3

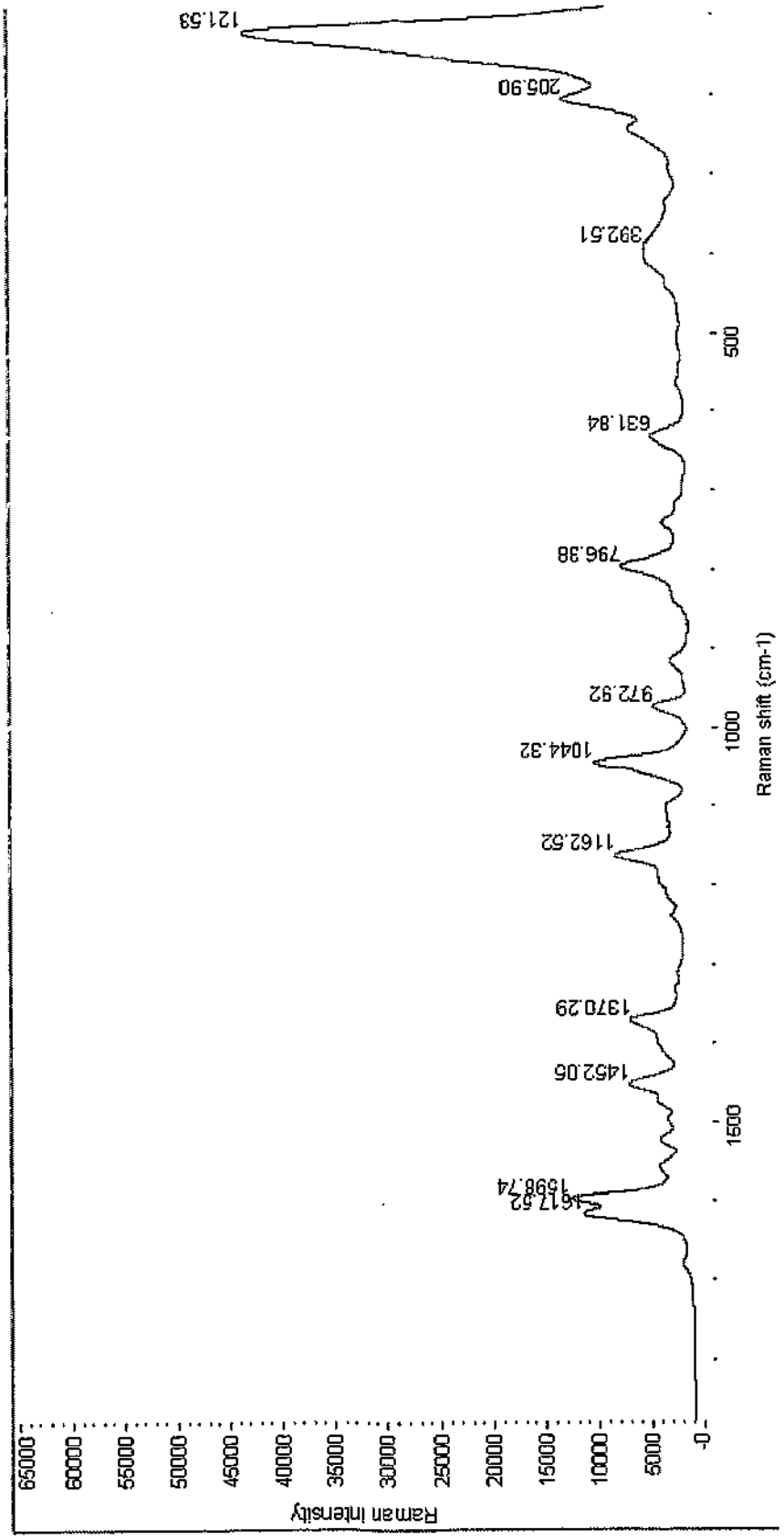

Raman intensity
65000
60000
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
Raman shift (cm-1)
500
1000
1500
121.53
205.90
392.51
631.84
796.38
972.92
1044.32
1162.52
1370.29
1452.06
1598.74
1617.52

FIG. 4

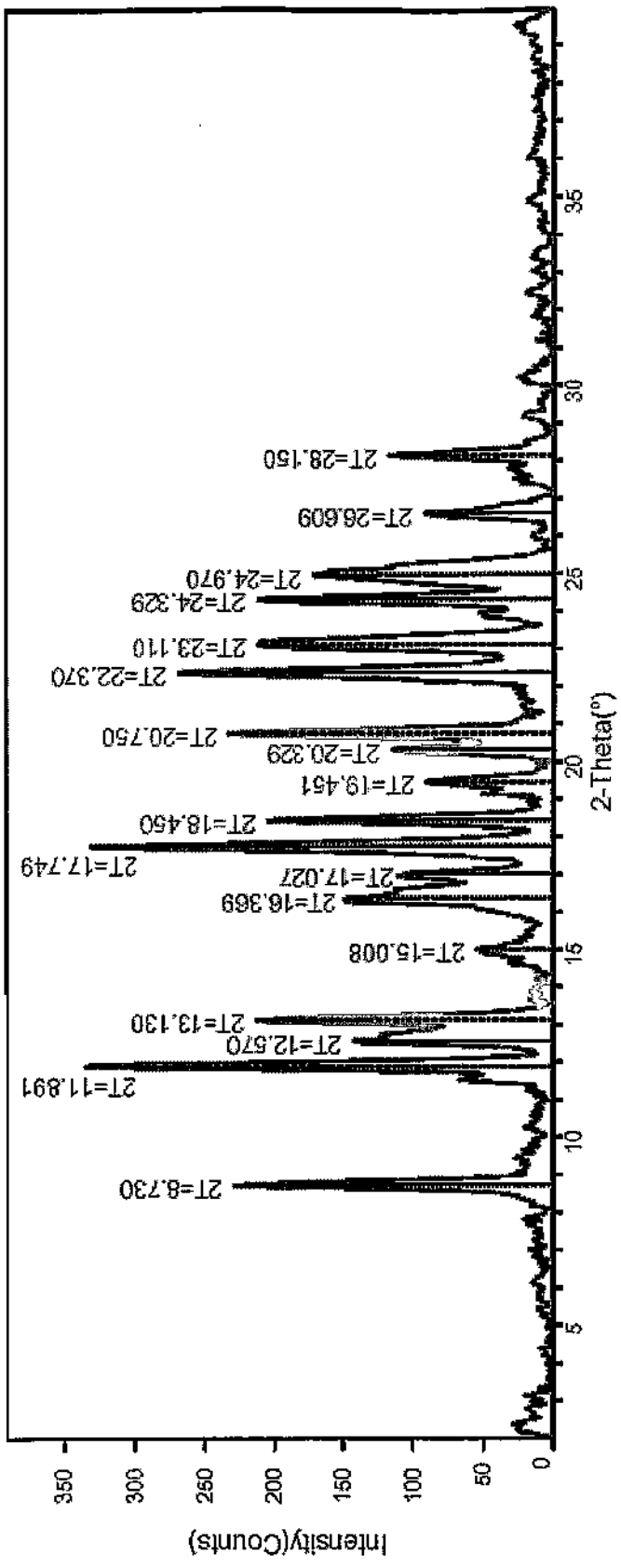

Intensity(Counts)
0
50
100
150
200
250
300
350
2-Theta(°)
5
10
15
20
25
30
35
2T=8.730
2T=11.891
2T=12.570
2T=13.130
2T=15.008
2T=16.369
2T=17.027
2T=17.749
2T=18.450
2T=19.451
2T=20.329
2T=20.750
2T=22.370
2T=23.110
2T=24.329
2T=24.970
2T=26.609
2T=28.150

FIG. 5A

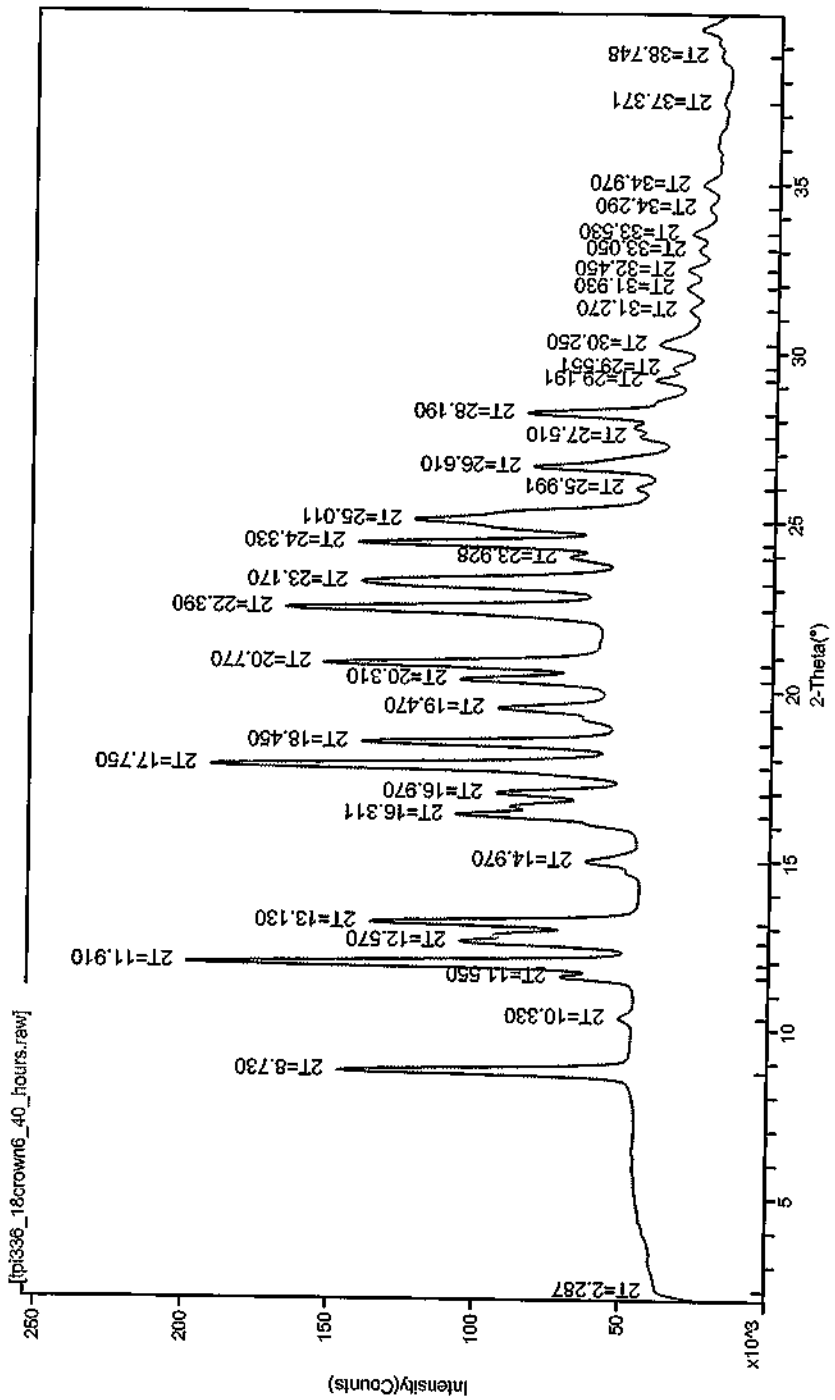

[tpi336_18crown6_40_hours.raw]
Intensity(Counts)
x10^3
2-Theta(°)
2T=2.287
2T=8.730
2T=10.330
2T=11.550
2T=11.910
2T=12.570
2T=13.130
2T=14.970
2T=16.311
2T=16.970
2T=17.750
2T=18.450
2T=19.470
2T=20.310
2T=20.770
2T=22.390
2T=23.170
2T=23.928
2T=24.330
2T=25.011
2T=25.991
2T=26.610
2T=27.510
2T=28.190
2T=29.191
2T=29.551
2T=30.250
2T=31.270
2T=31.930
2T=32.450
2T=33.050
2T=33.530
2T=34.290
2T=34.970
2T=37.371
2T=38.748

FIG. 5B

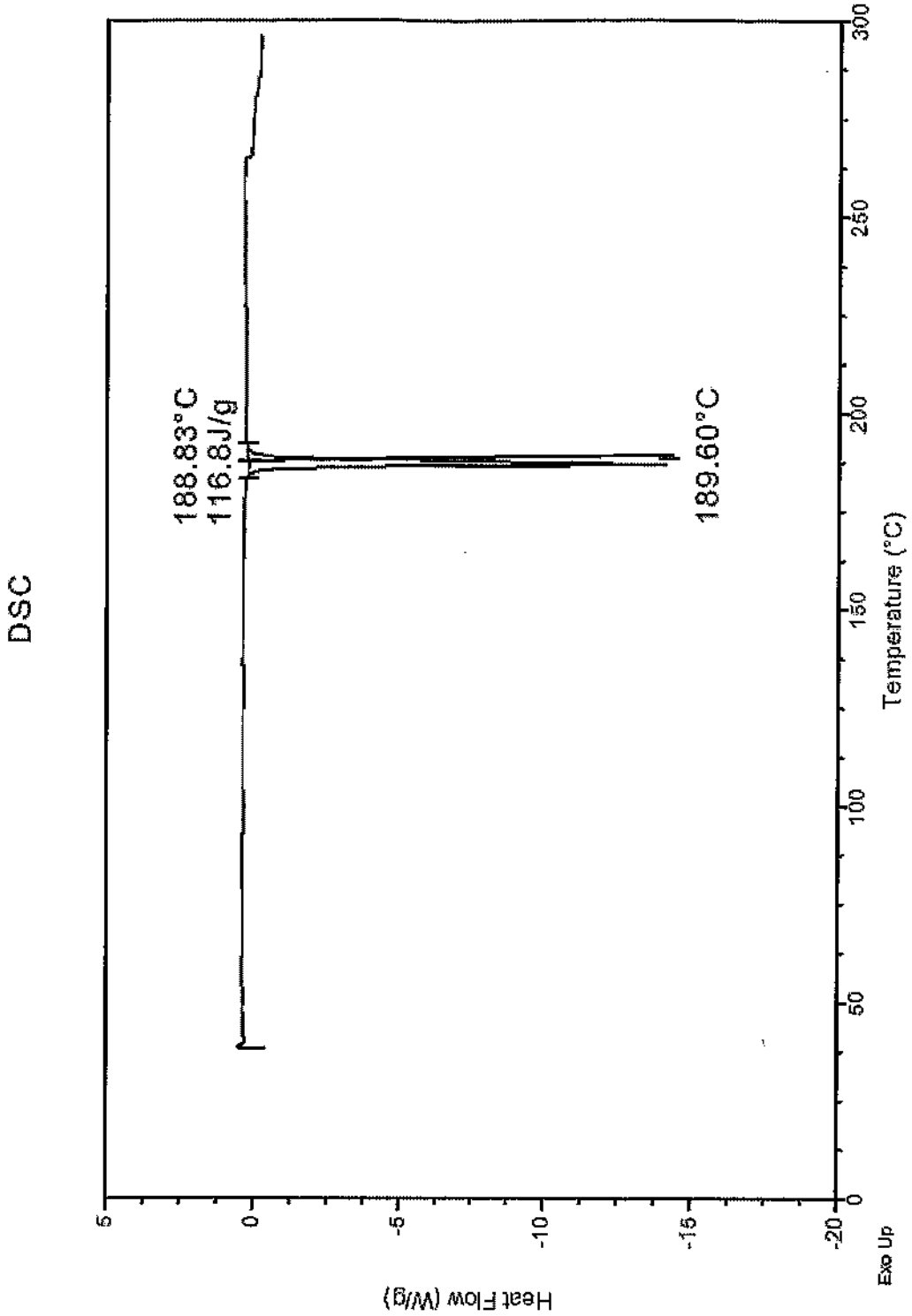

DSC
188.83°C
116.8J/g
189.60°C
Heat Flow (W/g)
Exo Up
Temperature (°C)
5
0
-5
-10
-15
-20
0
50
100
150
200
250
300

FIG. 6

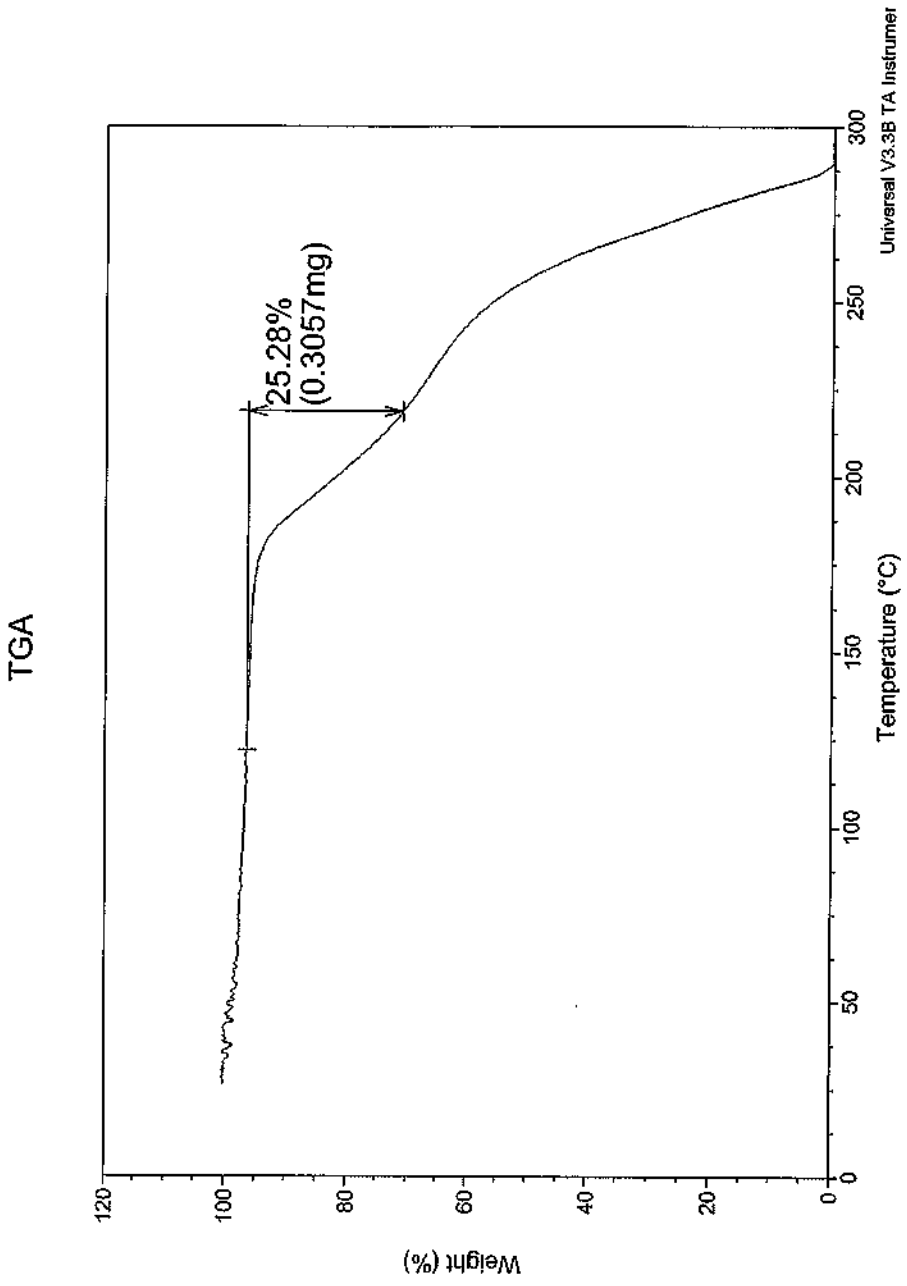

TGA
25.28%
(0.3057mg)
Weight (%)
Temperature (°C)
Universal V3.3B TA Instrumer
0
20
40
60
80
100
120
0
50
100
150
200
250
300

FIG. 7

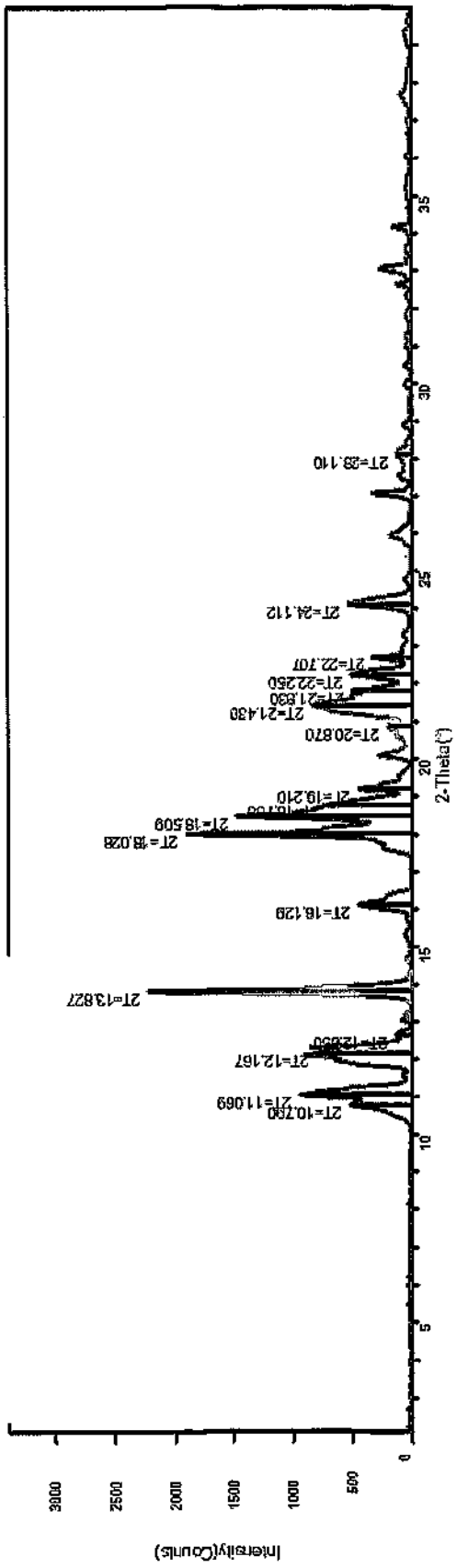

Intensity(Counts)
3000
2500
2000
1500
1000
500
0
5
10
15
20
25
30
35
2-Theta(°)
2T=13.827
2T=18.028
2T=18.509
2T=19.210
2T=20.870
2T=21.430
2T=21.830
2T=22.250
2T=22.707
2T=24.112
2T=28.110

FIG. 8A

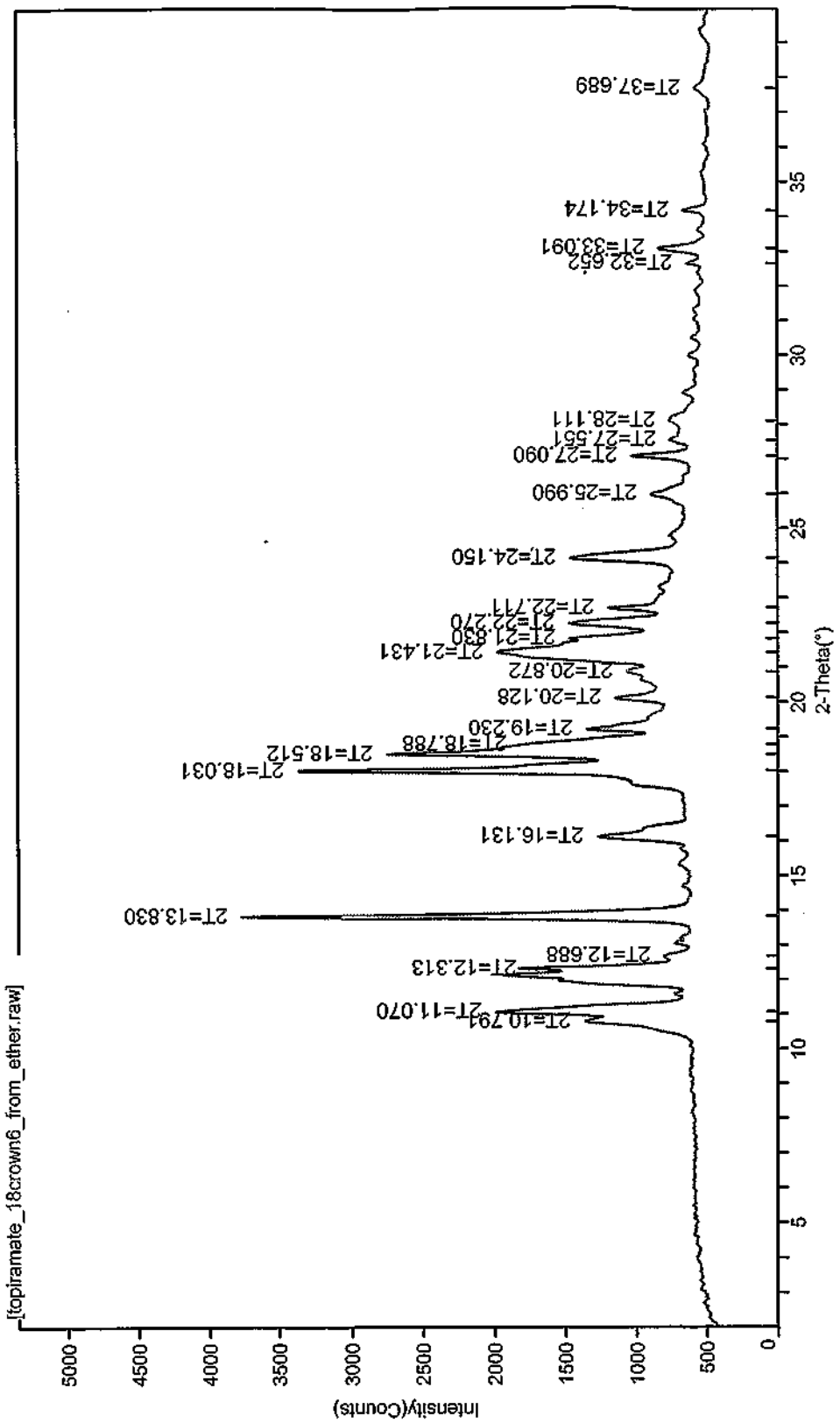

[topiramate_18crown6_from_ether.raw]
Intensity(Counts)
2-Theta(°)
2T=37.689
2T=34.174
2T=33.091
2T=32.652
2T=28.111
2T=27.551
2T=27.090
2T=25.990
2T=24.150
2T=22.711
2T=21.830
2T=21.431
2T=20.872
2T=20.128
2T=19.230
2T=18.788
2T=18.512
2T=18.031
2T=16.131
2T=13.830
2T=12.688
2T=12.313
2T=11.070
2T=10.794

FIG. 8B

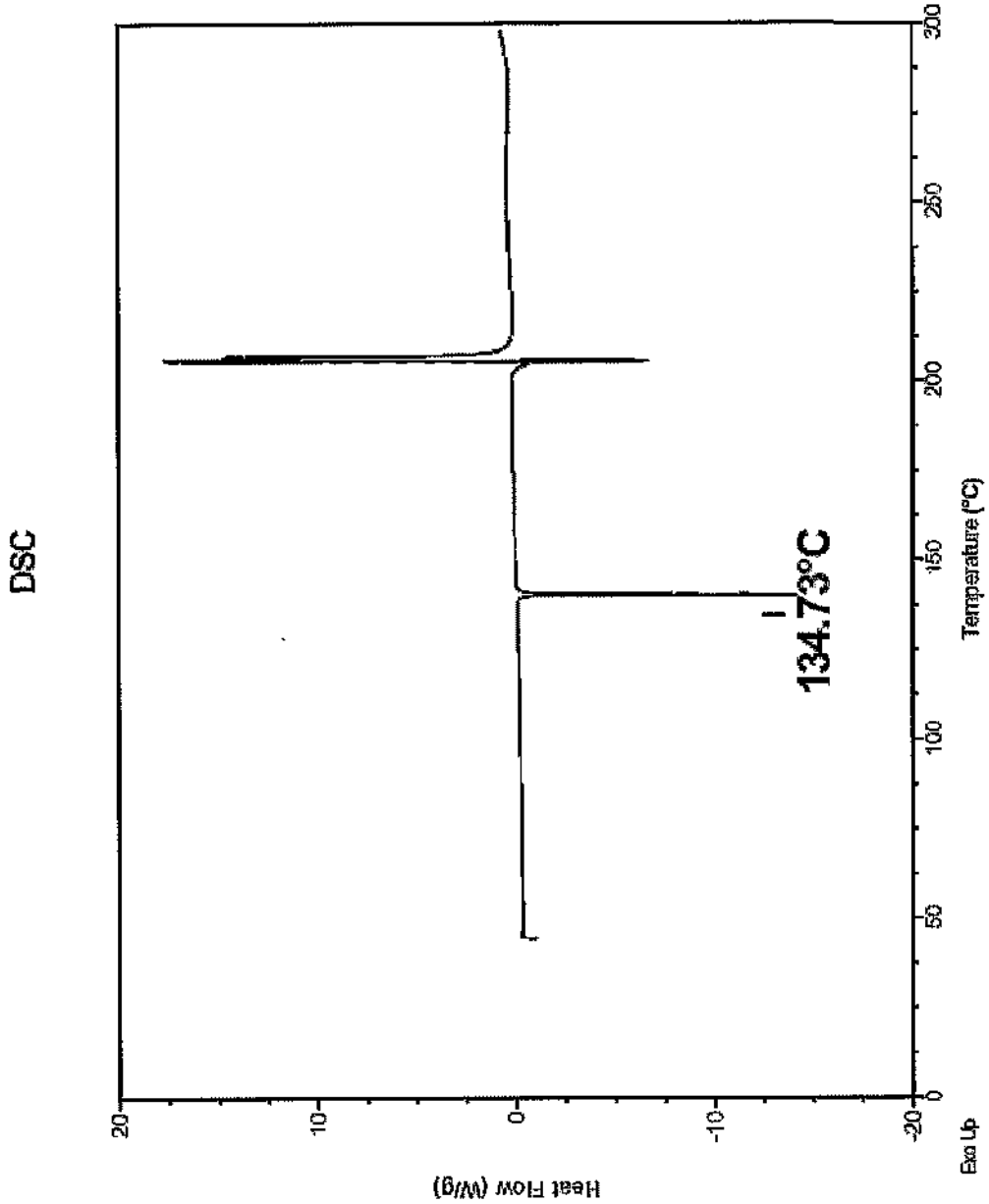

DSC
134.73°C
Heat Flow (W/g)
Temperature (°C)
Exo Up
20
10
0
-10
-20
0
50
100
150
200
250
300

FIG. 9

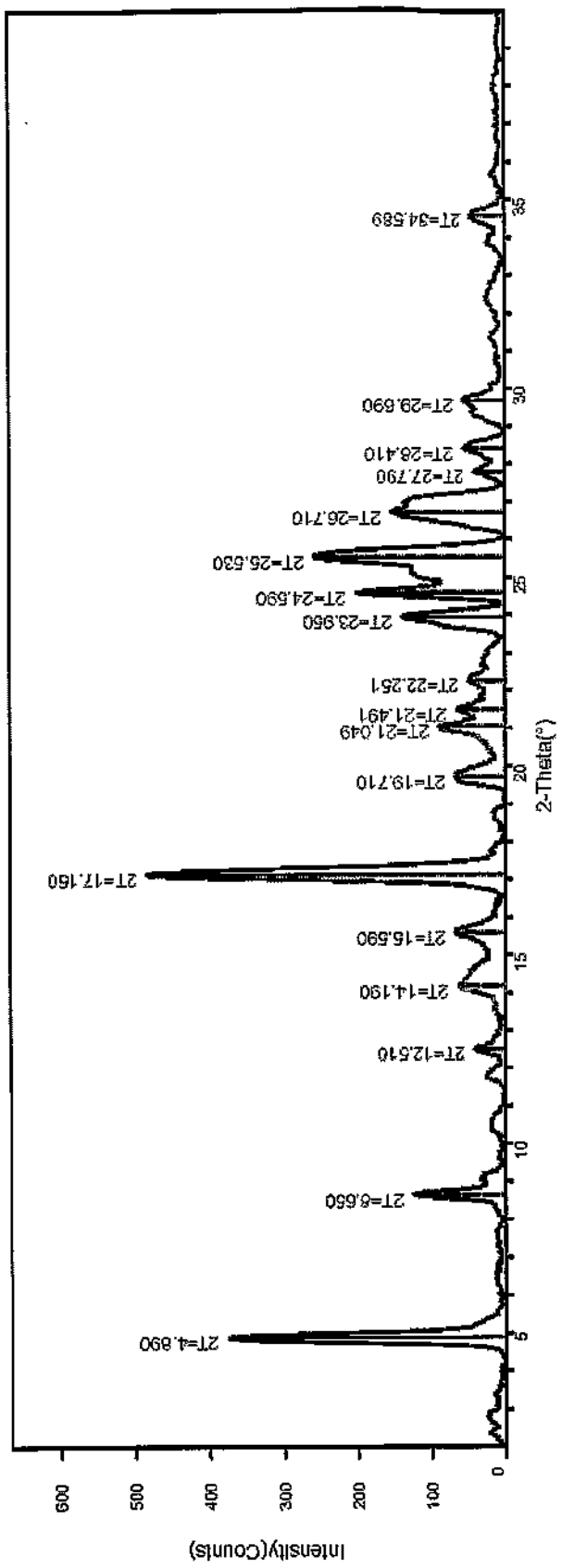

2T=4.890
2T=8.650
2T=12.510
2T=14.190
2T=15.590
2T=17.160
2T=19.710
2T=21.049
2T=21.491
2T=22.251
2T=23.960
2T=24.590
2T=25.630
2T=26.710
2T=27.790
2T=28.410
2T=29.690
2T=34.589
Intensity(Counts)
2-Theta(°)

FIG. 10A

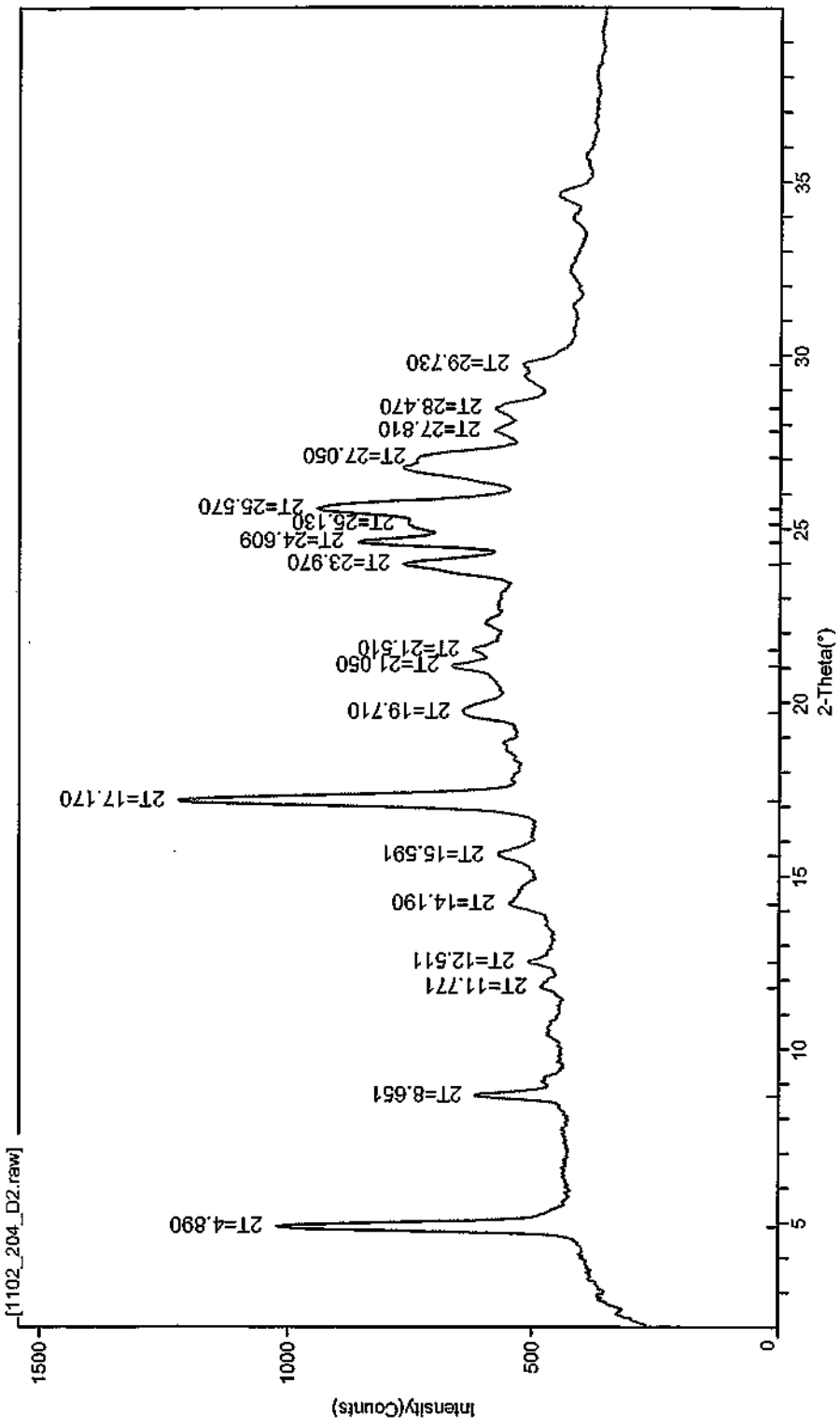

[1102_204_D2.raw]
Intensity(Counts)
2-Theta(°)
2T=4.890
2T=8.651
2T=11.771
2T=12.511
2T=14.190
2T=15.591
2T=17.170
2T=19.710
2T=21.050
2T=21.510
2T=23.970
2T=24.609
2T=26.130
2T=25.570
2T=27.050
2T=27.810
2T=28.470
2T=29.730

FIG. 10B

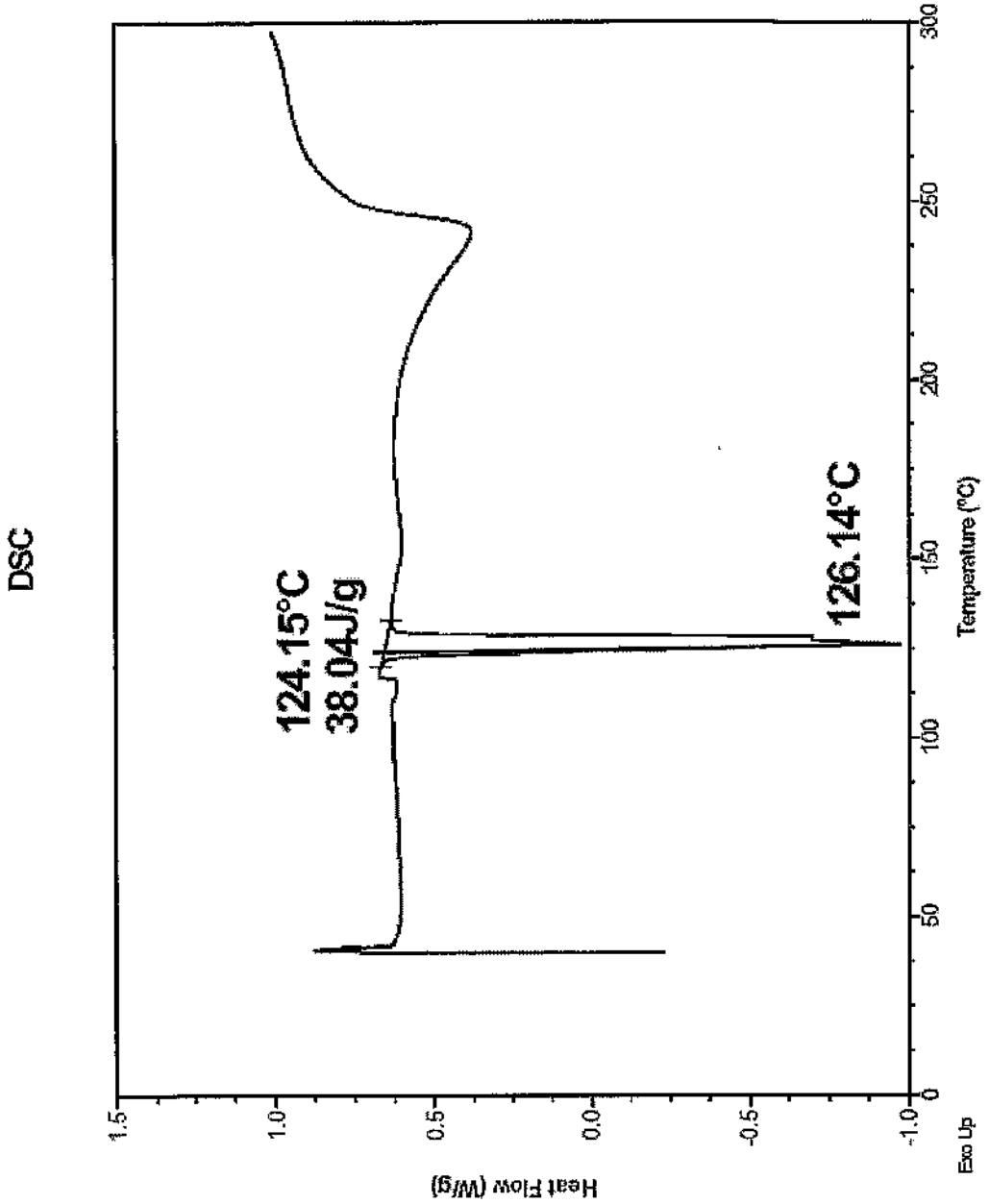

DSC
124.15°C
38.04J/g
126.14°C
Heat Flow (W/g)
Temperature (°C)
Exo Up
1.5
1.0
0.5
0.0
-0.5
-1.0
0
50
100
150
200
250
300

FIG. 11

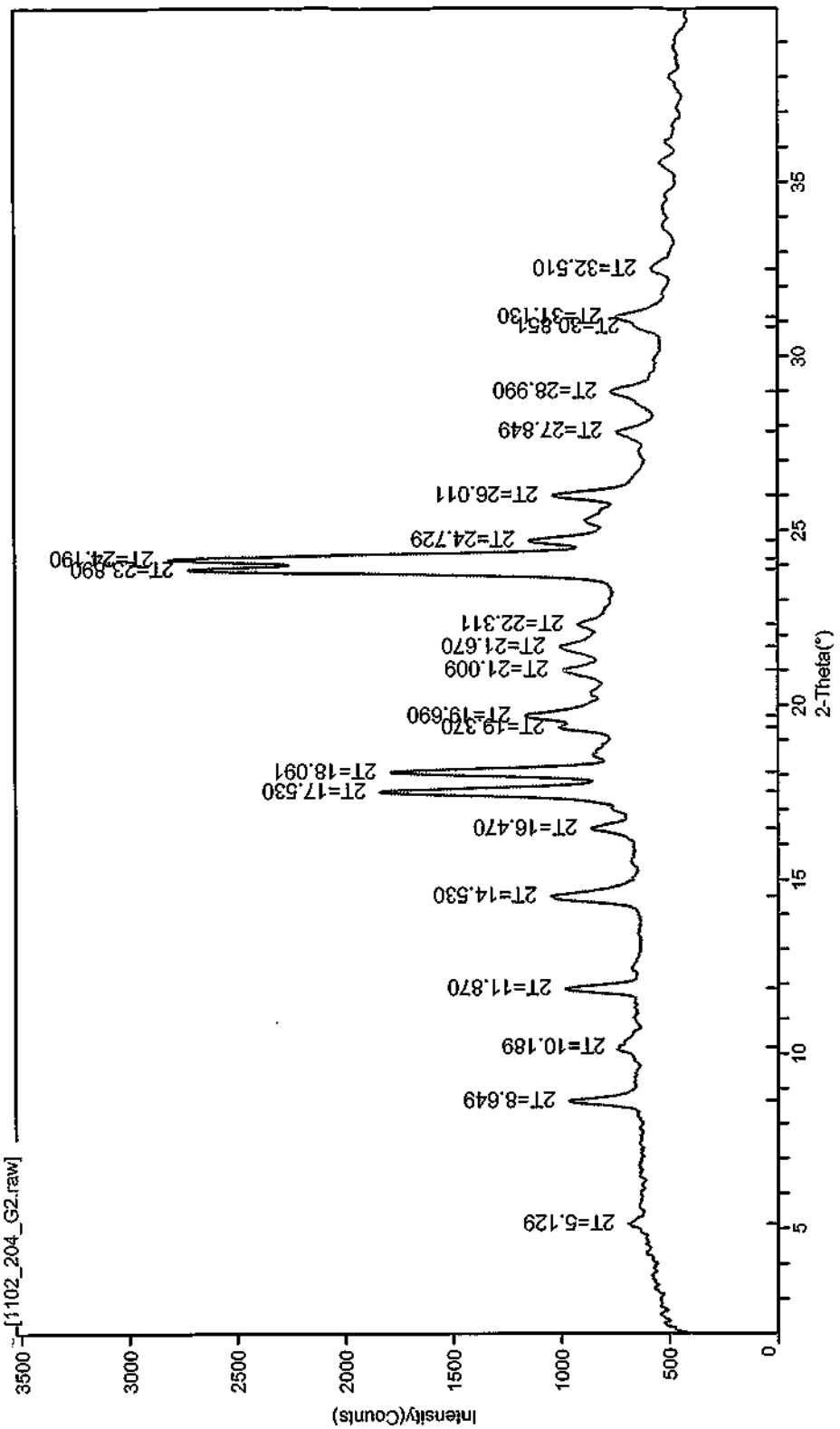

[1102_204_G2.raw]
Intensity(Counts)
3500
3000
2500
2000
1500
1000
500
0
5
10
15
20
25
30
35
2-Theta(°)
2T=5.129
2T=8.649
2T=10.189
2T=11.870
2T=14.530
2T=16.470
2T=17.530
2T=18.091
2T=19.370
2T=19.690
2T=21.009
2T=21.670
2T=22.311
2T=23.890
2T=24.190
2T=24.729
2T=26.011
2T=27.849
2T=28.990
2T=30.851
2T=31.130
2T=32.510

FIG. 12

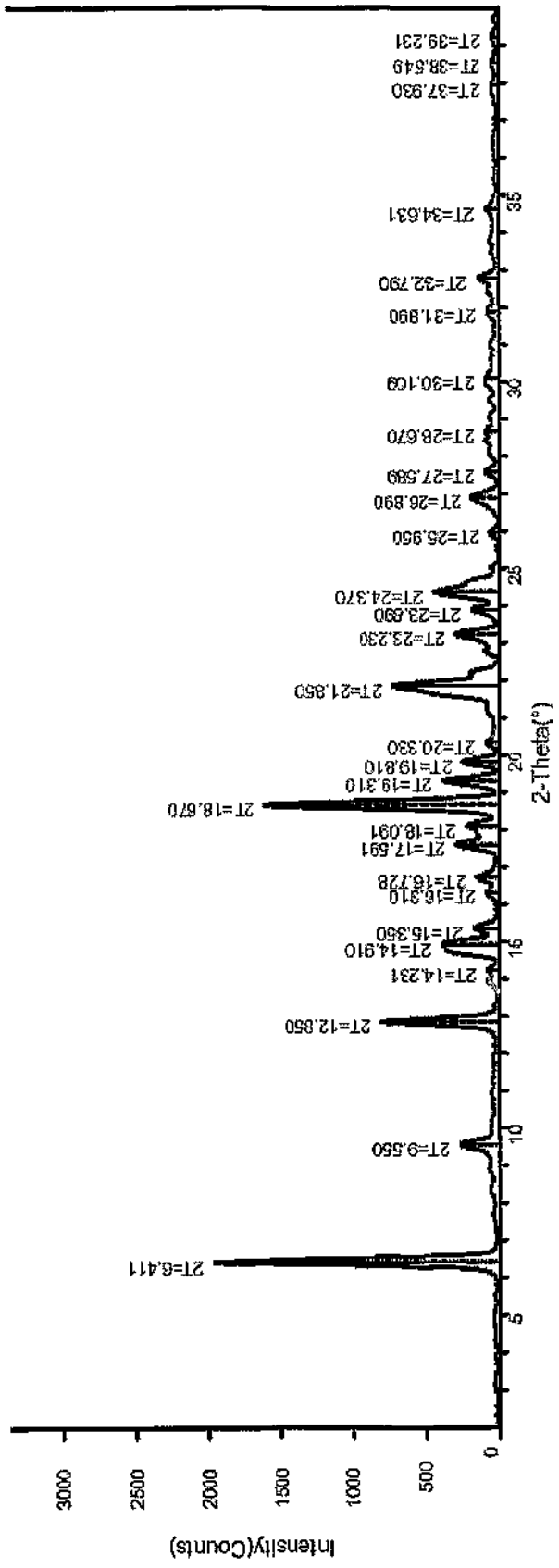

2T=39.231
2T=38.549
2T=37.930
2T=34.631
2T=32.790
2T=31.890
2T=30.109
2T=28.670
2T=27.589
2T=26.890
2T=25.950
2T=24.370
2T=23.890
2T=23.230
2T=21.850
2T=20.330
2T=19.810
2T=19.310
2T=18.670
2T=18.091
2T=17.691
2T=16.728
2T=16.310
2T=15.360
2T=14.910
2T=14.231
2T=12.850
2T=9.550
2T=8.411
Intensity(Counts)
3000
2500
2000
1500
1000
500
0
5
10
15
20
25
30
35
2-Theta(°)

FIG. 13A

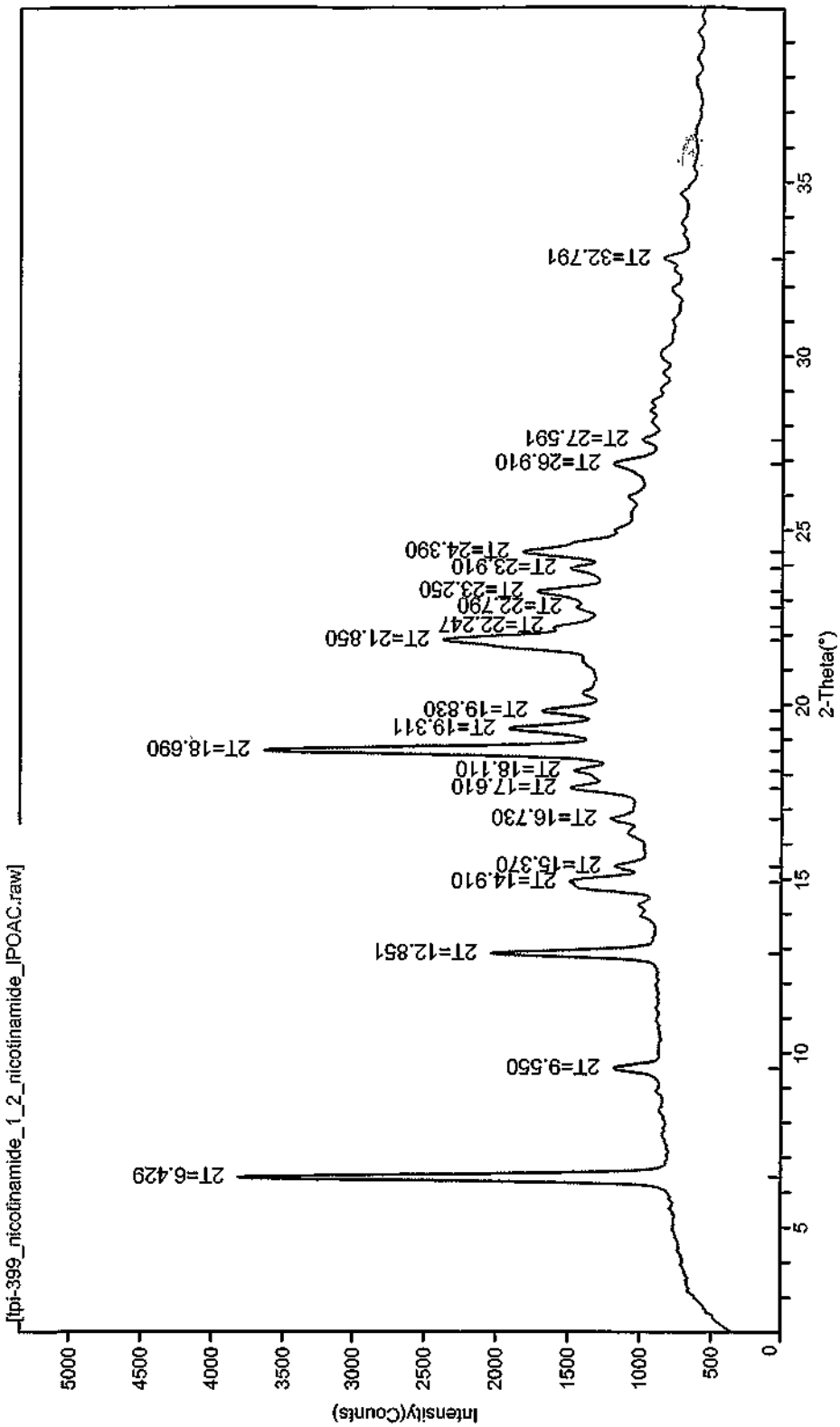

[tpi-399_nicotinamide_1_2_nicotinamide_IPOAC.raw]
Intensity(Counts)
2-Theta(°)
2T=6.429
2T=9.550
2T=12.851
2T=14.910
2T=15.370
2T=16.730
2T=17.610
2T=18.110
2T=18.690
2T=19.311
2T=19.830
2T=21.850
2T=22.247
2T=22.790
2T=23.250
2T=23.910
2T=24.390
2T=26.910
2T=27.591
2T=32.791

FIG. 13B

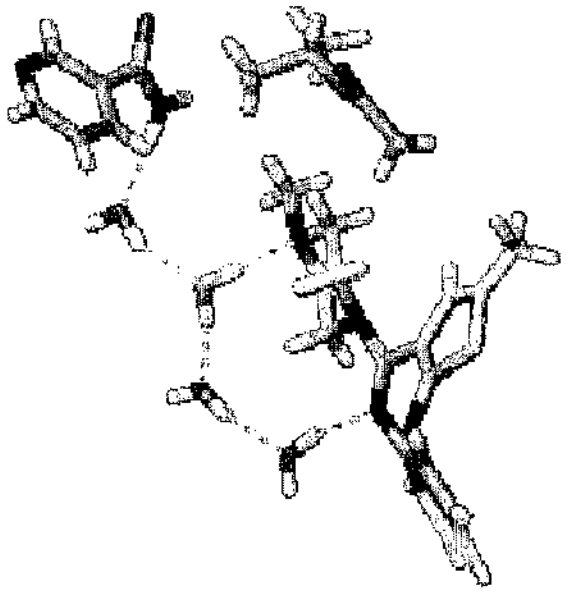


FIG. 14A

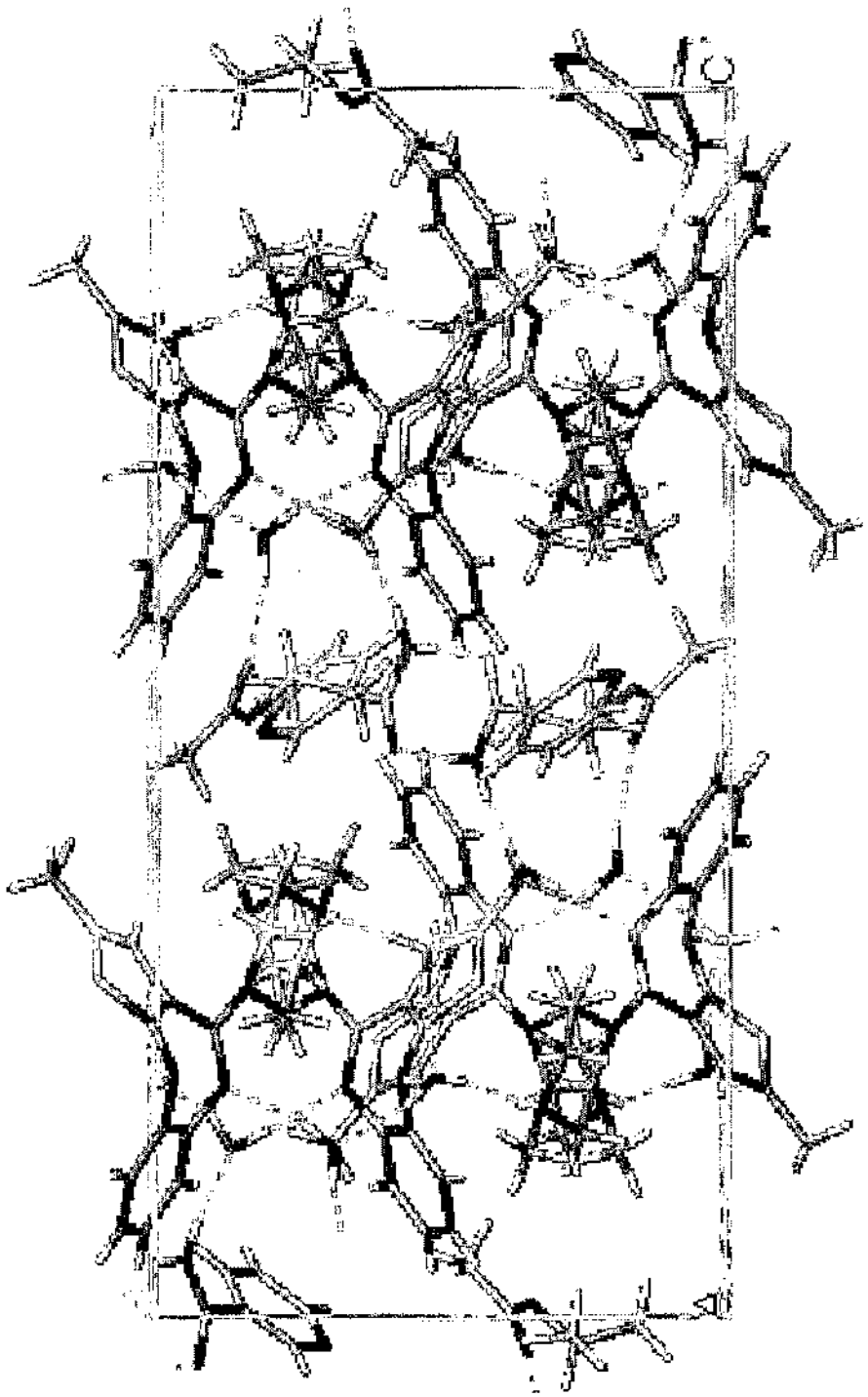


FIG. 14B

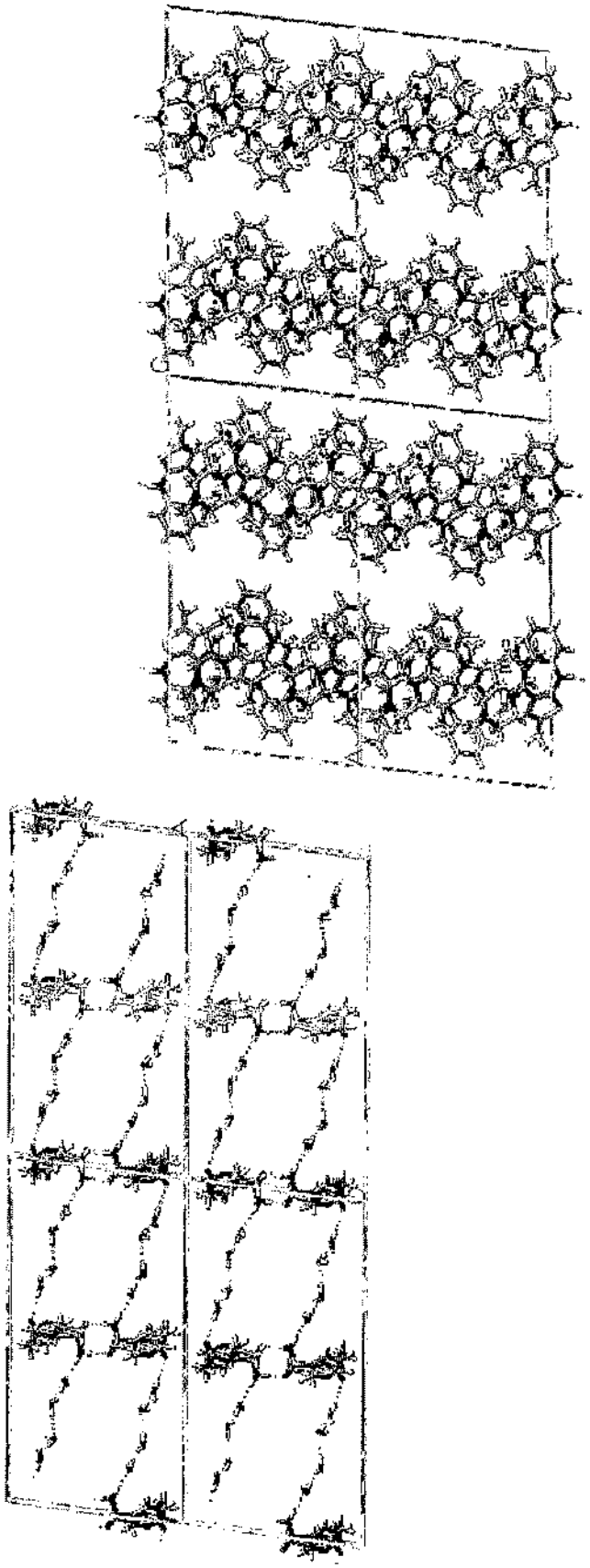


FIG. 14C

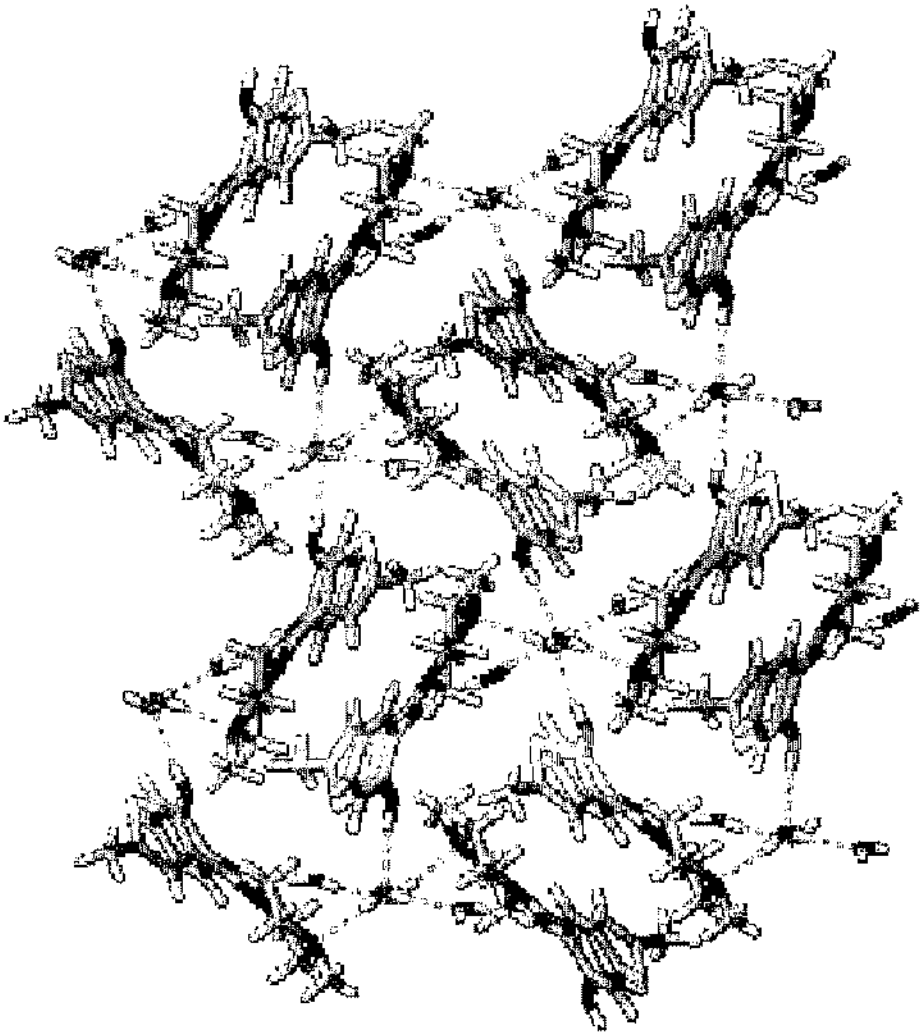


FIG. 14D

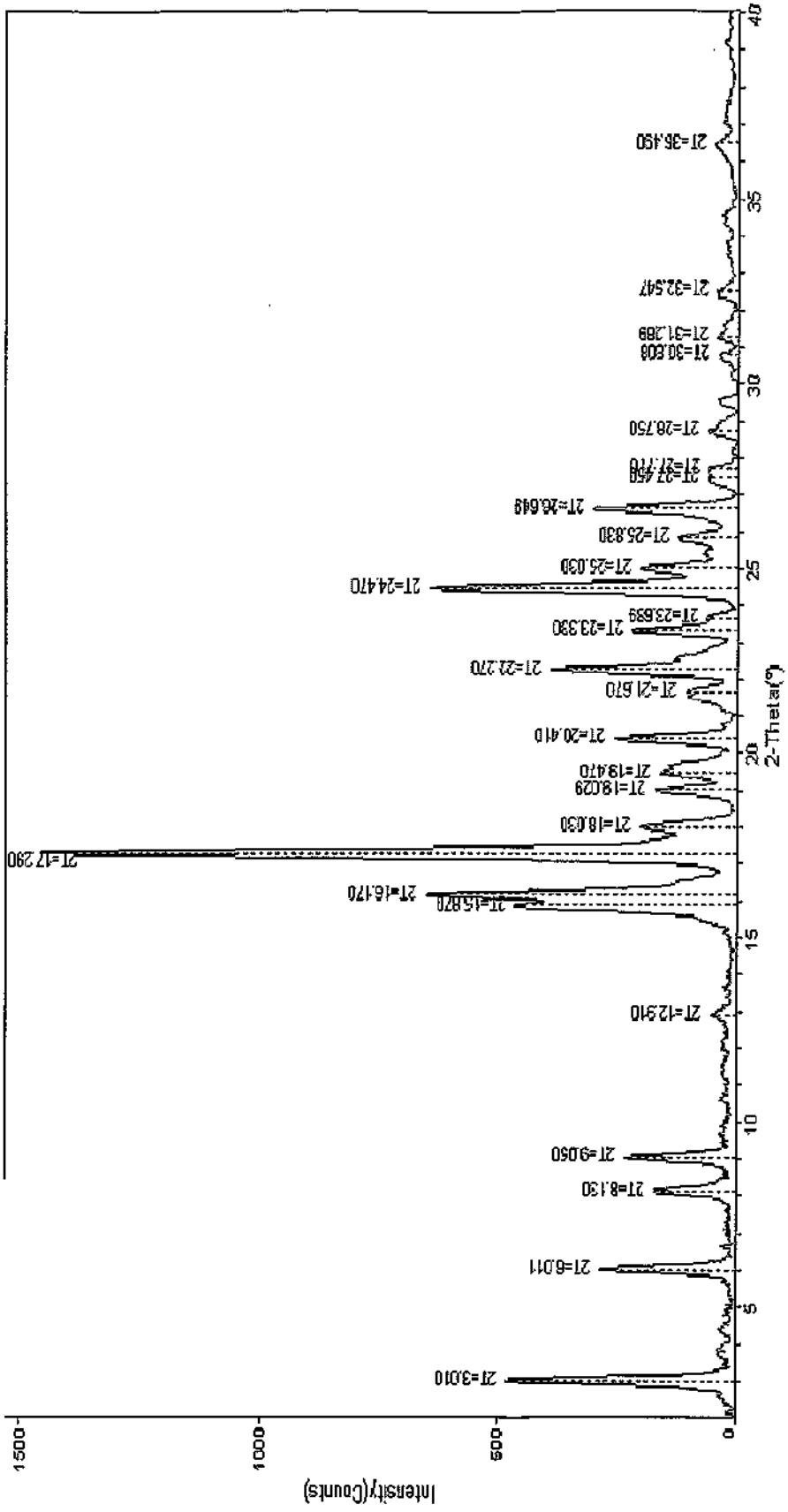

Intensity(Counts)
1500
1000
500
0
2-Theta(°)
5
10
15
20
25
30
35
40
2T=3.010
2T=6.011
2T=8.130
2T=9.050
2T=12.910
2T=15.820
2T=16.170
2T=17.290
2T=18.030
2T=18.029
2T=19.470
2T=20.410
2T=21.670
2T=22.270
2T=23.330
2T=23.689
2T=24.470
2T=25.030
2T=25.830
2T=26.649
2T=27.450
2T=27.710
2T=28.750
2T=30.608
2T=31.289
2T=32.547
2T=35.450

FIG. 15

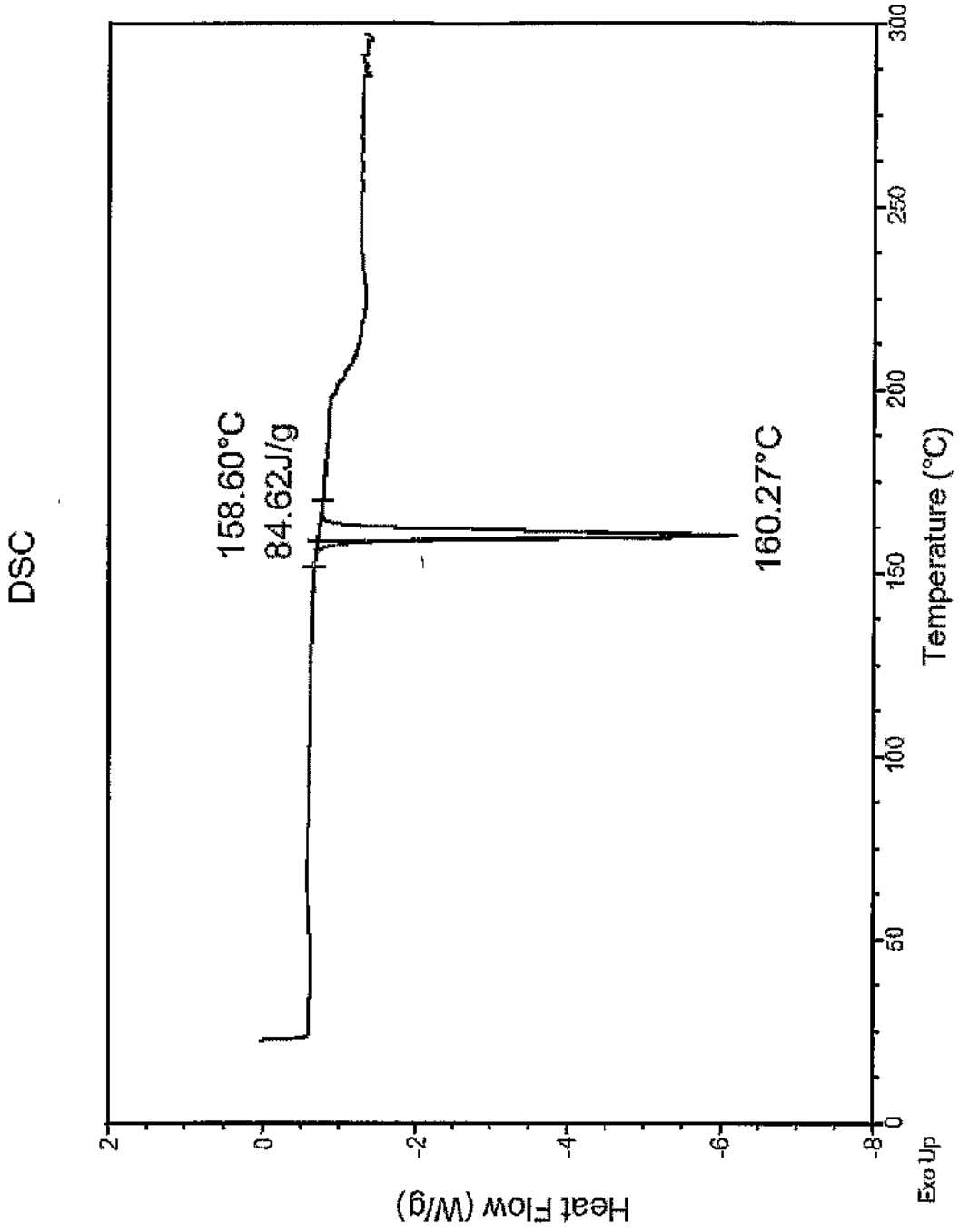

DSC
158.60°C
84.62J/g
160.27°C
Heat Flow (W/g)
Exo Up
Temperature (°C)
2
0
-2
-4
-6
-8
0
50
100
150
200
250
300

FIG. 16

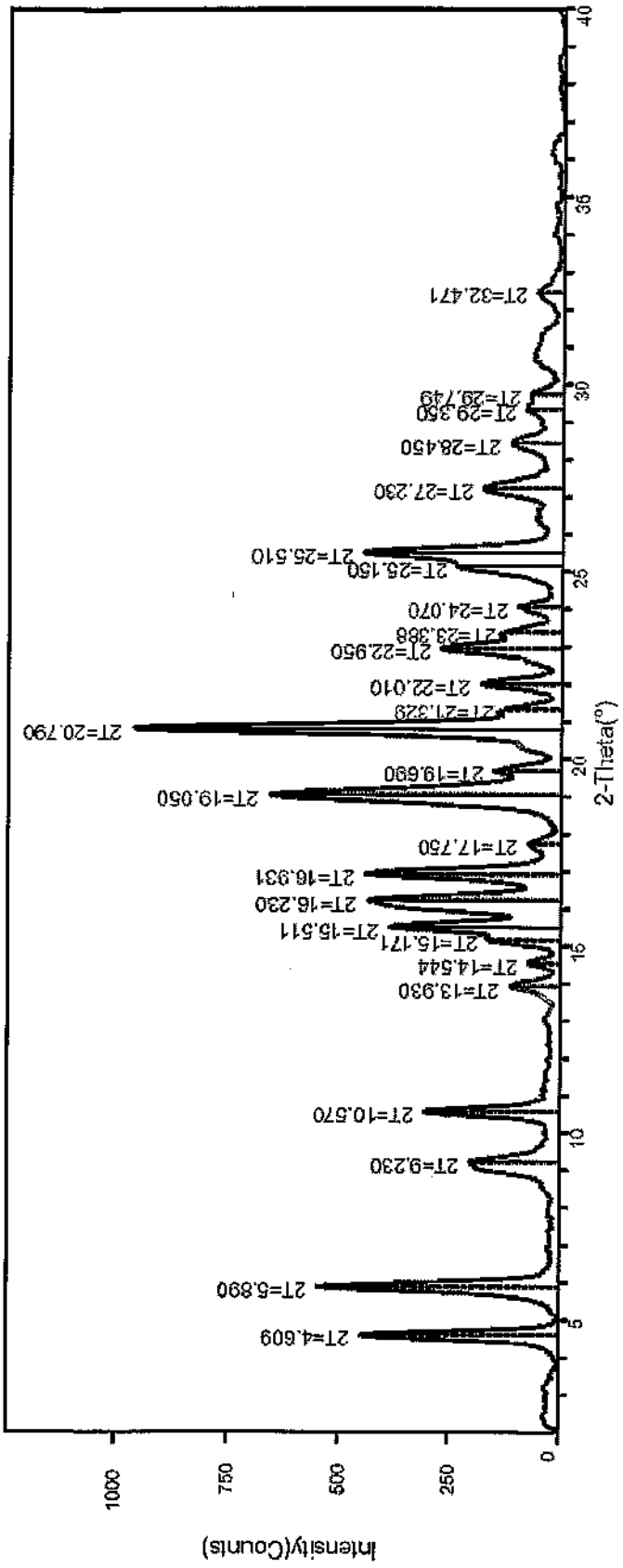

Intensity(Counts)
1000
750
500
250
0
5
10
15
20
25
30
35
40
2-Theta(°)
2T=4.609
2T=5.890
2T=9.230
2T=10.570
2T=13.930
2T=14.544
2T=15.171
2T=15.511
2T=16.230
2T=16.931
2T=17.750
2T=19.050
2T=19.690
2T=20.790
2T=21.329
2T=22.010
2T=22.950
2T=23.388
2T=24.070
2T=25.150
2T=25.510
2T=27.230
2T=28.450
2T=29.350
2T=29.749
2T=32.471

FIG. 17

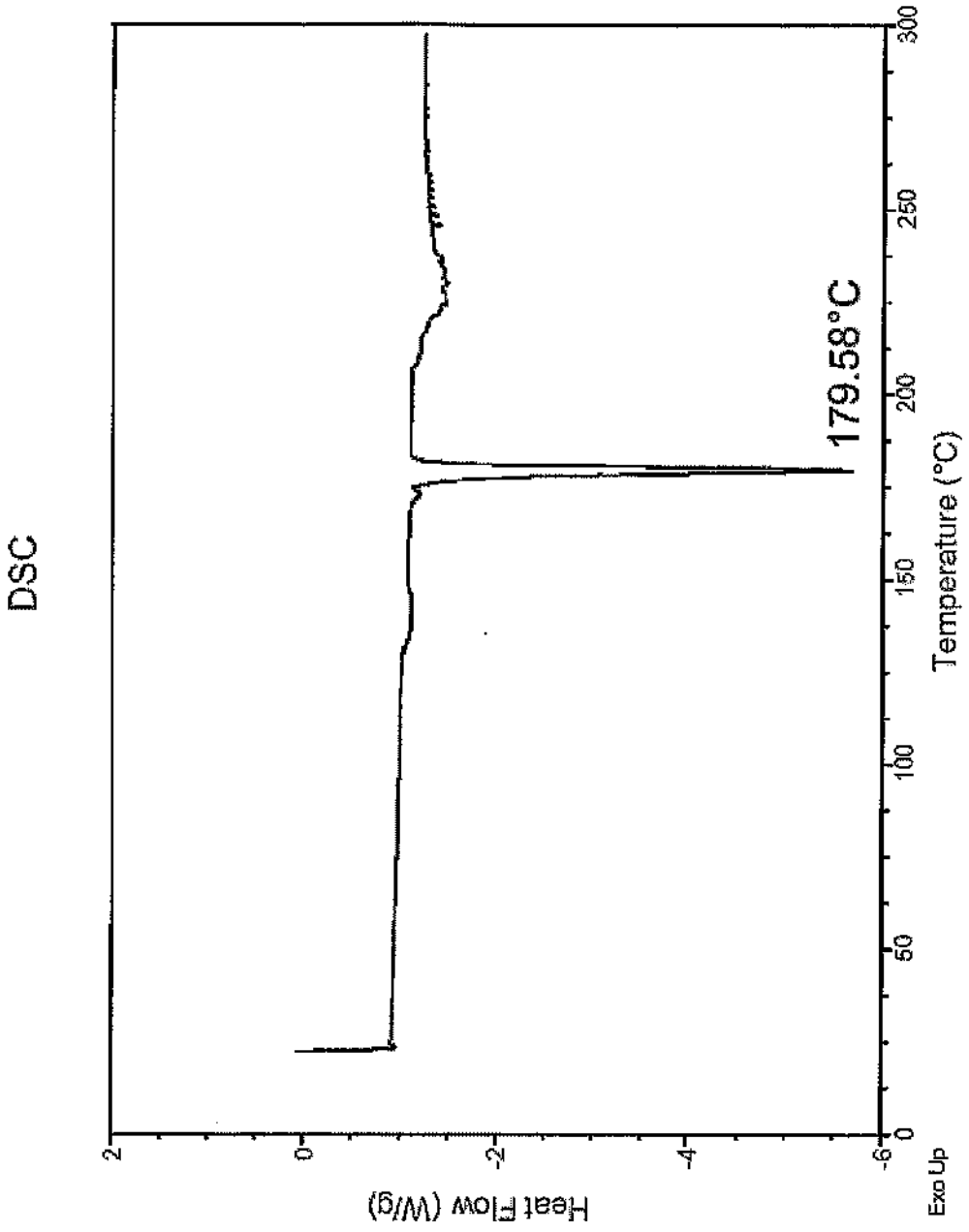

DSC
179.58°C
Heat Flow (W/g)
Temperature (°C)
Exo Up
2
0
-2
-4
-6
0
50
100
150
200
250
300

FIG. 18

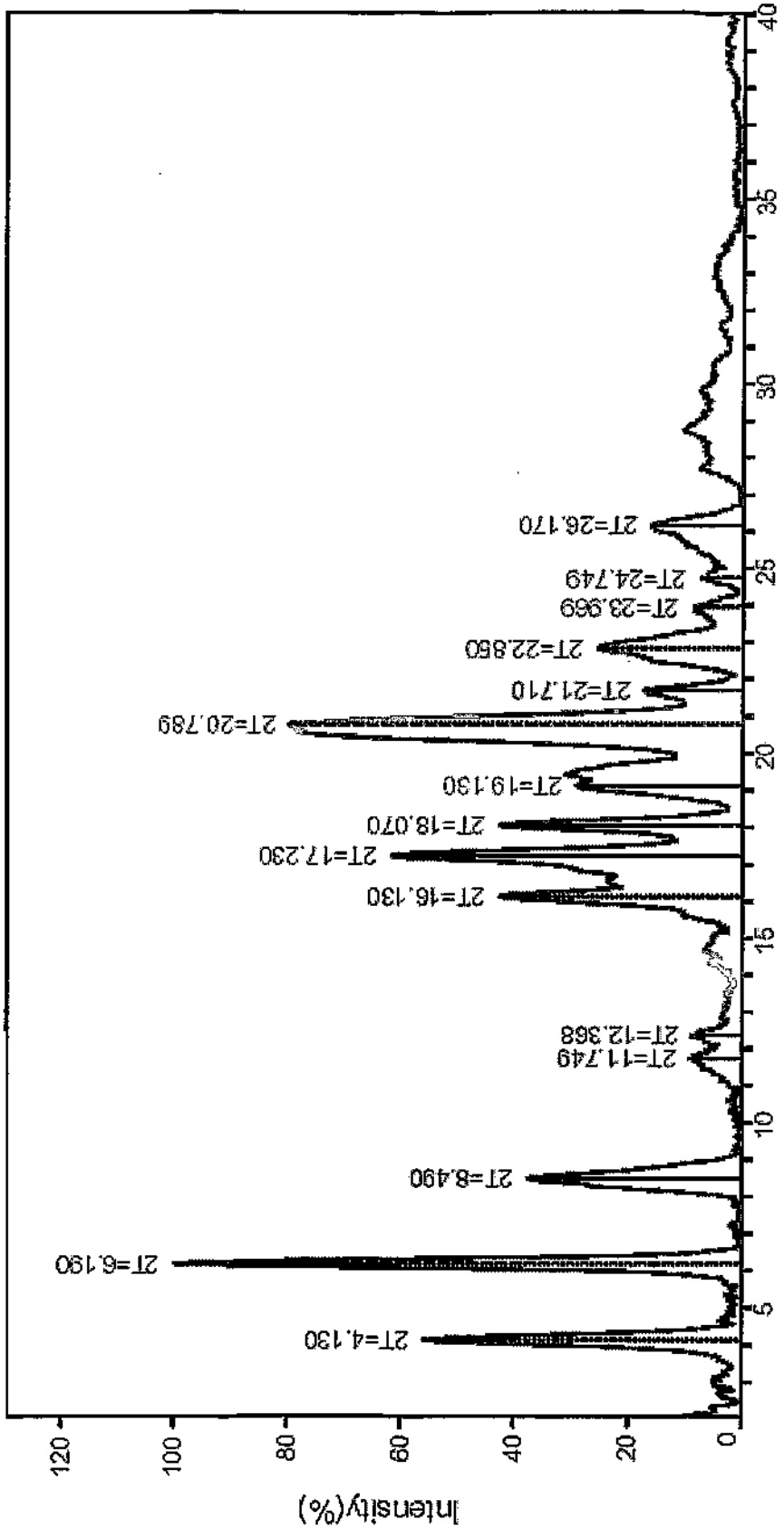

Intensity(%)
2-Theta(°)
2T=4.130
2T=6.190
2T=8.490
2T=11.749
2T=12.368
2T=16.130
2T=17.230
2T=18.070
2T=19.130
2T=20.789
2T=21.710
2T=22.850
2T=23.969
2T=24.749
2T=26.170

FIG. 19

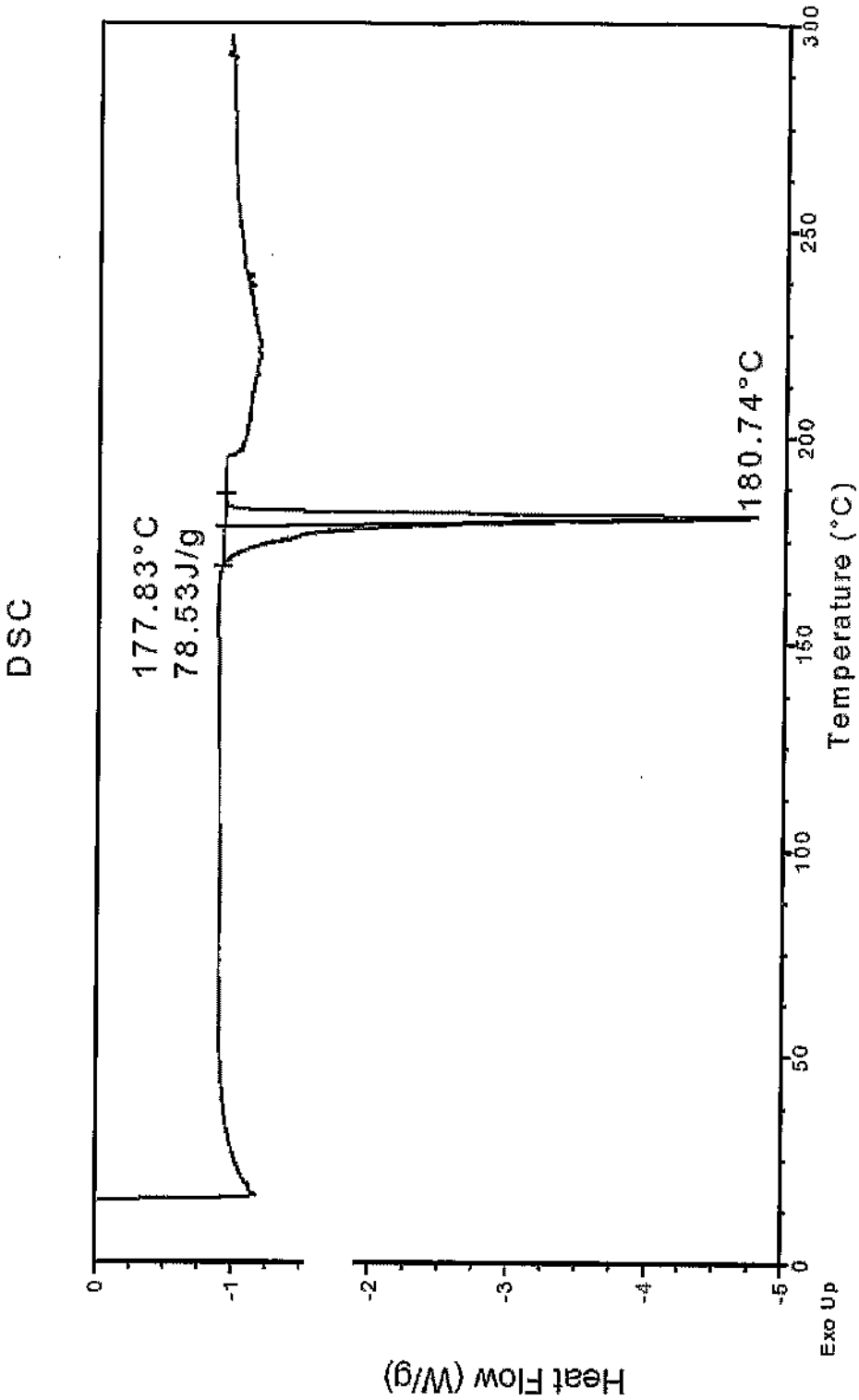

DSC
177.83°C
78.53J/g
180.74°C
Heat Flow (W/g)
Temperature (°C)
Exo Up
0
-1
-2
-3
-4
-5
50
100
150
200
250
300

FIG. 20

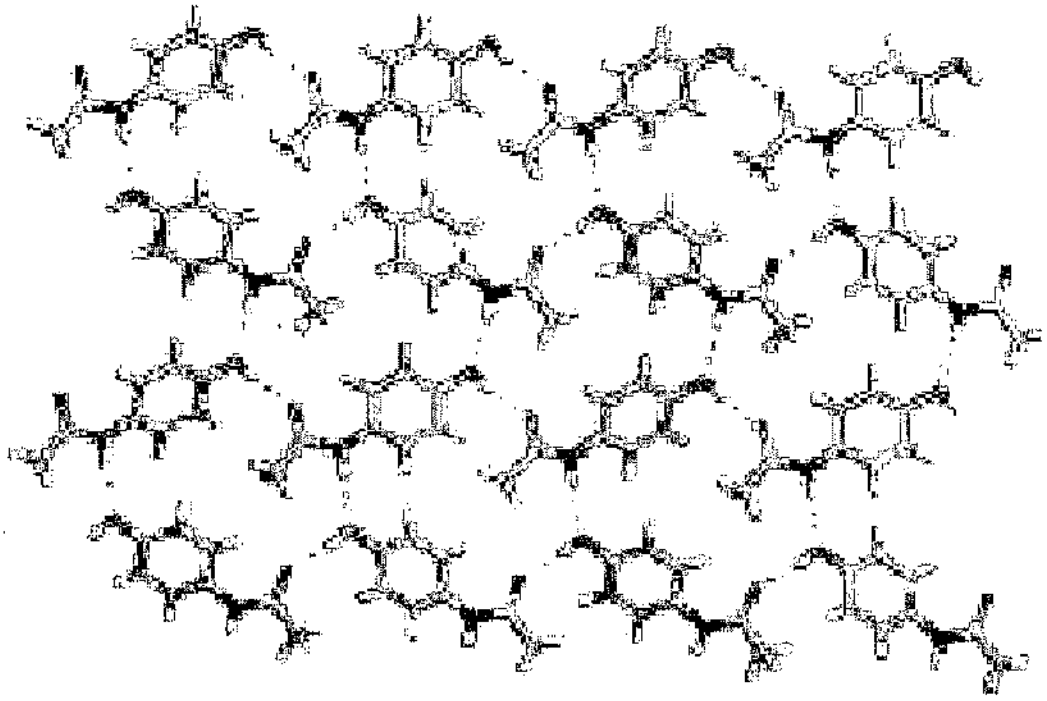


FIG. 38A

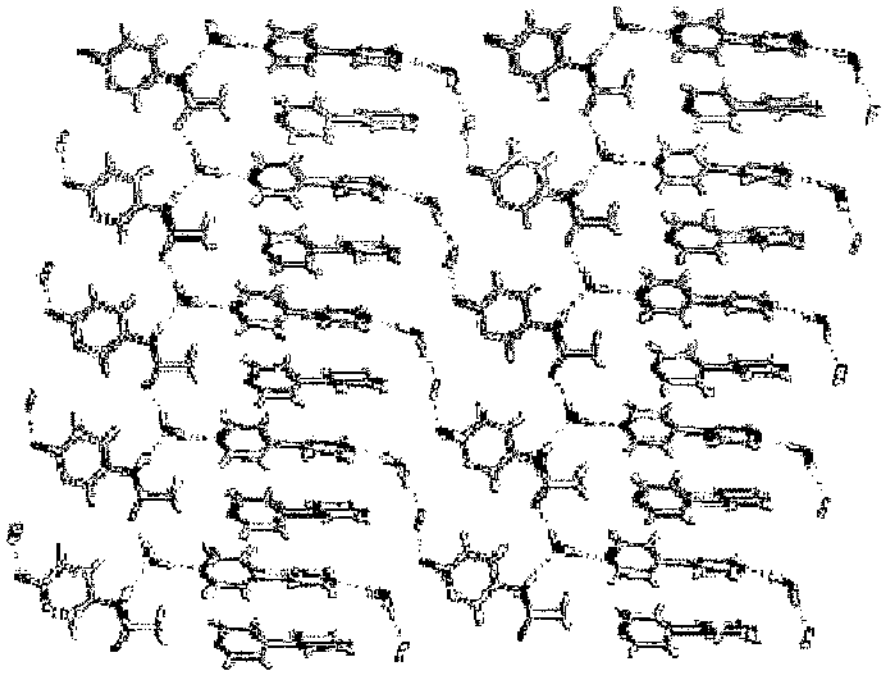


FIG. 38B

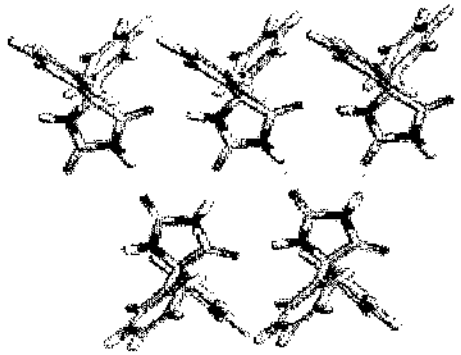


FIG. 39A

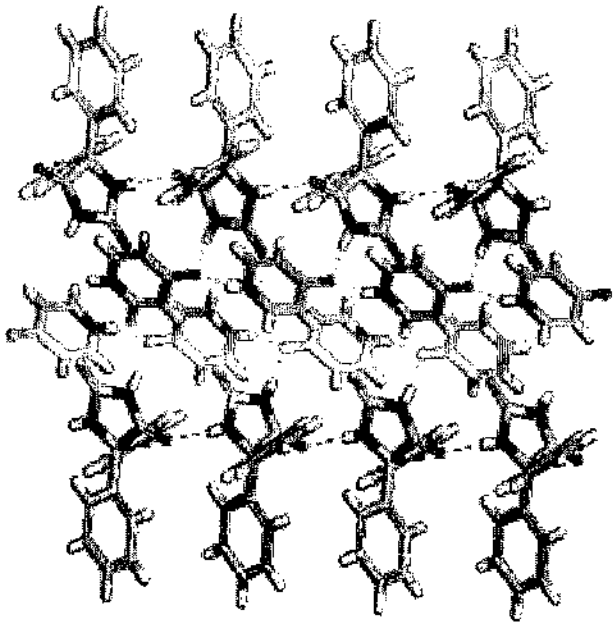


FIG. 39B

FIG. 40A

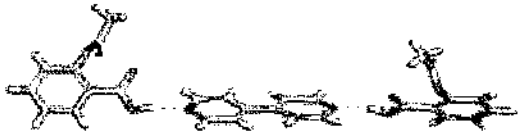


FIG. 40C

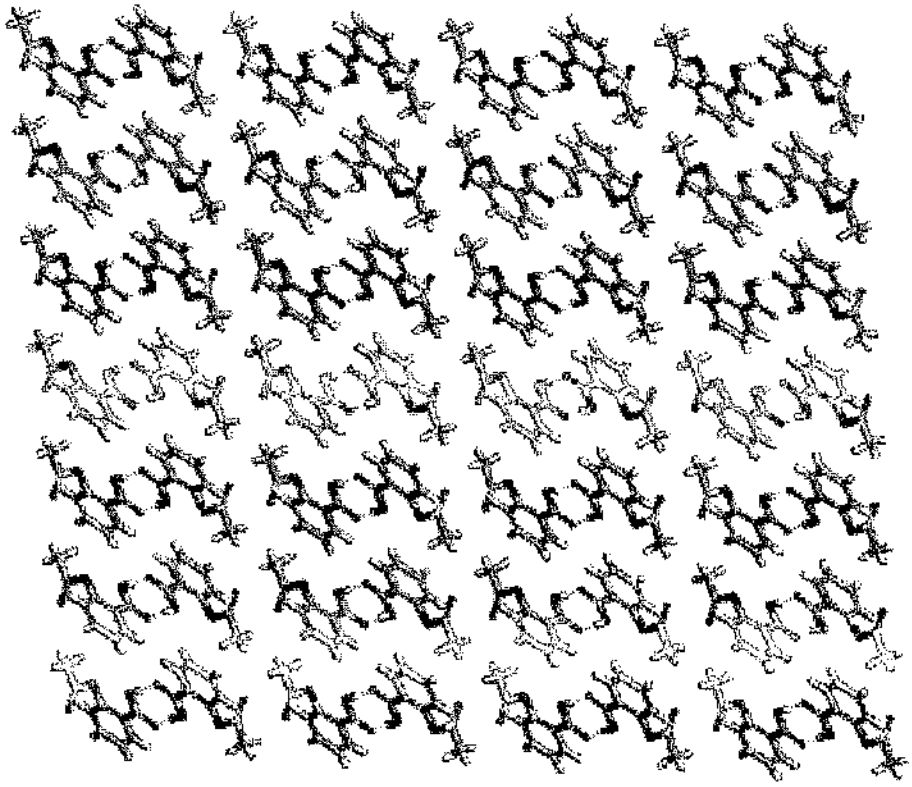


FIG. 40B

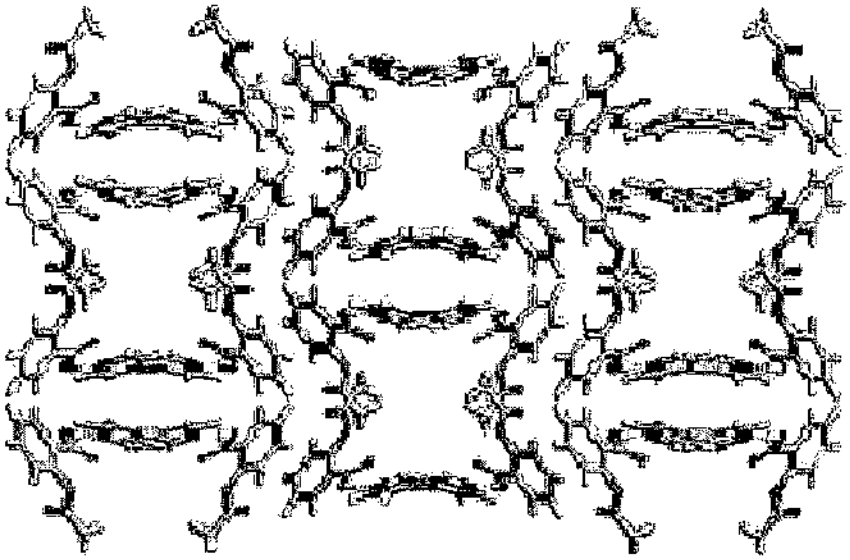


FIG. 40D

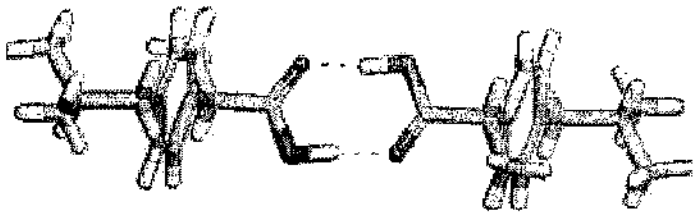


FIG. 41A

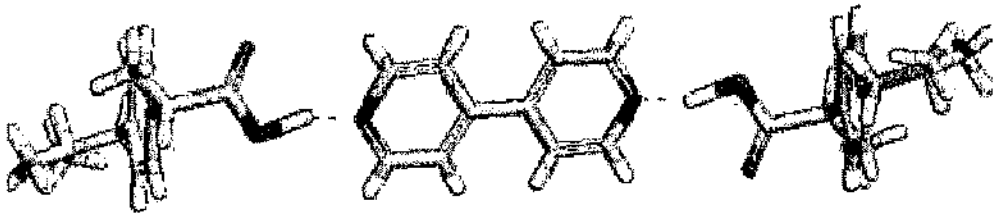


FIG. 41C

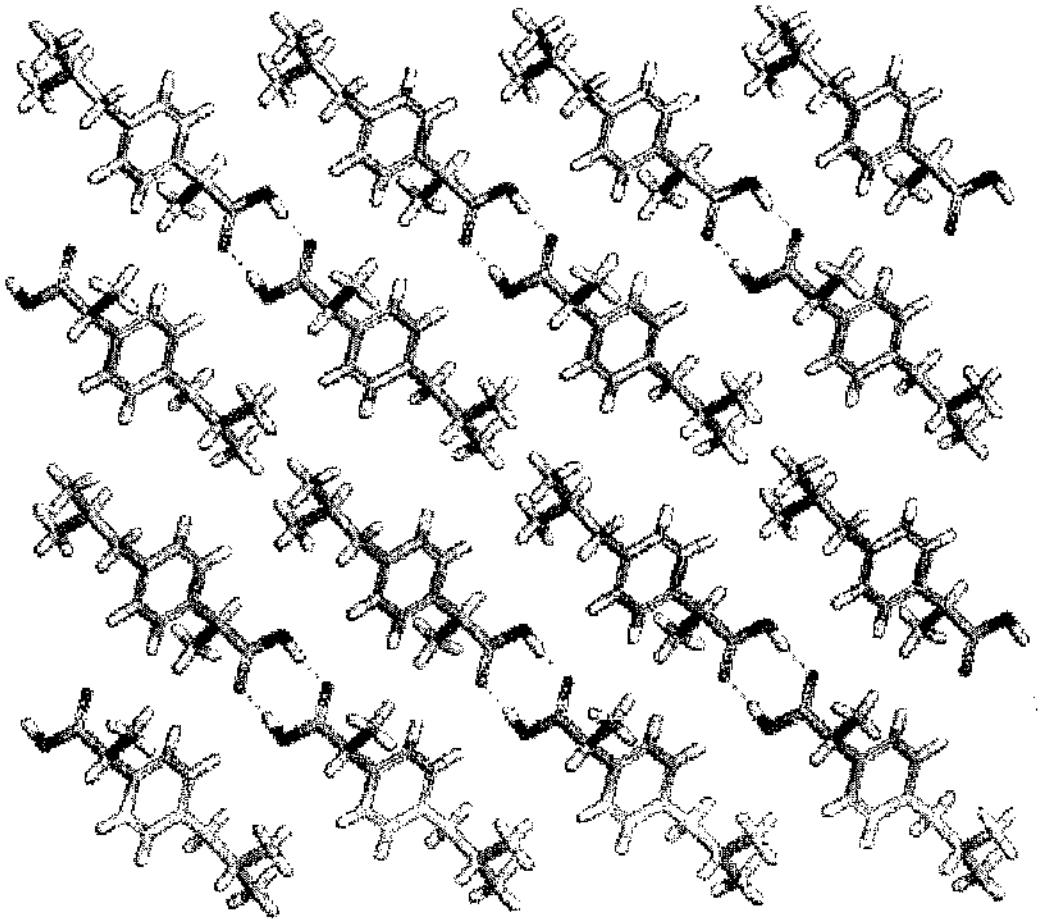


FIG. 41B

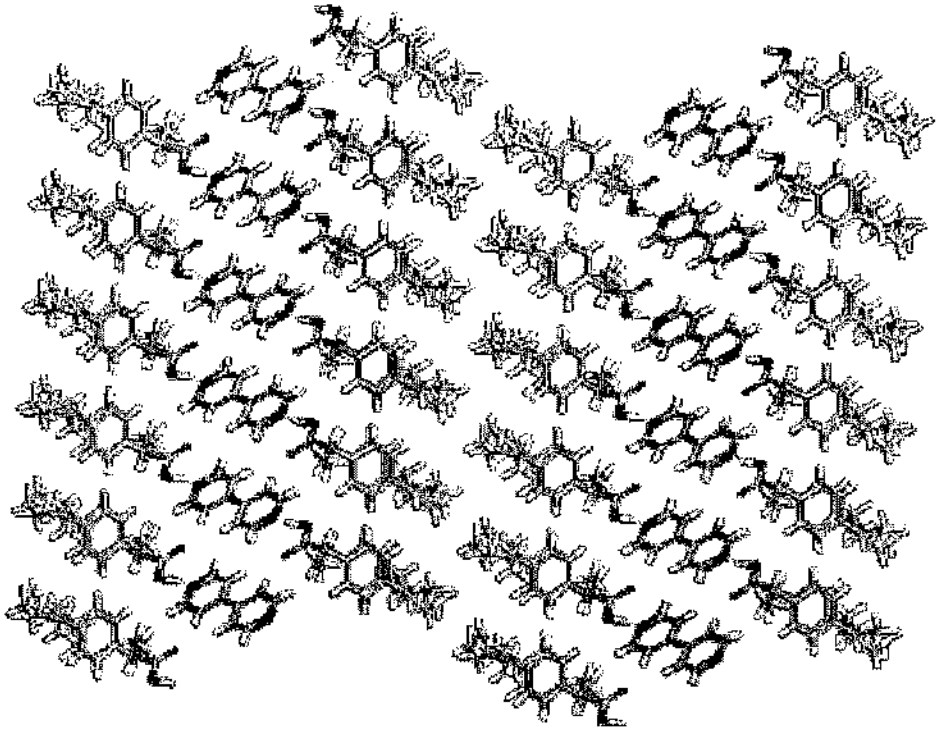


FIG. 41D

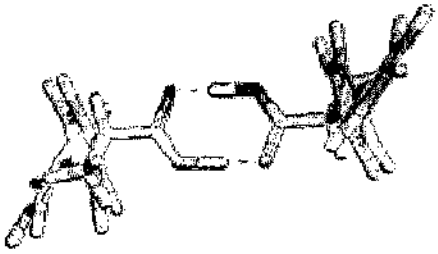


FIG. 42A

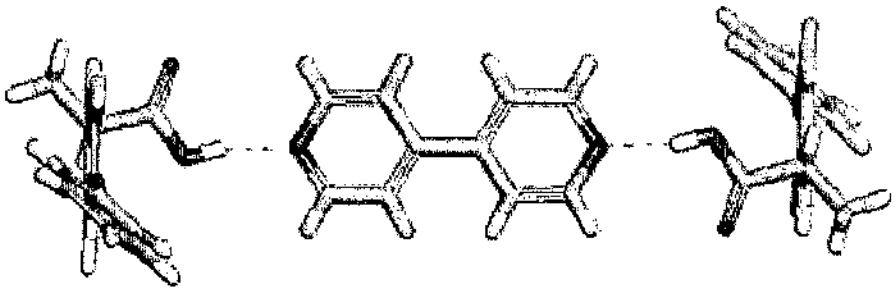


FIG. 42C

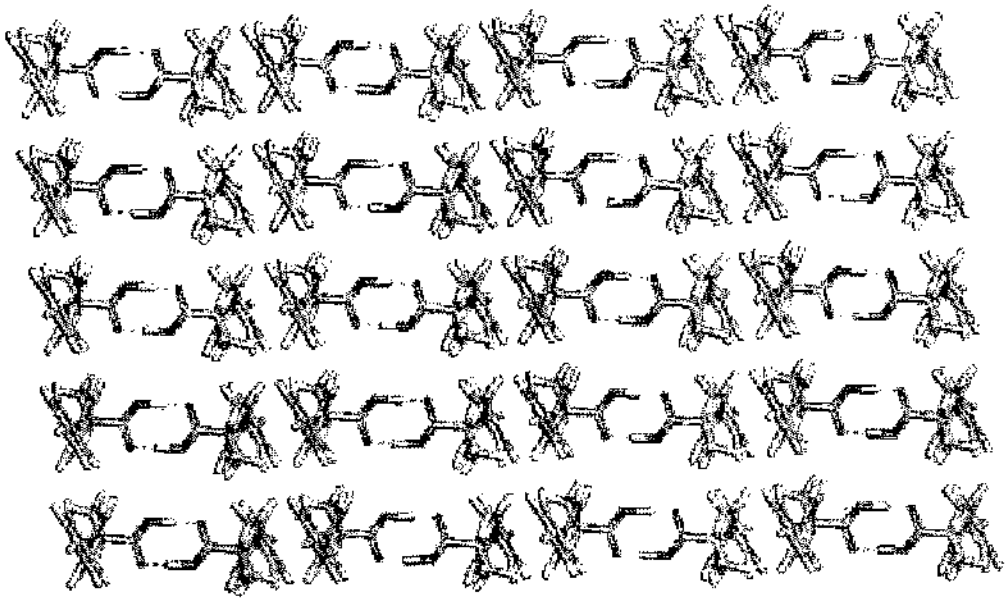


FIG. 42B

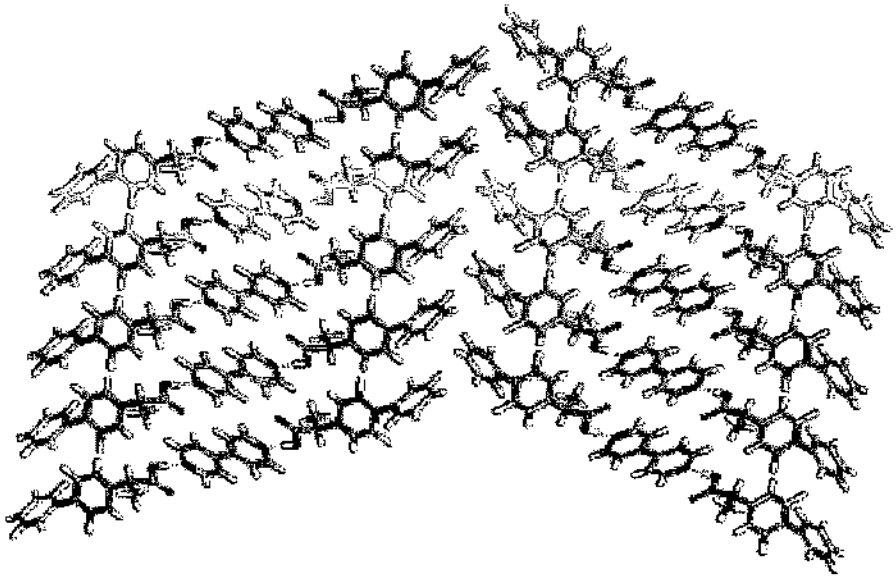


FIG. 42D

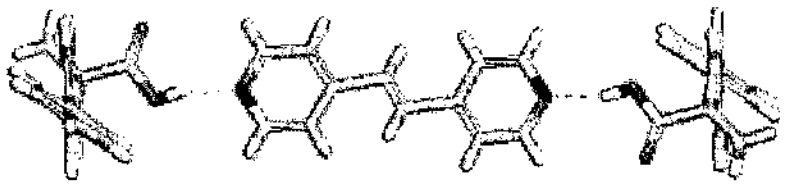


FIG. 43A

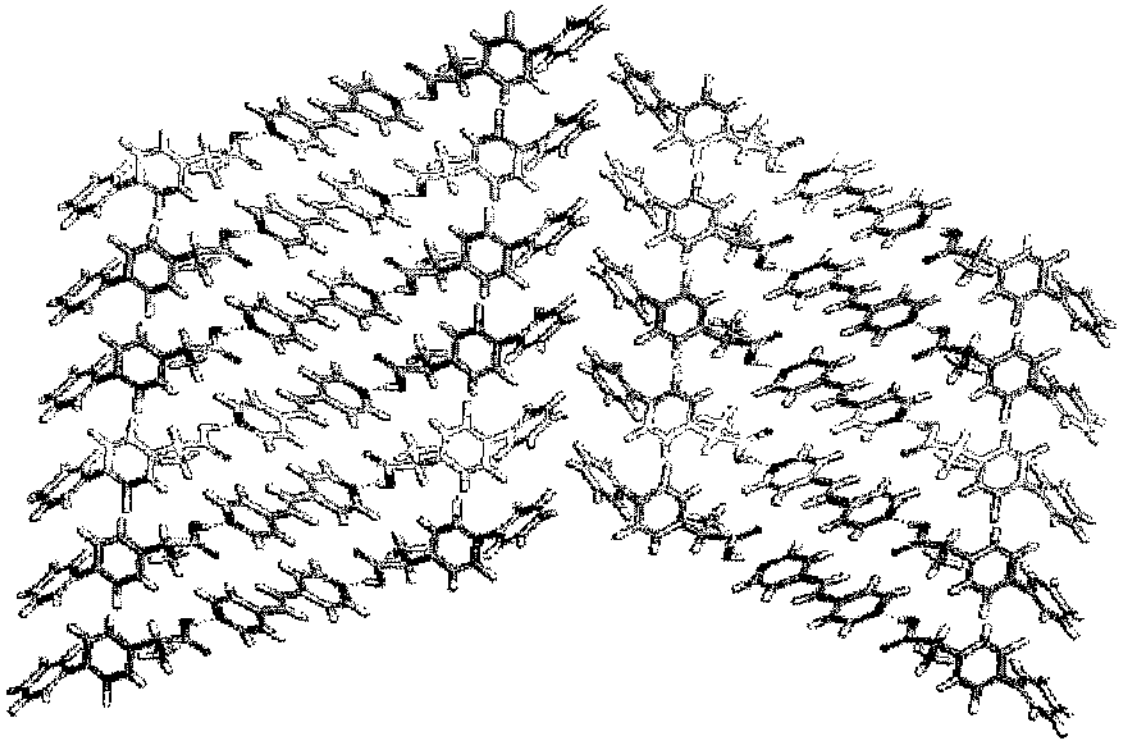


FIG. 43B

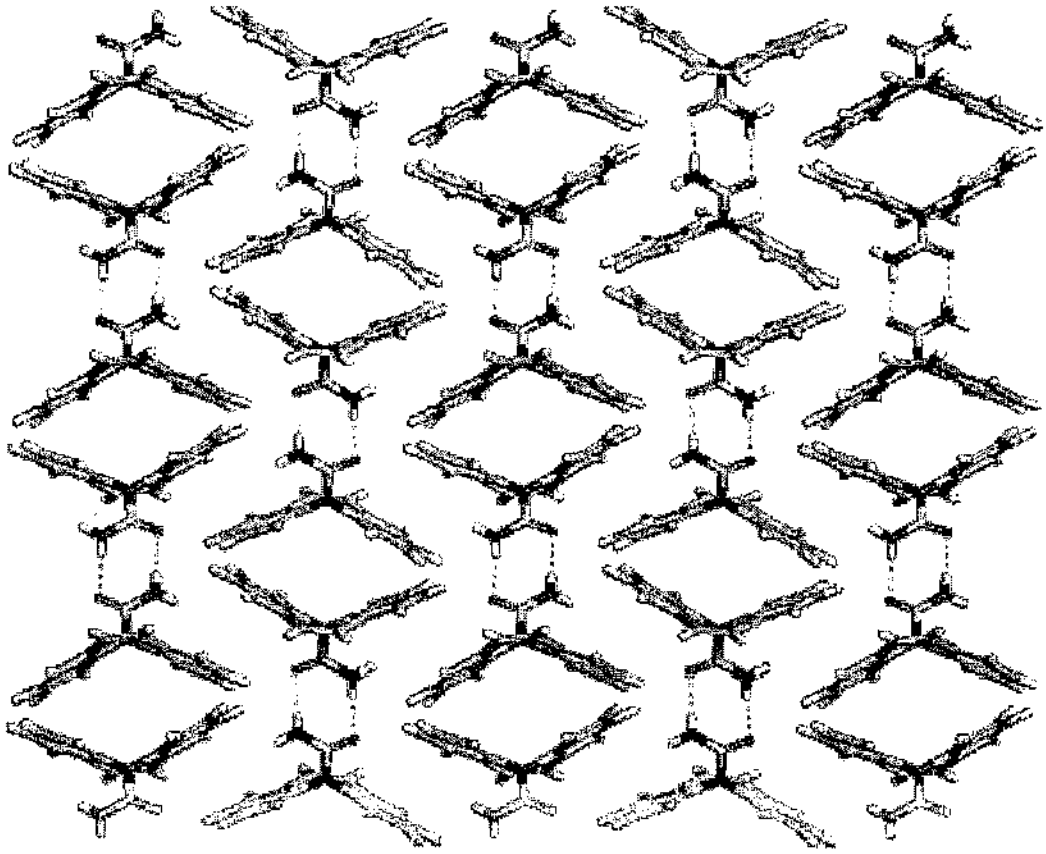


FIG. 44A

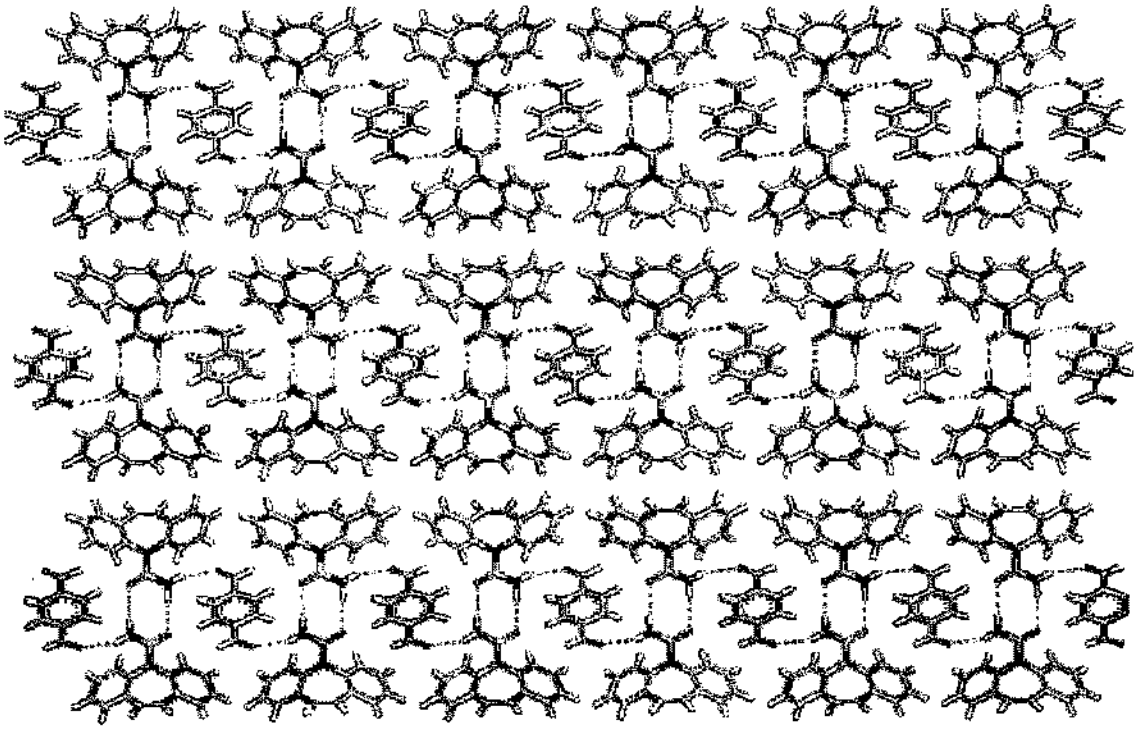


FIG. 44B

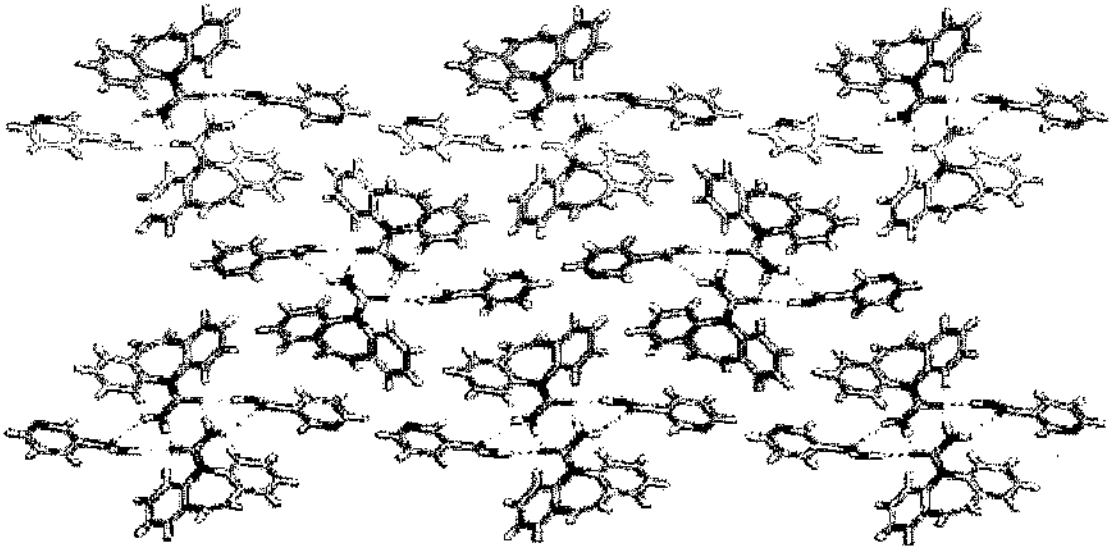


FIG. 45

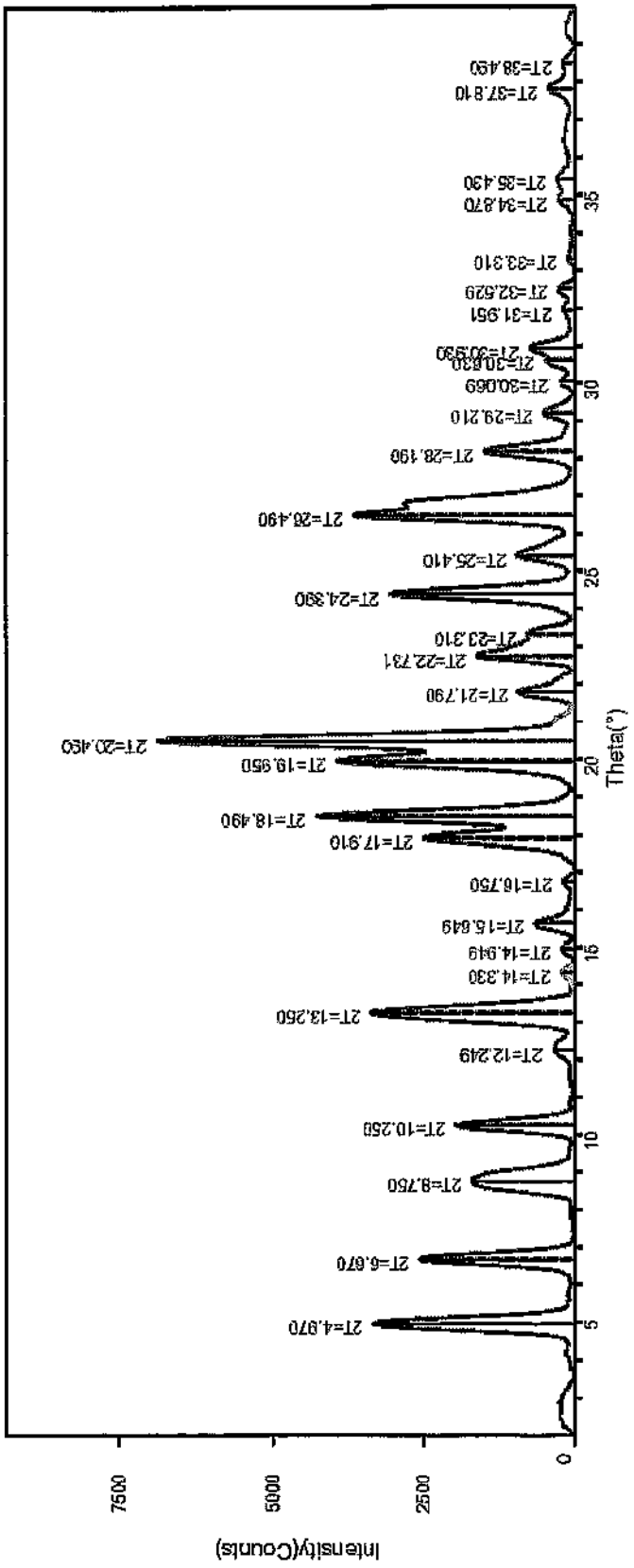

Intensity(Counts)
7500
5000
2500
0
5
10
15
20
25
30
35
Theta(°)
2T=4.870
2T=6.670
2T=8.750
2T=10.250
2T=12.249
2T=13.260
2T=14.330
2T=14.949
2T=15.649
2T=16.750
2T=17.910
2T=18.490
2T=19.950
2T=20.450
2T=21.790
2T=22.731
2T=23.310
2T=24.390
2T=25.410
2T=26.490
2T=28.190
2T=29.210
2T=30.069
2T=30.830
2T=30.930
2T=31.951
2T=32.529
2T=33.310
2T=34.870
2T=35.430
2T=37.810
2T=38.450

FIG. 46

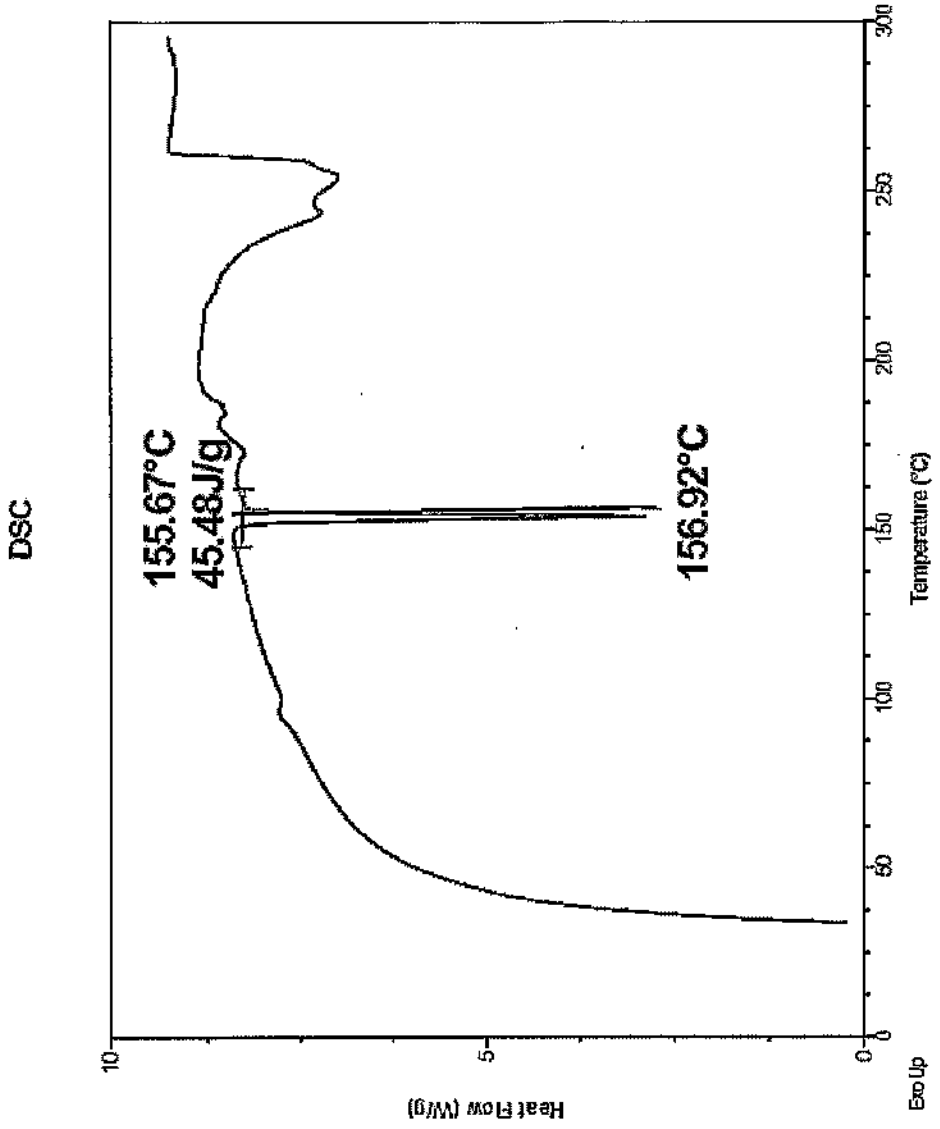

DSC
155.67°C
45.48J/g
156.92°C
Heat Flow (W/g)
Exo Up
Temperature (°C)
0
5
10
0
50
100
150
200
250
300

FIG. 47

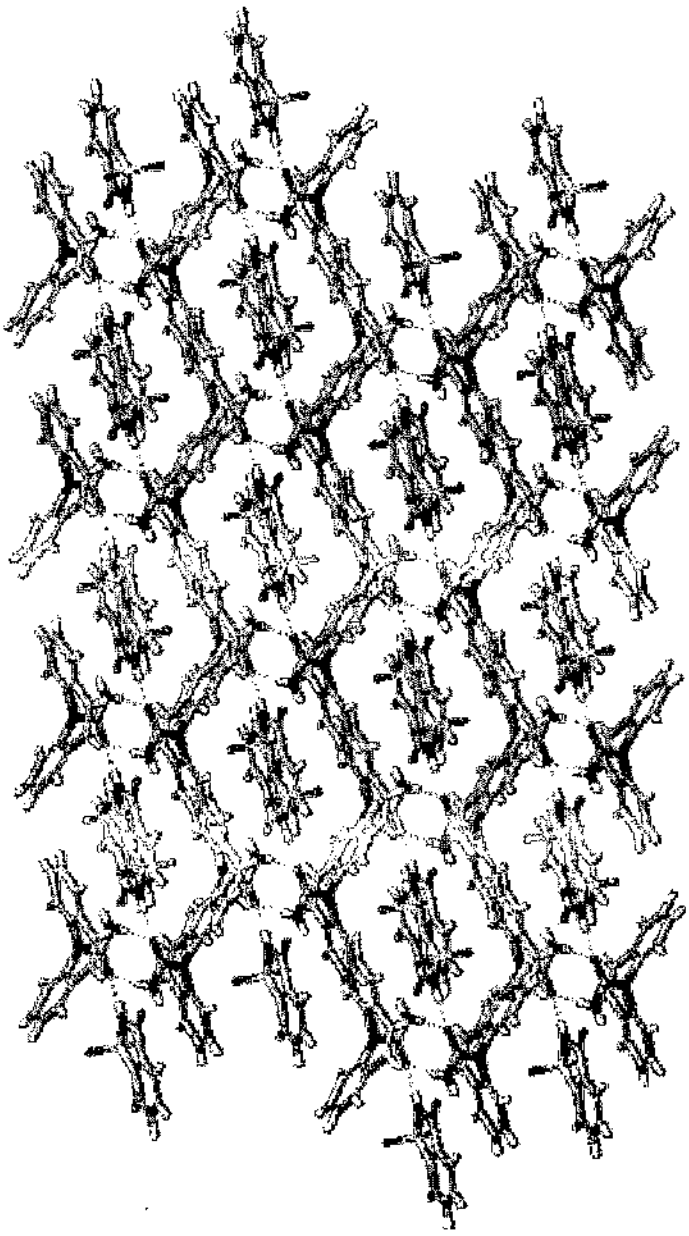


FIG. 48

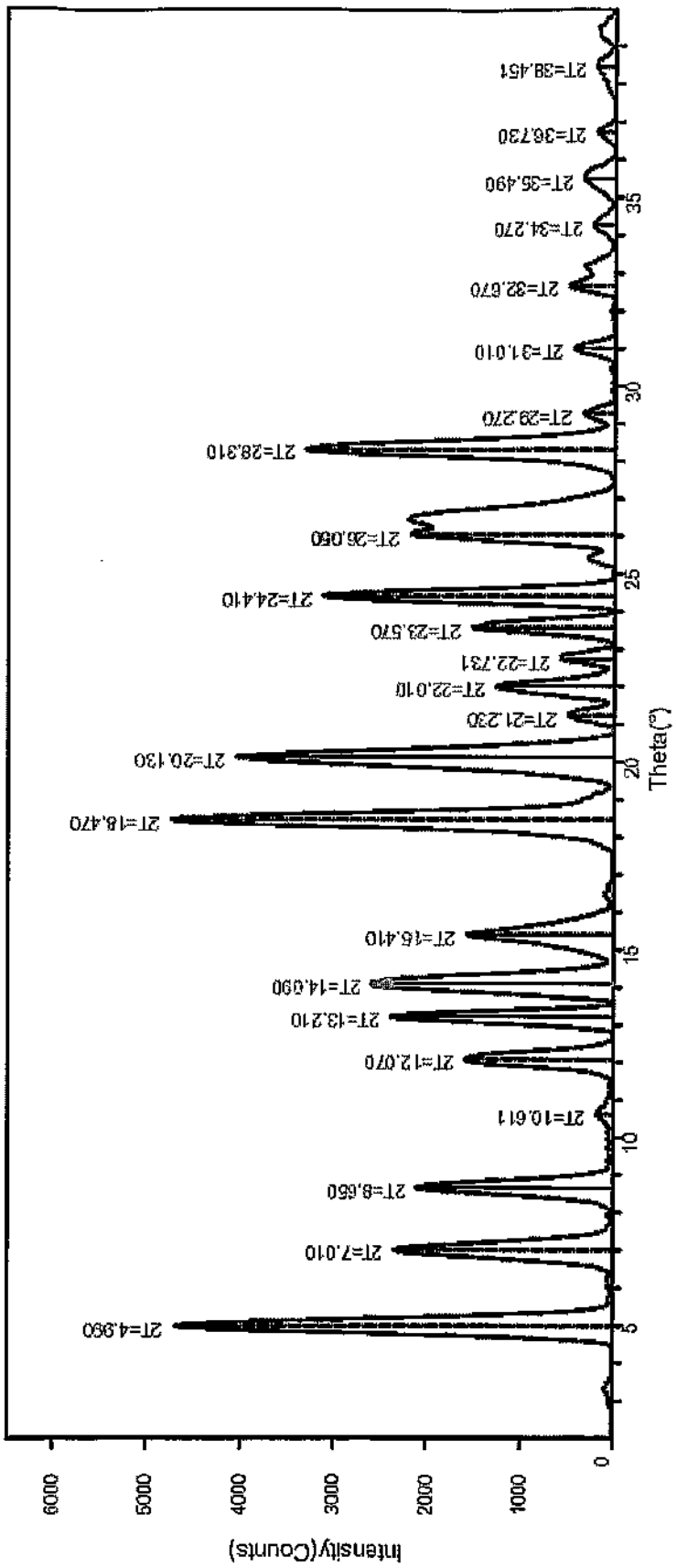

2T=4.360
2T=7.010
2T=8.660
2T=10.611
2T=12.070
2T=13.210
2T=14.090
2T=16.410
2T=18.470
2T=20.130
2T=21.230
2T=22.010
2T=22.731
2T=23.570
2T=24.410
2T=26.060
2T=28.310
2T=29.270
2T=31.010
2T=32.670
2T=34.270
2T=35.490
2T=36.730
2T=38.451
Theta(°)
Intensity(Counts)

FIG. 49

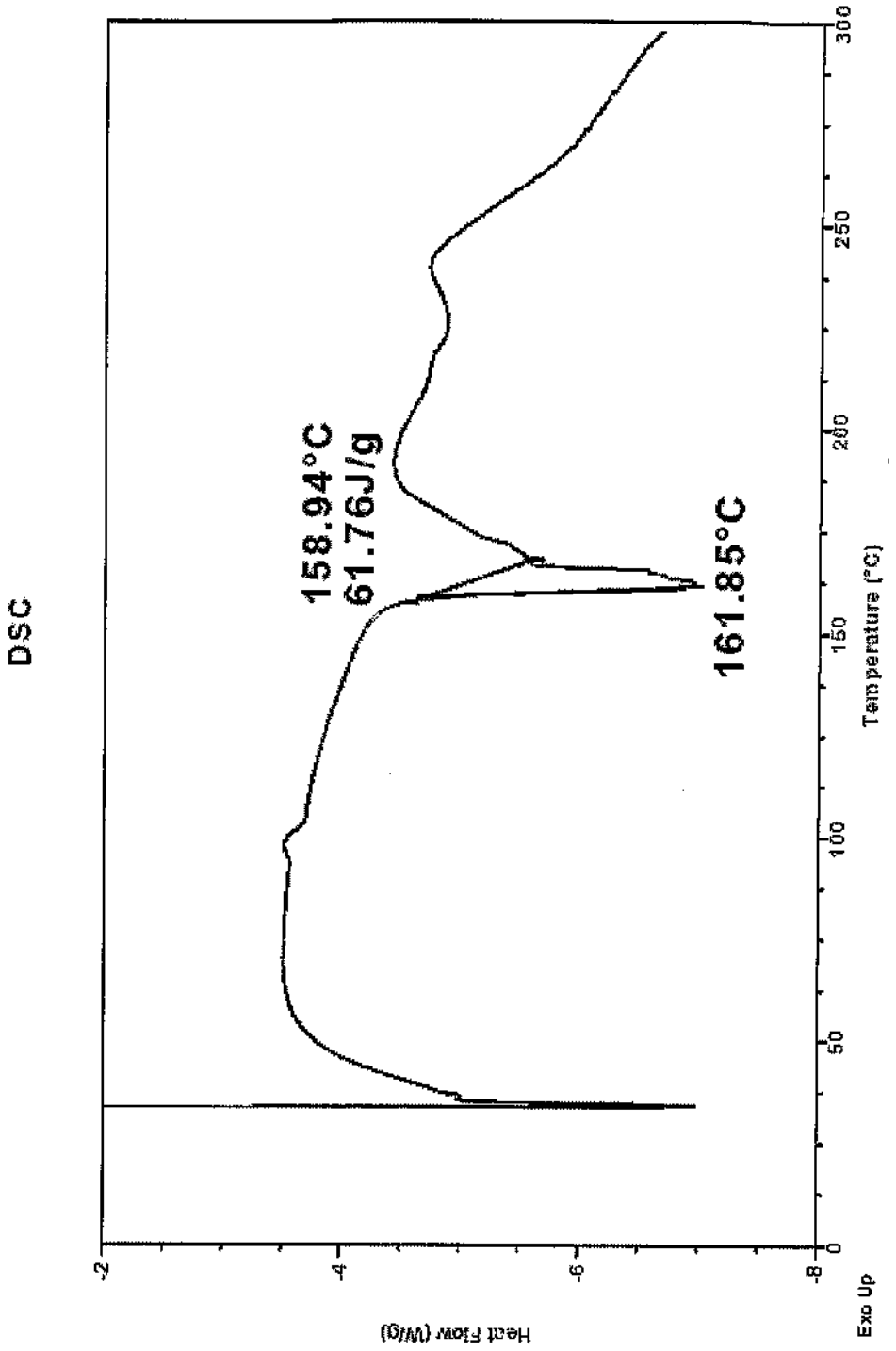

DSC
158.94°C
61.76J/g
161.85°C
Heat Flow (W/g)
Exo Up
Temperature (°C)
-2
-4
-6
-8
0
50
100
150
200
250
300

FIG. 50

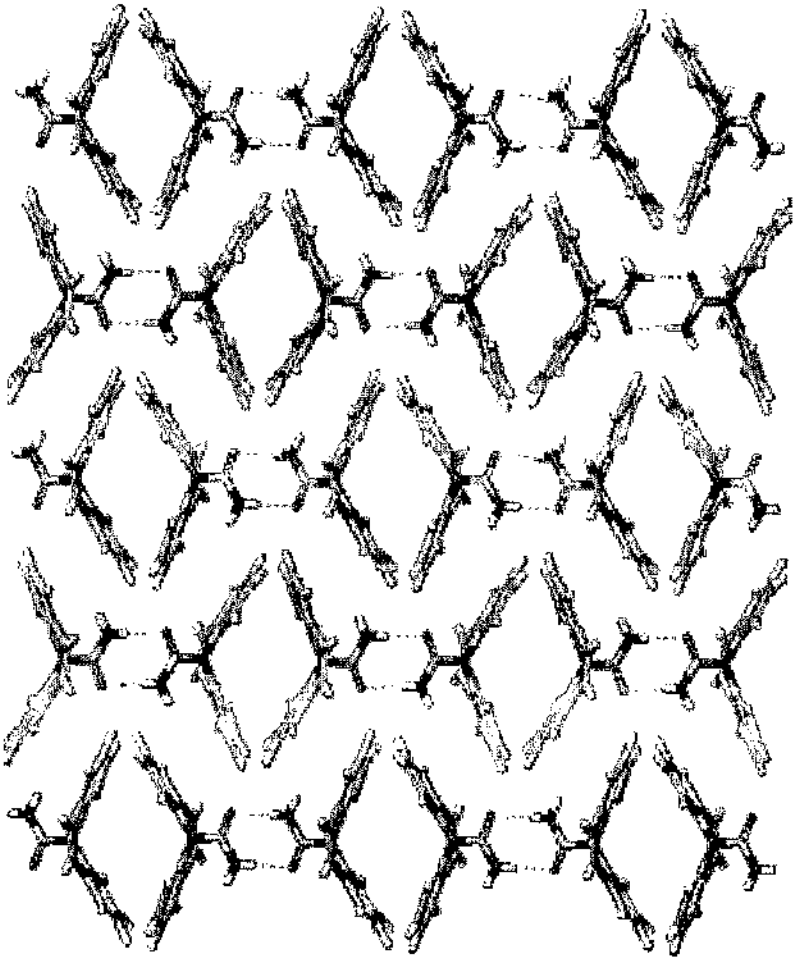


FIG. 51A

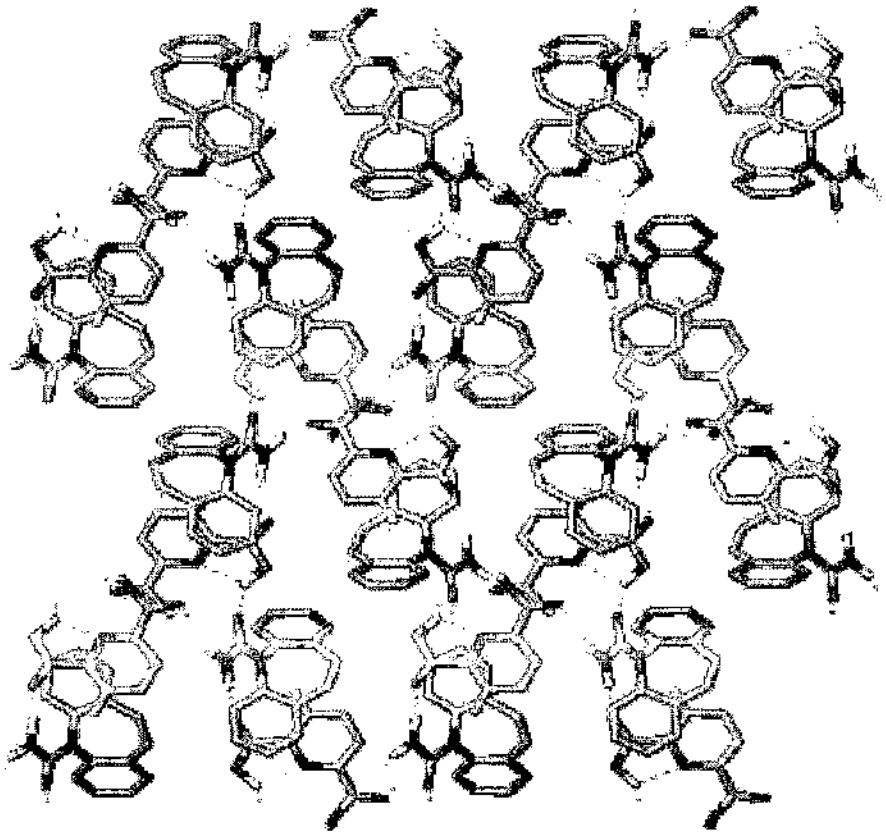


FIG. 51B

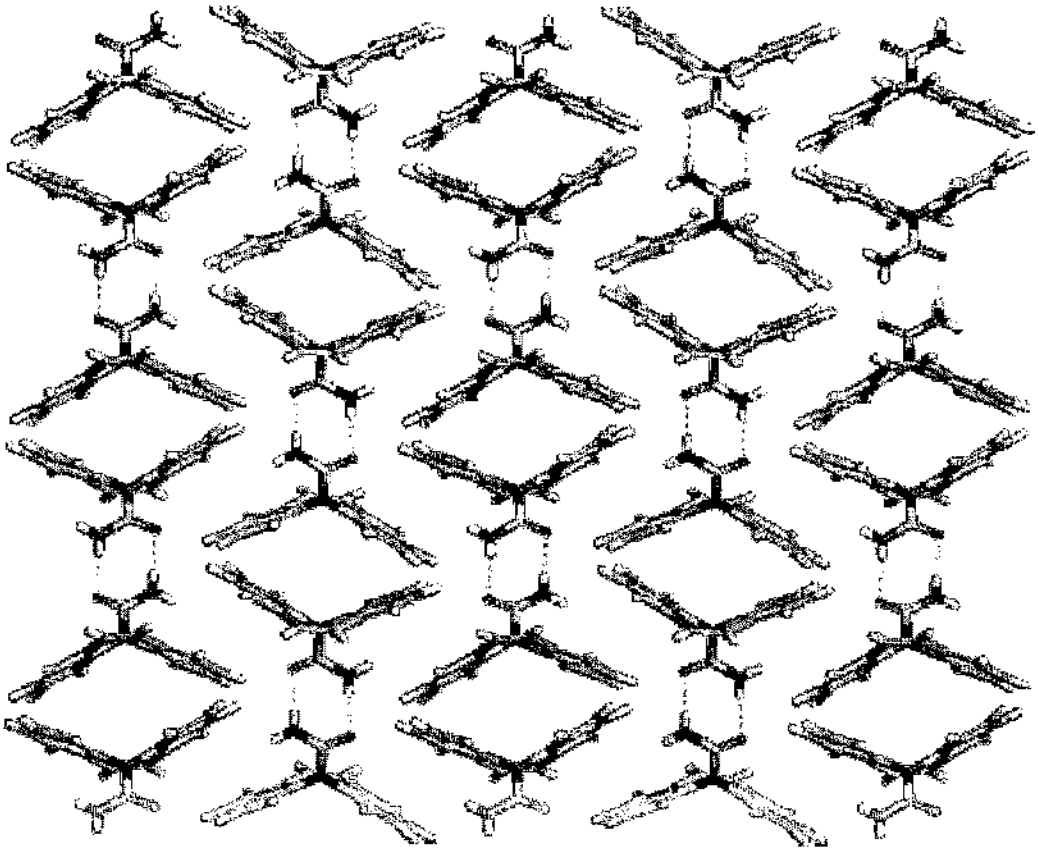


FIG. 52A

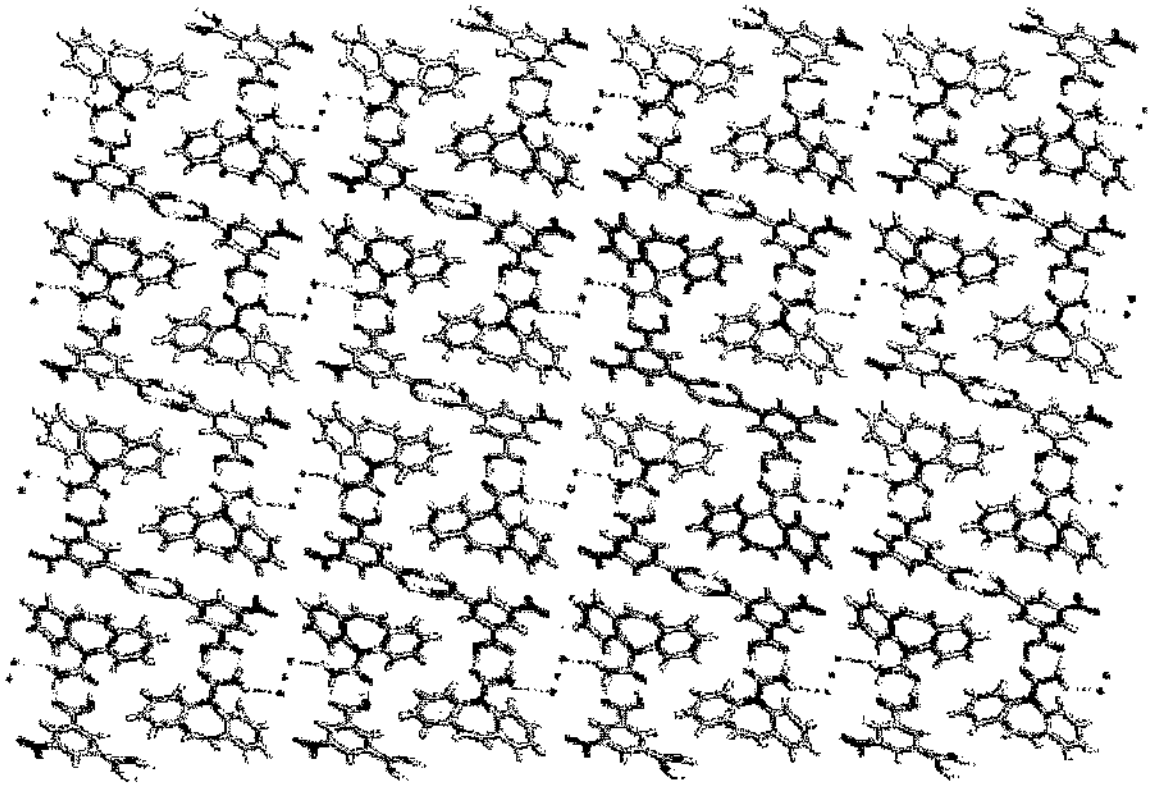


FIG. 52B

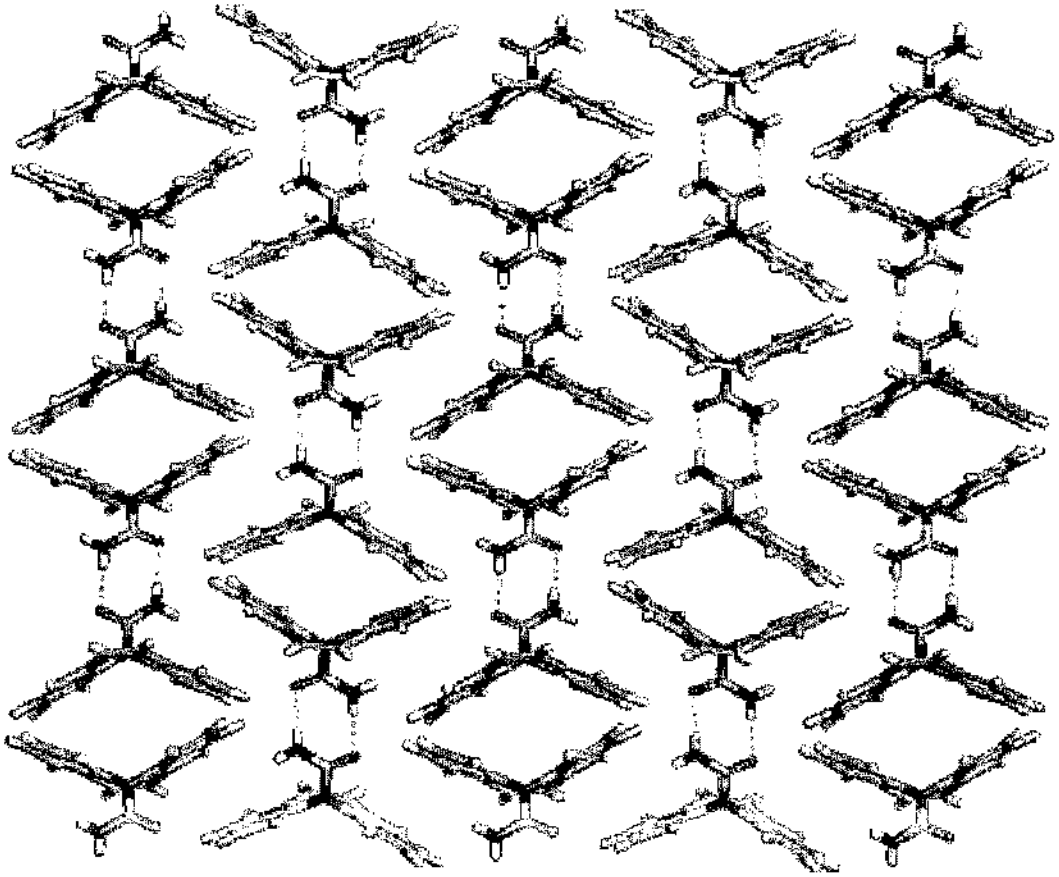


FIG. 53A

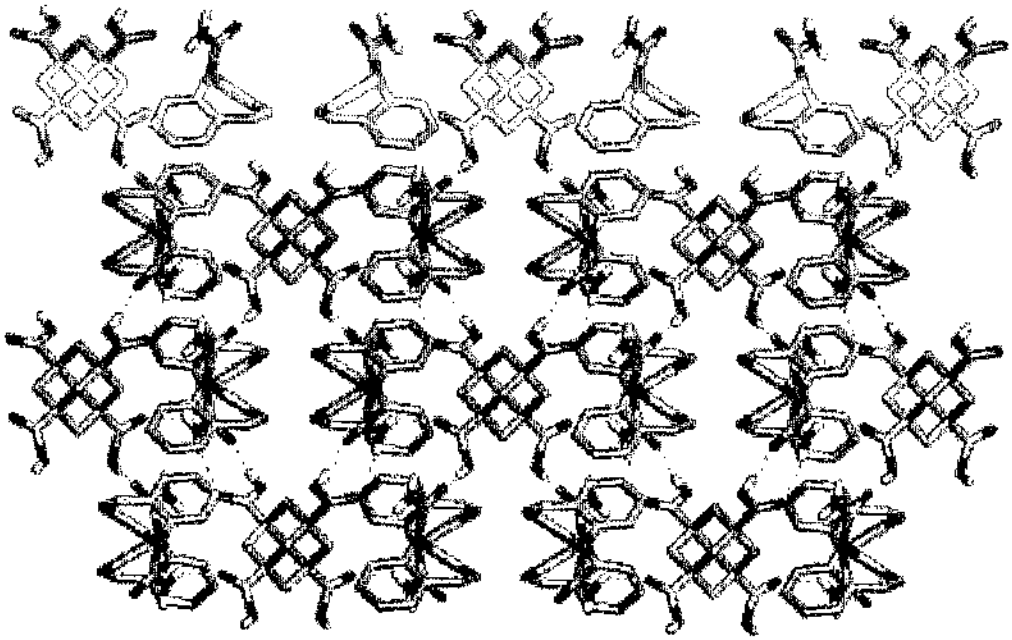


FIG. 53B

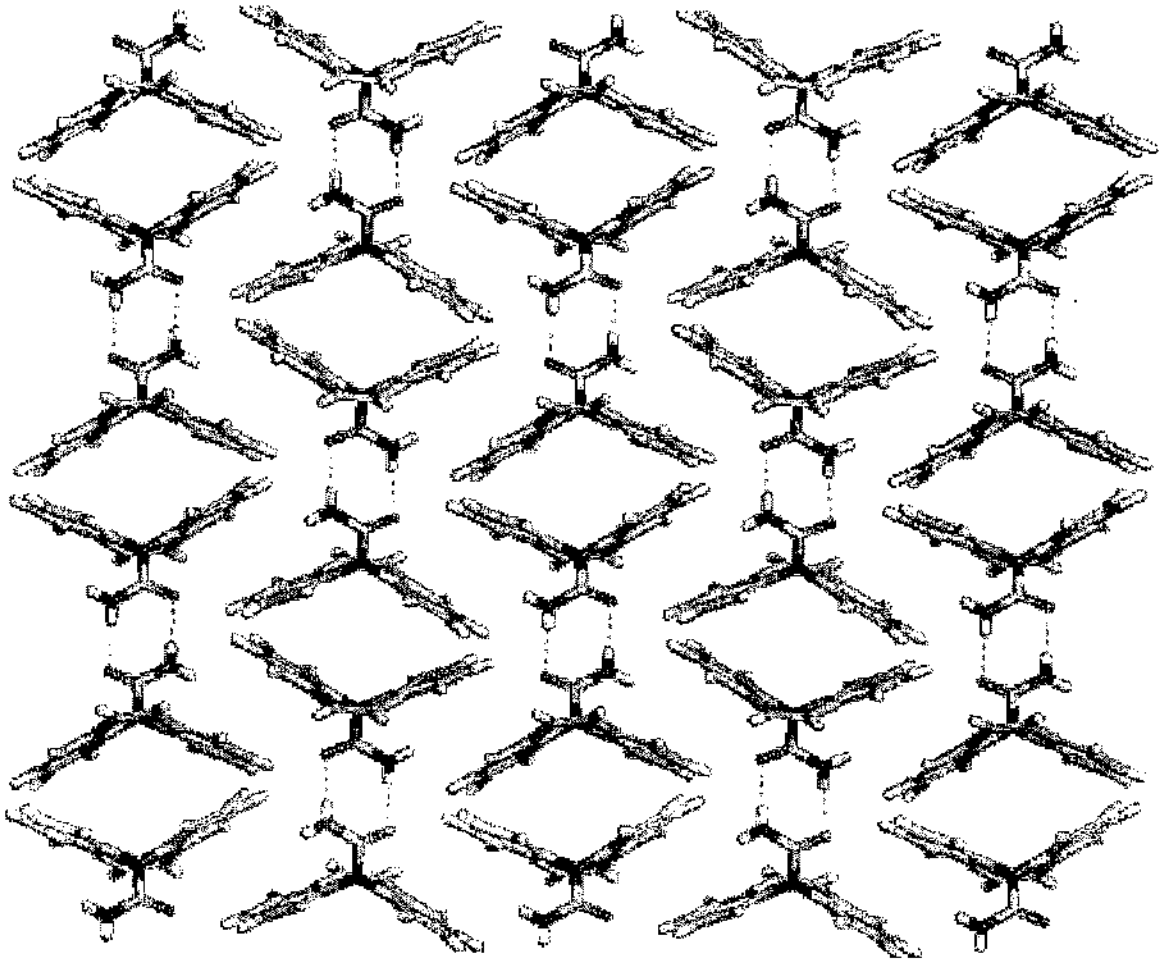


FIG. 54A

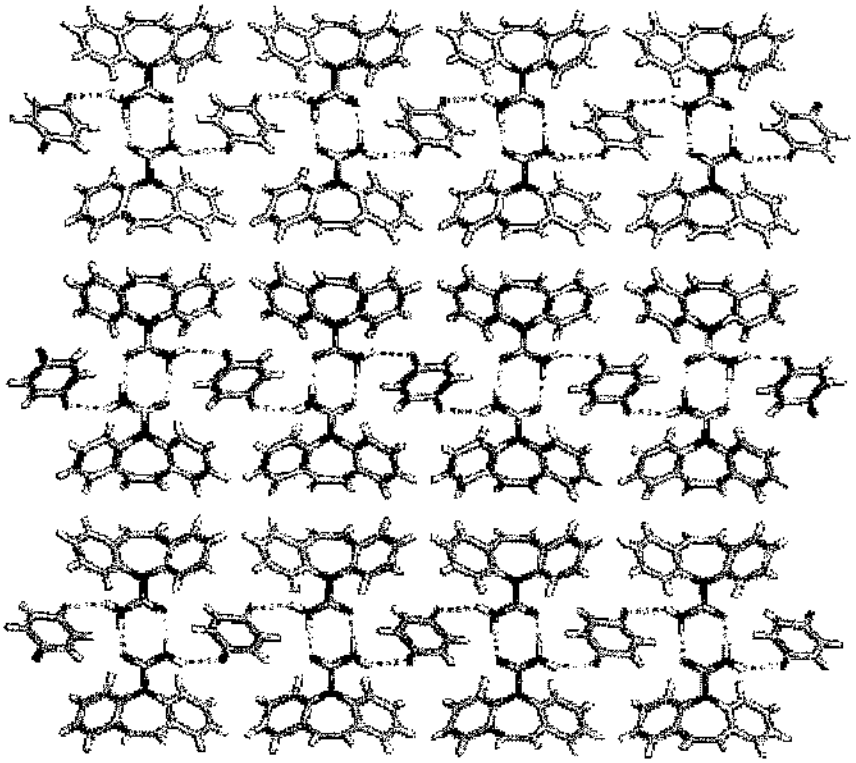


FIG. 54B

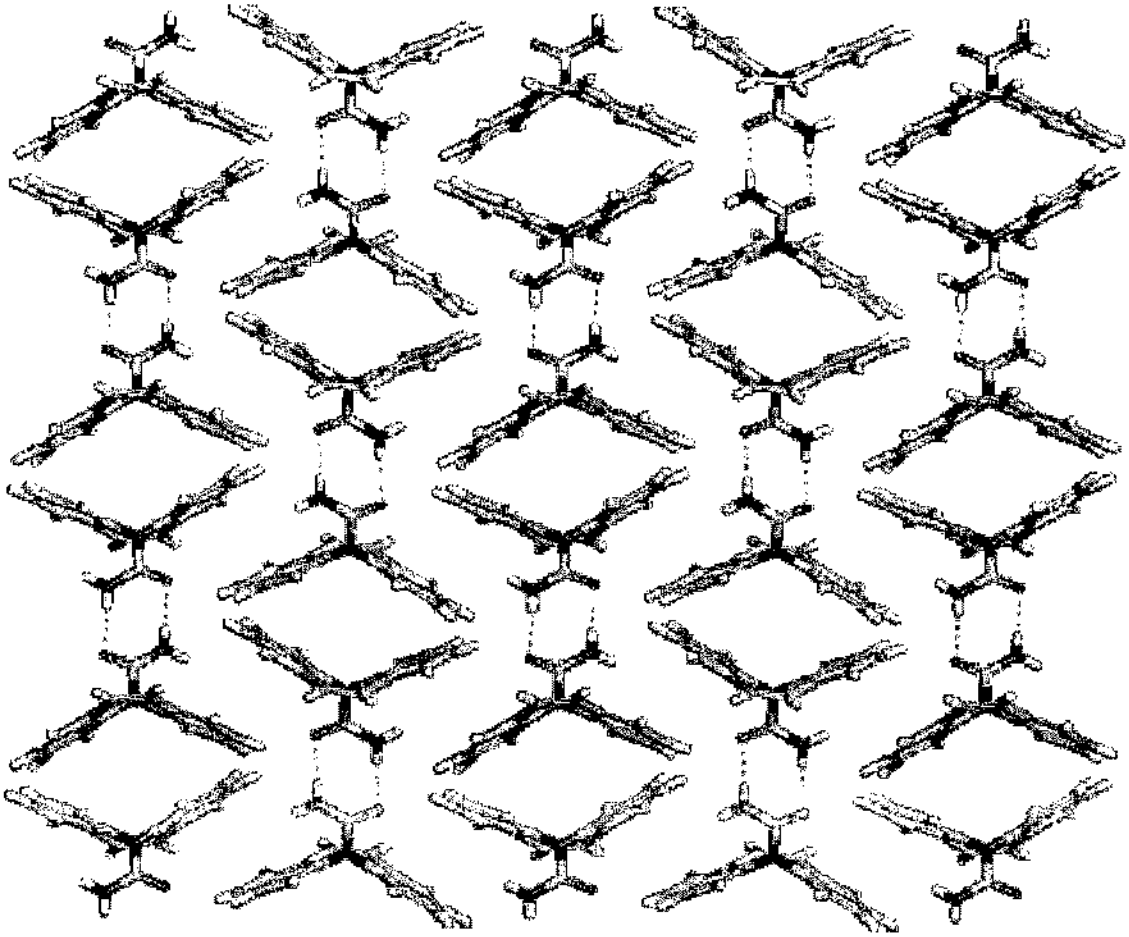


FIG. 55A

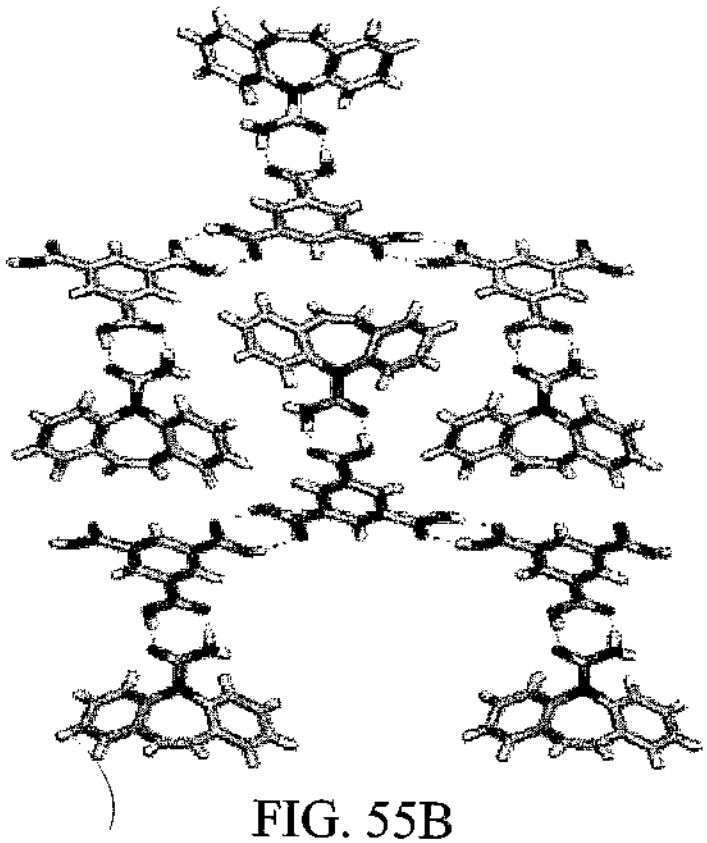


FIG. 55B

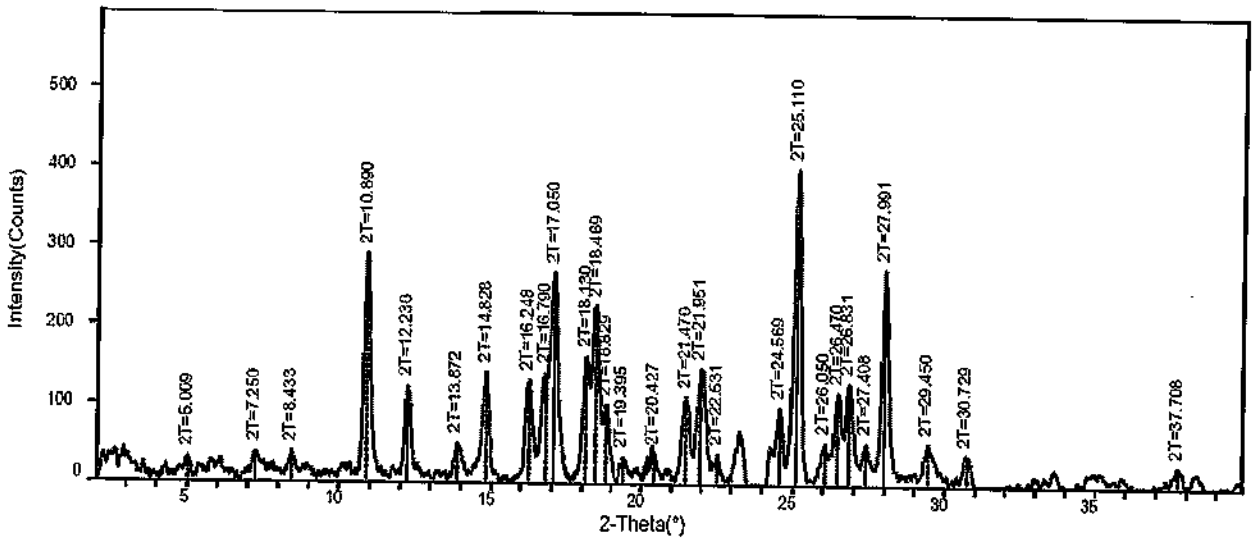


FIG. 56

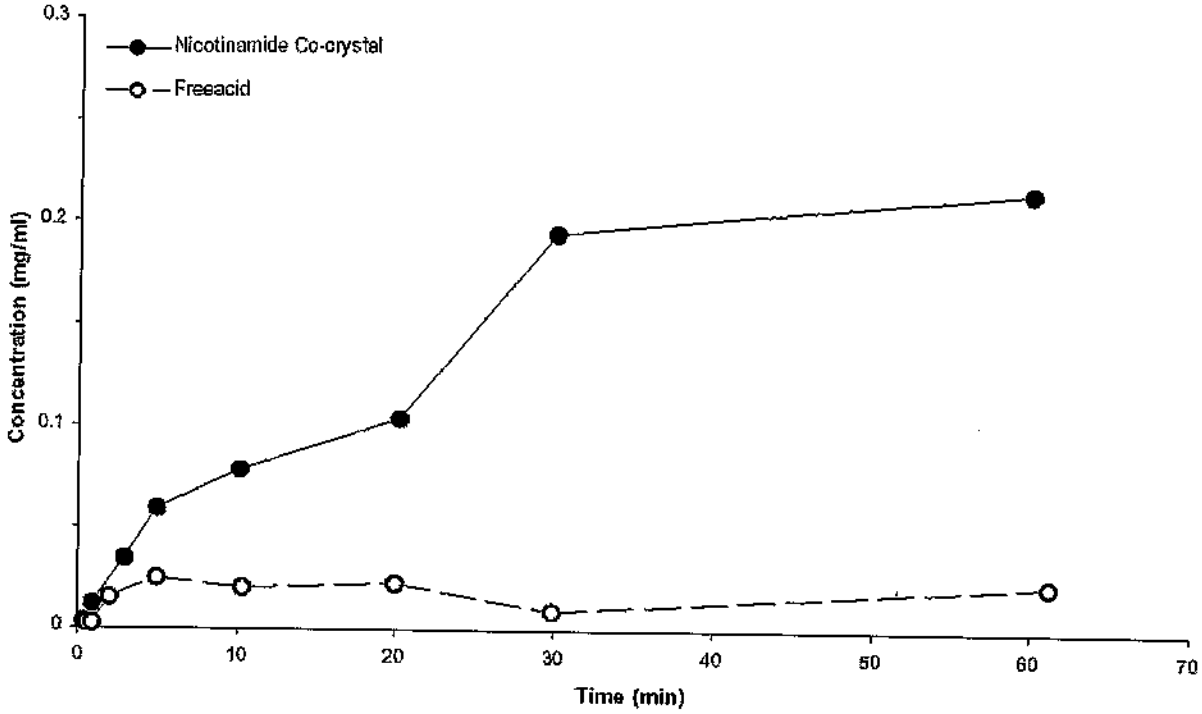
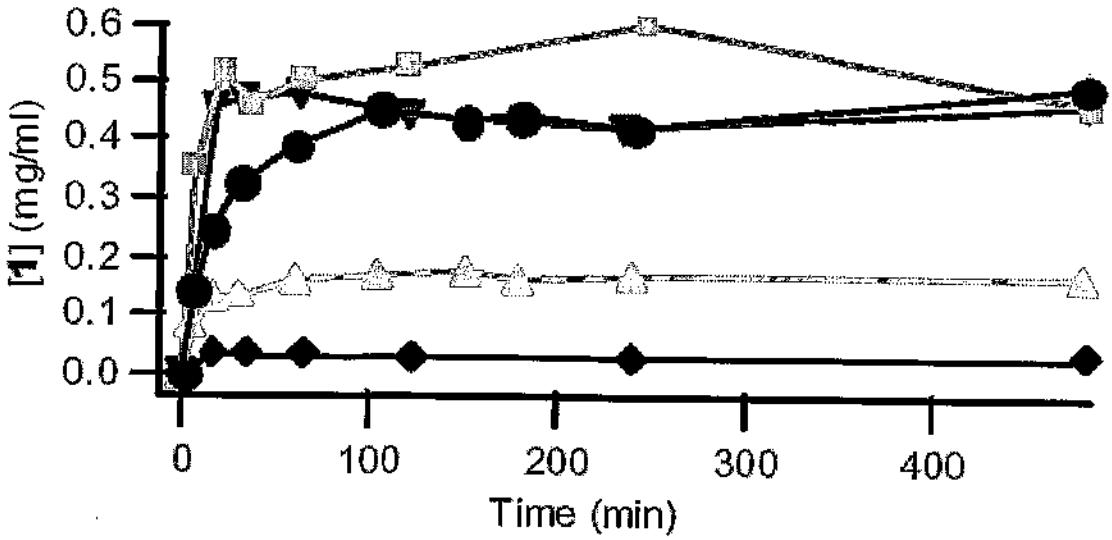

Nicotinamide Co-crystal
Freeacid
Concentration (mg/ml)
0.3
0.2
0.1
0
0
10
20
30
40
50
60
70
Time (min)

FIG. 57



Dissolution profiles into 0.1 N HCl at 25 °C
Sporanox Beads (amorphous freebase) (Rectangle)
l-Malate (Inverted triangle)
l-Tartrate (Oval)
Succinate (Triangle)
Crystalline Freebase (Diamond)

FIG. 58

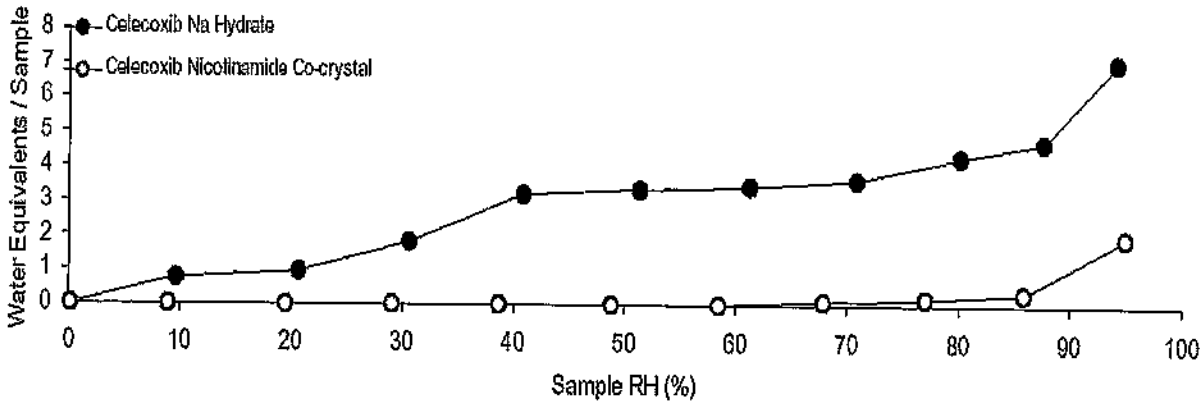
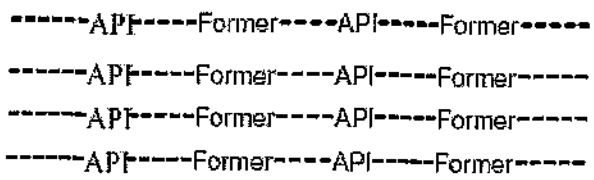
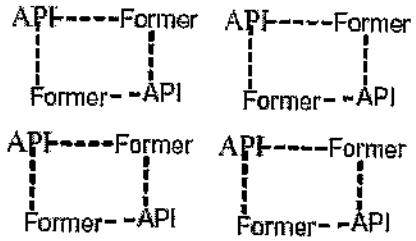


FIG. 59

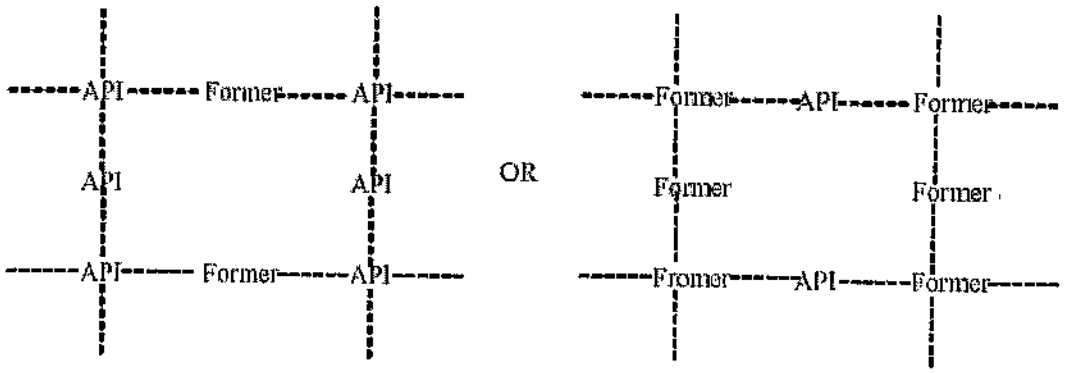
1. One-dimentional (linear) hydrogen-bonded chains:



2. Isolated rings:



3. Extended Networks:



4. Isolated triads:

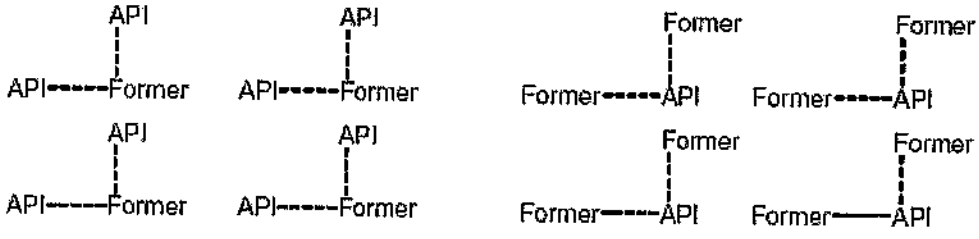


FIG. 60

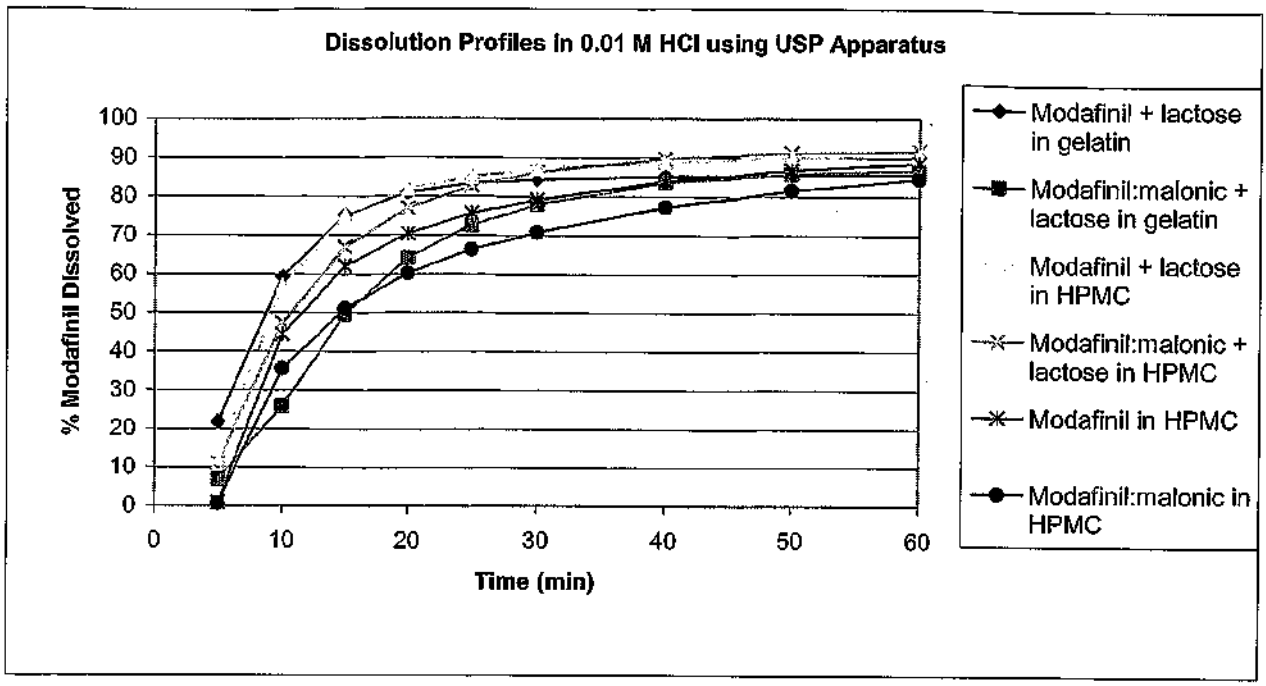

Dissolution Profiles in 0.01 M HCl using USP Apparatus
% Modafinil Dissolved
100
90
80
70
60
50
40
30
20
10
0
0
10
20
30
40
50
60
Time (min)
Modafinil + lactose in gelatin
Modafinil:malonic + lactose in gelatin
Modafinil + lactose in HPMC
Modafinil:malonic + lactose in HPMC
Modafinil in HPMC
Modafinil:malonic in HPMC

FIG. 61

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 0 443 983 B1

(12) **EUROPÄISCHE PATENTSCHRIFT**

(45) Veröffentlichungstag und Bekanntmachung des Hinweises auf die Patenterteilung:
28.02.1996 Patentblatt 1996/09

(21) Anmeldenummer: **91810098.3**

(22) Anmeldetag: **12.02.1991**

(51) Int. Cl.[6]: **C07D 257/04**, C07C 233/47, C07C 231/00, C07D 233/64, A61K 31/41, A61K 31/195

(54) Acylverbindungen

Acyl compounds

Composés acylés

(84) Benannte Vertragsstaaten:
AT BE CH DE DK ES FR GB GR IT LI LU NL SE

(30) Priorität: **19.02.1990 CH 518/90**
05.07.1990 CH 2234/90

(43) Veröffentlichungstag der Anmeldung:
28.08.1991 Patentblatt 1991/35

(73) Patentinhaber: **CIBA-GEIGY AG**
CH-4002 Basel (CH)

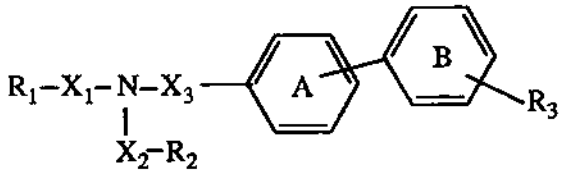
(72) Erfinder:
- **Bühlmayer, Peter, Dr.**
  CH-4144 Arlesheim (CH)
- **Ostermayer, Franz, Dr.**
  CH-4125 Riehen (CH)
- **Schmidlin, Tibur, Dr.**
  CH-4056 Basel (CH)

(56) Entgegenhaltungen:
EP-A- 0 148 752
EP-A- 0 253 310

EP 0 443 983 B1

Beschreibung

Die Erfindung betrifft Verbindungen der Formel



(I),

worin R_1 gegebenenfalls durch Halogen oder Hydroxy substituiertes Niederalkyl, Niederalkenyl oder Niederalkinyl oder C_3-C_7-Cycloalkyl- oder C_3-C_7-Cycloalkenyl oder Phenylniederalkyl, Phenylniederalkenyl oder Phenylniederalkinyl bedeutet; X_1 für CO, SO_2 oder -O-C(=O)- steht, wobei das Kohlenstoffatom der Carbonylgruppe an das in der Formel I eingezeichnete Stickstoffatom gebunden ist; X_2 gegebenenfalls durch Hydroxy, Carboxy, Amino, Guanidino, C_3-C_7-Cycloalkyl, C_3-C_7-Cycloalkenyl, Phenyl oder einen entsprechenden 5- oder 6-gliedrigen und monocyclischen aromatischen Rest, der bis zu vier gleiche oder verschiedene Heteroatome aufweist, substituiertes C_1-C_{10}-Alkylen, C_2-C_{10}-Alkyliden oder C_3-C_7-Cycloalkylen bedeutet, wobei ein Kohlenstoffatom von C_1-C_{10}-Alkylen bzw. C_2-C_{10}-Alkyliden zusätzlich durch C_2-C_6-Alkylen überbrückt sein kann, und wobei C_3-C_7-Cycloalkyl oder C_3-C_7-Cycloalkenyl gegebenenfalls ein- oder mehrfach substituiert sind durch Carboxy, Carboxy, welches durch einen Alkohol verestert ist, der sich von Niederalkyl, Phenylniederalkyl, Niederalkenyl, Niederalkinyl, Niederalkoxyniederalkyl, Niederalkoxyniederalkenyl oder Niederalkoxyniederalkinyl ableitet, Carbamoyl, Carbamoyl, in welchem die Aminogruppe durch Niederalkyl, Niederalkenyl, Niederalkinyl, Phenylniederalkyl, Phenylniederalkenyl oder Phenylniederalkinyl mono- oder unabhängig voneinander disubstituiert oder durch C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden disubstituiert ist, wobei C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden gegebenenfalls durch -O- unterbrochen oder an zwei benachbarten C-Atomen mit einem Benzolring kondensiert sind, Formyl, Diniederalkoxymethyl oder Oxyniederalkylenoxymethylen; R_2 Carboxy, Carboxy, welches durch einen Alkohol verestert ist, der sich von Niederalkyl, Phenylniederalkyl, Niederalkenyl, Niederalkinyl, Niederalkoxyniederalkyl, Niederalkoxyniederalkenyl oder Niederalkoxyniederalkinyl ableitet, Carbamoyl, Carbamoyl, in welchem die Aminogruppe durch Niederalkyl, Niederalkenyl, Niederalkinyl, Phenylniederalkyl, Phenylniederalkenyl oder Phenylniederalkinyl mono- oder unabhängig voneinander disubstituiert oder durch C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden disubstituiert ist, wobei C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden gegebenenfalls durch -O- unterbrochen oder an zwei benachbarten C-Atomen mit einem Benzolring kondensiert sind, Amino, Amino, welches durch Niederalkyl, Niederalkenyl, Niederalkinyl, Phenylniederalkyl, Phenylniederalkenyl oder Phenylniederalkinyl mono- oder unabhängig voneinander disubstituiert oder durch C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden disubstituiert ist, wobei C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden gegebenenfalls durch -O- unterbrochen oder an zwei benachbarten C-Atomen mit einem Benzolring kondensiert sind, Niederalkanoyl-, Phenylniederalkanoyl-, Benzoyl-, Niederalkansulfonyl-, Benzolsulfonyl-amino, Formyl, Diniederalkoxymethyl, Oxyniederalkylenoxymethylen, 1H-Tetrazol-5-yl, Pyridyl, Hydroxy, Niederalkoxy, Niederalkenyloxy, Phenylniederalkoxy, Phenoxy, $S(O)_m$-R, wobei m für 0, 1 oder 2 steht und R Wasserstoff, Niederalkyl, Niederalkenyl oder Niederalkinyl bedeutet, Niederalkanoyl, Sulfamoyl, Sulfamoyl, in welchem die Aminogruppe durch Niederalkyl, Niederalkenyl, Niederalkinyl, Phenylniederalkyl, Phenylniederalkenyl oder Phenylniederalkinyl mono- oder unabhängig voneinander disubstituiert oder durch C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden disubstituiert ist, wobei C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden gegebenenfalls durch -O- unterbrochen oder an zwei benachbarten C-Atomen mit einem Benzolring kondensiert sind, oder PO_nH_2 bedeutet, wobei n für 2 oder 3 steht; X_3 C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden bedeutet; R_3 Carboxy, 5-Tetrazolyl, SO_3H, PO_2H_2, PO_3H_2 oder Halogenniederalkylsulfamoyl ist; und wobei (hetero-)aromatische Reste einschliesslich der Ringe A und B unabhängig voneinander gegebenenfalls substituiert sind durch Substituenten ausgewählt aus der Gruppe bestehend aus: Halogen, Hydroxy, Niederalkoxy, Niederalkenyloxy, Phenylniederalkoxy, Phenoxy, $S(O)_m$-R und gegebenenfalls durch Halogen oder Hydroxy substituiertes Niederalkyl, Niederalkenyl oder Niederalkinyl, wobei Niederalkyl, Niederalkenyl oder Niederalkinyl gegebenenfalls durch -O- unterbrochen sind, sowie, im Falle von (hetero-)aromatischen Resten, gegebenenfalls zusätzlich substituiert sind durch Carboxy, Carboxy, welches durch einen Alkohol verestert ist, der sich von Niederalkyl, Phenylniederalkyl, Niederalkenyl, Niederalkinyl, Niederalkoxyniederalkyl, Niederalkoxyniederalkenyl oder Niederalkoxyniederalkinyl ableitet, durch Carbamoyl, Carbamoyl, in welchem die Aminogruppe durch Niederalkyl, Niederalkenyl, Niederalkinyl, Phenylniederalkyl, Phenylniederalkenyl oder Phenylniederalkinyl mono- oder unabhängig voneinander disubstituiert oder durch C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden disubstituiert ist, wobei C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden gegebenenfalls durch -O- unterbrochen oder an zwei benachbarten C-Atomen mit einem Benzolring kondensiert sind, durch Formyl, Diniederalkoxymethyl oder Oxyniederalkylenoxymethylen; wobei mit "nieder" bezeichnete Reste und Gruppen bis
und mit 7 Kohlenstoffatome enthalten; in freier Form oder in Salzform, ein Verfahren zur Herstellung dieser Verbindungen,

die Verwendung dieser Verbindungen und pharmazeutische Präparate, enthaltend eine solche Verbindung I in freier Form oder in Form eines pharmazeutisch verwendbaren Salzes.

Die Verbindungen I können als, insbesondere pharmazeutisch verwendbare, Salze vorliegen. Weisen die Verbindungen I z. B. mindestens ein basisches Zentrum auf, können sie Säureadditionssalze bilden. Diese werden beispielsweise mit starken anorganischen Säuren, wie Mineralsäuren, z.B. Schwefelsäure, einer Phosphorsäure oder einer Halogenwasserstoffsäure, mit starken organischen Carbonsäuren, wie gegebenenfalls, z.B. durch Halogen, substituierten C_1-C_4-Alkancarbonsäuren, z.B. Essigsäure, wie gegebenenfalls ungesättigten Dicarbonsäuren, z.B. Oxal-, Malon-, Bernstein-, Malein-, Fumar-, Phthal- oder Terephthalsäure, wie Hydroxycarbonsäuren, z.B. Ascorbin-, Glykol-, Milch-, Äpfel-, Wein- oder Zitronensäure, wie Aminosäuren, z.B. Asparagin- oder Glutaminsäure, oder wie Benzoesäure, oder mit organischen Sulfonsäuren, wie gegebenenfalls, z.B. durch Halogen, substituierten C_1-C_4-Alkan- oder Arylsulfonsäuren, z.B. Methan- oder p-Toluolsulfonsäure, gebildet. Entsprechende Säureadditionssalze können auch mit einem gegebenenfalls zusätzlich vorhandenen basischen Zentrum gebildet werden. Ferner können die Verbindungen I mit mindestens einer aciden Gruppe (beispielsweise COOH oder 5-Tetrazolyl) Salze mit Basen bilden. Geeignete Salze mit Basen sind beispielsweise Metallsalze, wie Alkali- oder Erdalkalimetallsalze, z.B. Natrium-, Kalium- oder Magnesiumsalze, oder Salze mit Ammoniak oder einem organischen Amin, wie Morpholin, Thiomorpholin, Piperidin, Pyrrolidin, einem Mono-, Di- oder Triniederalkylamin, z. B. Ethyl-, tert.-Butyl-, Diethyl-, Diisopropyl-, Triethyl-, Tributyl- oder Dimethylpropyl-amin, oder einem Mono-, Di- oder Trihydroxyniederalkylamin, z.B. Mono-, Di- oder Triethanolamin. Weiterhin können entsprechende innere Salze gebildet werden. Umfasst sind ferner für pharmazeutische Verwendungen nicht geeignete Salze, die beispielsweise für die Isolierung bzw. Reinigung von freien Verbindungen I oder deren pharmazeutisch verwendbaren Salzen eingesetzt werden.

Überbrückendes C_2-C_8-Alkylen ist insbesondere C_4-C_5-Alkylen.

Ein 5- oder 6-gliedriger und monocyclischer aromatischer Rest, der bis zu vier gleiche oder verschiedene Heteroatome, wie Stickstoff-, Sauerstoff- bzw. Schwefelatome, vorzugsweise ein, zwei, drei oder vier Stickstoffatome, ein Sauerstoff- oder ein Schwefelatom, aufweist, ist z.B. ein 5-gliedriger monoaza-, diaza-, triaza-, tetraaza-, monooxa- oder monothia-cyclischer Arylrest, wie Pyrrolyl, Pyrazolyl, Imidazolyl, Triazolyl, Tetrazolyl, Furyl und Thienyl, während als entsprechender 6-gliedriger Rest insbesondere Pyridyl in Frage kommt. Entsprechende aromatische Reste sind gegebenenfalls ein- oder mehrfach, z.B. zwei- oder dreifach, substituiert, beispielsweise durch gleiche oder verschiedene Reste, z.B. ausgewählt aus: Halogen, Hydroxy, Niederalkoxy, Niederalkenyloxy, Phenylniederalkoxy, Phenoxy, $S(O)_m$-R und gegebenenfalls durch Halogen oder Hydroxy substituiertes Niederalkyl, Niederalkenyl oder Niederalkinyl, wobei Niederalkyl, Niederalkenyl oder Niederalkinyl gegebenenfalls durch -O-unterbrochen sind, sowie gegebenenfalls zusätzlich substituiert sind durch Carboxy, Carboxy, welches durch einen Alkohol verestert ist, der sich von Niederalkyl, Phenylniederalkyl, Niederalkenyl, Niederalkinyl, Niederalkoxyniederalkyl, Niederalkoxyniederalkenyl oder Niederalkoxyniederalkinyl ableitet, durch Carbamoyl, Carbamoyl, in welchem die Aminogruppe durch Niederalkyl, Niederalkenyl, Niederalkinyl, Phenylniederalkyl, Phenylniederalkenyl oder Phenylniederalkinyl mono- oder unabhängig voneinander disubstituiert oder durch C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden disubstituiert ist, wobei C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden gegebenenfalls durch -O- unterbrochen oder an zwei benachbarten C-Atomen mit einem Benzolring kondensiert sind, durch Formyl, Diniederalkoxymethyl oder Oxyniederalkylenoxymethylen.

Als Beispiele für entsprechend verestertes Carboxy seien Niederalkoxy-, Phenylniederalkoxy-, Niederalkenyloxy- und Niederalkoxyniederalkoxy-carbonyl genannt.

Als Beispiele für entsprechend substituierte Aminogruppen in substituiertem Carbamoyl seien Niederalkyl-, Niederalkenyl-, Niederalkinyl-, Phenylniederalkyl-, Phenylniederalkenyl-, Phenylniederalkinyl-, Diniederalkyl-, N-Niederalkyl-N-phenylniederalkyl- und Diphenylniederalkylamino sowie Chinol-1-yl, Isochinol-2-yl, Niederalkylen- und Niederalkylenoxyniederalkylen-amino genannt.

Ein entsprechender aliphatischer Kohlenwasserstoffrest, der durch -O- unterbrochen ist, bedeutet insbesondere Niederalkoxyniederalkyl, -niederalkenyl oder -niederalkinyl, Niederalkenyloxyniederalkyl, -niederalkenyl oder -niederalkinyl.

Vor- und nachstehend sind ungesättigte aliphatische, cycloaliphatische und araliphatische Substituenten in erster Linie nicht über das C-Atom, von dem eine Mehrfachbindung ausgeht, mit einem aromatischen Rest verknüpft.

(Hetero-)Aromatische Reste sind insbesondere, sofern nicht abweichend definiert, jeweils unsubstituiert oder ein- oder mehrfach, z.B. zwei- oder dreifach, insbesondere z.B. durch einen Substituenten ausgewählt aus Halogen, Hydroxy, Niederalkoxy, Niederalkenyloxy, Phenylniederalkoxy, Phenoxy, $S(O)_m$-R und gegebenenfalls durch Halogen oder Hydroxy substituiertes Niederalkyl, Niederalkenyl oder Niederalkinyl, wobei Niederalkyl, Niederalkenyl oder Niederalkinyl gegebenenfalls durch -O- unterbrochen sind.

Die Ringe A und B stellen in erster Linie ein 4-Biphenylyl-, ferner 2- oder 3- Biphenylylringsystem dar, wobei der Rest R_3 vorzugsweise in ortho-Position des Ringes B lokalisiert ist Entsprechend sind die Ringe A und B gegebenenfalls ein- oder mehrfach, z.B. zwei- oder dreifach, substituiert, beispielsweise durch gleiche oder verschiedene Reste z.B. ausgewählt aus: Halogen, Hydroxy, Niederalkoxy, Niederalkenyloxy, Phenylniederalkoxy, Phenoxy, $S(O)_m$-R und gegebenenfalls durch Halogen oder Hydroxy substituiertes Niederalkyl, Niederalkenyl oder Niederalkinyl, wobei Niederalkyl, Niederalkenyl oder Niederalkinyl gegebenenfalls durch -O- unterbrochen sind.

Die vor- und nachstehend verwendeten Allgemeindefinitionen haben, sofern nicht abweichend definiert, folgende Bedeutungen:

Der Ausdruck "Nieder" bedeutet, dass entsprechende Gruppen und Verbindungen jeweils insbesondere bis und mit 7, vorzugsweise bis und mit 4, Kohlenstoffatome enthalten.

Halogen ist insbesondere Halogen mit Atomnummer bis und mit 35, wie Fluor, Chlor oder Brom, und umfasst ferner Iod.

Alkanoyl ist beispielsweise Niederalkanoyl und bedeutet insbesondere C_2-C_7-Alkanoyl, wie Acetyl, Propionyl, Butyryl, Isobutyryl oder Pivaloyl. Bevorzugt ist C_2-C_5-Alkanoyl.

Halogenalkylsulfamoyl bedeutet insbesondere Halogen-C_1-C_7-alkansulfamoyl und ist z.B. Trifluormethan-, Difluormethan-,1,1,2-Trifluorethan- oder Heptafluorpropansulfamoyl. Bevorzugt ist Halogen-C_1-C_4-alkansulfamoyl.

Niederalkyl bedeutet insbesondere C_1-C_7-Alkyl, z.B. Methyl, Ethyl, n-Propyl, Isopropyl, n-Butyl, Isobutyl, sek.-Butyl, tert.-Butyl, und umfasst ferner entsprechende Pentyl-, Hexyl- und Heptylreste. Bevorzugt ist C_1-C_4-Alkyl.

Niederalkenyl bedeutet insbesondere C_3-C_7-Alkenyl und ist z.B. 2-Propenyl oder 1-, 2-oder 3-Butenyl. Bevorzugt ist C_3-C_5-Alkenyl.

Niederalkinyl ist insbesondere C_3-C_7-Alkinyl und bedeutet vorzugsweise Propargyl.

Halogenniederalkyl bedeutet insbesondere Halogen-C_1-C_4-alkyl, wie Trifluormethyl, 1,1,2-Trifluor-2-chlor-ethyl oder Chlormethyl.

Halogenniederalkenyl bedeutet insbesondere Halogen-C_3-C_5-alkenyl, wie 3-Chlorallyl.

Halogenniederalkinyl ist insbesondere Halogen-C_3-C_5-alkinyl, wie 3-Chlorpropargyl.

Hydroxyniederalkyl bedeutet insbesondere Hydroxy-C_1-C_4-alkyl, wie Hydroxymethyl, 2-Hydroxyethyl oder 3-Hydroxypropyl.

Hydroxyniederalkenyl bedeutet insbesondere Hydroxy-C_3-C_5-alkenyl, wie 3-Hydroxyallyl.

Hydroxyniederalkinyl bedeutet insbesondere Hydroxy-C_3-C_5-alkinyl, wie 3-Hydroxypropargyl.

Cycloalkyl ist insbesondere C_3-C_7-Cycloalkyl und bedeutet z.B. Cyclopropyl, Cyclobutyl, Cyclopentyl, Cyclohexyl und Cycloheptyl. Bevorzugt ist Cyclopentyl und Cyclohexyl.

Cycloalkenyl ist insbesondere C_3-C_7-Cycloalkenyl und bedeutet vorzugsweise Cyclopent-2-, -3-enyl, Cyclohex-2- und -3-en-yl.

Phenylniederalkyl ist insbesondere Phenyl-C_1-C_4-alkyl und bedeutet vorzugsweise Benzyl, 1-und 2-Phenethyl, während Phenylniederalkenyl und Phenylniederalkinyl insbesondere Phenyl-C_3-C_5-alkenyl und -alkinyl bedeuten, insbesondere 3-Phenylallyl und 3-Phenylpropargyl.

Pyrrolyl ist z.B. 2- oder 3-Pyrrolyl. Pyrazolyl ist 3- oder 4-Pyrazolyl. Imidazolyl ist 2- oder 4-Imidazolyl. Triazolyl ist z.B. 1,3,5-1H-Triazol-2-yl oder 1,3,4-Triazol-2-yl. Tetrazolyl ist z.B. 1,2,3,4-Tetrazol-5-yl, Furyl ist 2- oder 3-Furyl und Thienyl ist 2- oder 3-Thienyl, während als Pyridyl 2-, 3- und 4-Pyridyl in Frage kommt.

Alkylen bedeutet insbesondere C_1-C_{10}-Alkylen oder Niederalkylen, wie C_1-C_7-Alkylen, und ist geradkettig oder verzweigt und bedeutet insbesondere Methylen, Ethylen, Propylen und Butylen sowie 1,2-Propylen, 2-Methyl-1,3-propylen und 2,2-Dimethyl-1,3-propylen. Bevorzugt ist C_1-C_5-Alkylen.

Alkyliden bedeutet insbesondere C_2-C_{10}-Alkyliden, wie Ethyliden, 1,1-oder 2,2-Propyliden, ferner 1,1- oder 2,2-Butyliden oder 1,1-, 2,2- oder 3,3-Pentyliden. Bevorzugt ist C_2-C_5-Alkyliden.

Cycloalkylen ist insbesondere C_3-C_7-Cycloalkylen und bedeutet z.B. 1,2-Cyclopropylen, 1,2- oder 1,3-Cyclobutylen, 1,2-, 1,3-Cyclopentylen, 1,2-, 1,3- oder 1,4-Cyclohexylen und 1,2-, 1,3- oder 1,4-Cycloheptylen. Bevorzugt ist 1,3-Cyclopentylen und 1,4-Cyclohexylen.

Niederalkoxy bedeutet insbesondere C_1-C_7-Alkoxy und ist z.B. Methoxy, Ethoxy, n-Propyloxy, Isopropyloxy, n-Butyloxy, Isobutyloxy, sek.-Butyloxy, tert.-Butyloxy und umfasst ferner entsprechende Pentyloxy-, Hexyloxy- und Heptyloxyreste. Bevorzugt ist C_1-C_4-Alkoxy.

Niederalkoxyniederalkyl bedeutet insbesondere C_1-C_4-Alkoxy-C_1-C_4-alkyl, wie 2-Methoxy-ethyl, 2-Ethoxy-ethyl, 2-n-Propyloxy-ethyl oder Ethoxymethyl.

Niederalkoxyniederalkenyl bzw. -niederalkinyl bedeutet insbesondere C_1-C_5-Alkoxy-C_3-C_5-alkenyl bzw. -alkinyl.

Niederalkoxycarbonyl bedeutet insbesondere C_2-C_8-Alkoxycarbonyl und ist z.B. Methoxy-, Ethoxy-, Propyloxy- oder Pivaloyloxy-carbonyl. Bevorzugt ist C_2-C_5-Alkoxycarbonyl.

Phenylniederalkoxycarbonyl bedeutet insbesondere Phenyl-C_1-C_4-alkoxy-carbonyl und ist z.B. Benzyloxy-, 1- oder 2-Phenylethoxy-, 3-Phenylpropyloxy- oder 4-Phenylbutyloxy-carbonyl. Bevorzugt ist Benzyloxycarbonyl.

Niederalkenyloxycarbonyl bedeutet insbesondere C_3-C_5-Alkenyloxy-carbonyl, vorzugsweise Allyloxycarbonyl, während Niederalkinyloxycarbonyl insbesondere C_3-C_5-Alkinyloxy-carbonyl, wie Propargyloxycarbonyl, bedeutet.

Niederalkoxyniederalkoxycarbonyl bedeutet insbesondere C_1-C_4-Alkoxy-C_1-C_4-alkoxycarbonyl, vorzugsweise Ethoxy-ethoxycarbonyl, Methoxyethoxycarbonyl und Isopropyloxy-ethoxycarbonyl.

Niederalkylenoxyniederalkylen bedeutet insbesondere C_1-C_4-Alkylenoxy-C_2-C_4-alkylen, vorzugsweise Ethylenoxyethylen.

Niederalkylamino bedeutet insbesondere C_1-C_7-Alkylamino und ist z.B. Methyl-, Ethyl-, n-Propyl- und Isopropylamino. Bevorzugt ist C_1-C_4-Alkylamino.

Niederalkenylamino bedeutet vorzugsweise C_3-C_5-Alkylamino, wie Allyl-und Methallylamino.

Niederalkinylamino bedeutet vorzugsweise C_3-C_5-Alkinylamino, wie Propargylamino.

Phenylniederalkylamino bedeutet vorzugsweise Phenyl-C_1-C_4-alkylamino, insbesondere Benzyl-, 1- und 2-Phenylethylamino.

Phenylniederalkenylamino bedeutet vorzugsweise Phenyl-C_3-C_5-alkenyl-amino, insbesondere 3-Phenylallylamino und 3-Phenylmethallylamino.

Phenylniederalkenylamino bedeutet vorzugsweise Phenyl-C_3-C_5-alkinylamino, insbesondere 3-Phenylpropargylamino.

Diniederalkylamino bedeutet insbesondere Di-C_1-C_4-alkylamino, wie Dimethyl-, Diethyl-, Di-n-propyl-, Methyl-propyl-, Methyl-ethyl-, Methyl-butyl-amino und Dibutylamino.

N-Niederalkyl-N-phenylniederalkylamino bedeutet insbesondere N-C_1-C_4-Alkyl-N-phenyl-C_1-C_4-alkylamino, vorzugsweise Methyl-benzyl-amino und Ethyl-benzyl-amino.

Diphenylniederalkylamino bedeutet insbesondere Di-phenyl-C_1-C_4-alkyl-amino, vorzugsweise Dibenzylamino.

Niederalkylenamino bedeutet insbesondere C_2-C_6-Alkylenamino, vorzugsweise Pyrrolidin-1-yl oder Piperidin-1-yl.

Niederalkylenoxyniederalkylenamino bedeutet insbesondere C_2-C_3-Alkylenoxy-C_2-C_3-alkylenamino, insbesondere Morpholino.

Niederalkanoylamino bedeutet insbesondere C_1-C_5-Alkanoylamino, wie Formyl-, Acetyl-, Propionyl-, Butyryl- oder Pivaloylamino. Bevorzugt ist C_2-C_5-Alkanoylamino.

Phenylniederalkanoylamino bedeutet insbesondere Phenyl-C_2-C_5-alkanoylamino, wie Phenylacetyl- oder Phenylpropionylamino.

Niederalkansulfonylamino bedeutet insbesondere C_1-C_7-Alkansulfonylamino, wie Methan-, Ethan-, Propan- oder Butansulfonylamino. Bevorzugt ist C_1-C_4-Alkansulfonylamino.

Niederalkenyloxy bedeutet insbesondere C_3-C_7-Alkenyloxy und ist z.B. Allyloxy oder But-2-en- oder But-3-enyloxy. Bevorzugt ist C_3-C_5-Alkenyloxy.

Phenylniederalkoxy bedeutet insbesondere Phenyl-C_1-C_4-alkoxy, wie Benzyloxy, 1-oder 2-Phenylethoxy, 3-Phenylpropyloxy oder 4-Phenylbutyloxy.

Niederalkenyloxyniederalkyl bedeutet insbesondere C_3-C_5-Alkenyloxy-C_1-C_4-alkyl, wie 2-Allyloxyethyl, und Niederalkenyloxyniederalkenyl bzw. -niederalkinyl bedeutet insbesondere C_3-C_5-Alkenyloxy-C_3-C_5-alkenyl bzw. -alkinyl.

Ausgedehnte pharmakologische Untersuchungen haben ergeben, dass die Verbindungen I und ihre pharmazeutisch verwendbaren Salze z. B. ausgeprägte Angiotensin-II-antagonisierende Eigenschaften aufweisen.

Bekanntlich hat Angiotensin-II starke vasokonstriktorische Eigenschaften und stimuliert ausserdem die Aldosteronsekretion und bewirkt somit eine deutliche Natrium/Wasser-Retention. Die Folge der Angiotensin-II-Aktivität manifestiert sich unter anderem in einer Erhöhung des Blutdrucks. Die Bedeutung von Angiotensin-II-Antagonisten besteht darin, durch kompetitive Hemmung der Bindung von Angiotensin-II an die Rezeptoren die durch Angiotensin-II bewirkten vasokonstriktorischen und die Aldosteronsekretion-stimulierenden Effekte zu unterdrücken.

Die Angiotensin-II-antagonisierenden Eigenschaften der Verbindungen der Formel I und ihrer pharmazeutisch verwendbaren Salze können im Angiotensin-II-Bindungstest erfasst werden. Dabei werden glatte Muskelzellen der Ratte aus homogenisierter Rattenaorta verwendet. Das feste Zentrifugat wird in 50 mM Tris-Puffer (pH 7,4) unter Einsatz von Peptidaseinhibitoren suspendiert. Die Proben werden 60 Minuten bei 25°C mit ^{125}I-Angiotensin-II (0,175 nM) und einer variierenden Konzentration an Angiotensin-II oder an Testsubstanz inkubiert. Die Inkubation wird dann durch Zugabe von mit eiskaltem Phosphat gepuffertem Kochsalz beendet und es wird durch Whatman GF/F Filter filtriert. Die Filter werden mit einem Gamma-Zähler gezählt. Aus der Dosis-Wirkungs-Kurve werden die IC_{50}-Werte bestimmt. Für die Verbindungen der Formel I und ihre pharmazeurisch verwendbaren Salze werden IC_{50}-Werte ab etwa 10 nM ermittelt.

Zur Bestimmung der Angiotensin-II induzierten Vasokonstriktion können Untersuchungen an dem isolierten Kaninchen-Aortaring herangezogen werden. Hierzu werden von jeder Brust Aortaringe präpariert und zwischen 2 parallelen Klammern bei einer anfänglich bestehenden Spannung von 2 g fixiert. Anschliessend werden die Ringe bei 37°C in 20 ml eines Gewebebades getaucht und mit einem Gemisch aus 95 % O_2 und 5 % CO_2 begast. Die isometrischen Reaktionen werden gemessen. In 20-minütigen Intervallen werden die Ringe abwechselnd mit 10 nM Angiotensin-II (Hypertensin-CIBA) und 5 nM Noradrenalinchlorid stimuliert. Anschliessend werden die Ringe mit ausgewählten Konzentrationen der Testsubstanzen vor der Behandlung mit den Agonisten inkubiert. Die Daten werden mit einem Buxco Digitalcomputer analysiert. Die Konzentrationen, die eine 50%-ige Hemmung der Anfangskontrollwerte bewirken, werden als IC_{50}-Werte angegeben. Für die Verbindungen der Formel I und ihre pharmazeutisch verwendbaren Salze werden IC_{50}-Werte ab etwa 5 nM bestimmt.

Dass die Verbindungen der Formel I und ihre pharmazeutisch verwendbaren Salze durch Angiotensin-II induzierten Bluthochdruck reduzieren können, kann im Testmodell der normotensiven, narkotisierten Ratte verifiziert werden. Nach Kalibration der Präparationen mit jeweils 0,9 % NaCl (1 ml/kg i.v.), Noradrenalin (1 µg/kg i.v.) bzw. Angiotensin-II (0,3 µg/kg i.v.) werden steigende Dosen (3-6) der Testsubstanz durch Bolusinjektion intravenös injiziert, worauf nach jeder Dosis in 5 Minuten-Intervallen Angiotensin-II bzw. Noradrenalin appliziert wird. Der Blutdruck wird direkt in der Halsschlagader gemessen und mit einem on-line Datenerfassungssystem aufgezeichnet (Buxco). Die Spezifität des Angio-

tensin-II-Antagonismus wird angezeigt durch die selektive Hemmung des von Angiotensin-II, nicht aber des durch Noradrenalin hervorgerufenen Druckeffektes. In diesem Testmodell zeigen die Verbindungen der Formel I und ihre pharmazeutisch verwendbaren Salze ab einer Dosis von etwa 0,3 mg/kg i.v. einen hemmenden Effekt.

Auch im Testmodell der renalen hypertensiven Ratte kann die antihypertensive Aktivität der Verbindungen der Formel I und ihrer pharmazeutisch verwendbaren Salze manifestiert werden. Bei männlichen Ratten wird durch Verengung einer renalen Arterie gemäss der Goldblatt-Methode Bluthochdruck erzeugt. Den Ratten werden mittels einer Magensonde Dosen der Testsubstanz verabreicht. Kontrolltiere erhalten ein äquivalentes Volumen an Lösungsmittel. Blutdruck und Herzschlag werden indirekt an wachen Tieren nach der Schwanzklemm-Methode von Gerold et al. [Helv. Physiol. Acta 24 (1966), 58] vor Verabreichung der Testsubstanz bzw. des Lösungsmittels sowie während des Verlaufs der Experimente in Intervallen gemessen. Der ausgeprägte antihypertensive Effekt kann ab einer Dosis von etwa 30 mg/kg p.o. nachgewiesen werden.

Dementsprechend können die Verbindungen der Formel I und ihre pharmazeutisch verwendbaren Salze z.B. als Wirkstoffe in Antihypertensiva verwendet werden, welche z.B. zur Behandlung von Bluthochdruck sowie von Herzinsuffizienz eingesetzt werden. Ein Erfindungsgegenstand ist somit die Verwendung der Verbindungen der Formel I und ihrer pharmazeutisch verwendbaren Salze zur Herstellung von entsprechenden Arzneimitteln und zur therapeutischen Behandlung von Bluthochdruck sowie von Herzinsuffizienz. Bei der Herstellung der Arzneimittel ist auch die gewerbsmässige Herrichtung der Wirksubstanzen eingeschlossen.

Die Erfindung betrifft in erster Linie Verbindungen der Formel I und ihre Salze, worin R_1 gegebenenfalls durch Halogen oder Hydroxy substituiertes Niederalkyl, Niederalkenyl oder Niederalkinyl oder C_3-C_7-Cycloalkyl oder C_3-C_7-Cycloalkenyl oder Phenylniederalkyl, Phenylniederalkenyl oder Phenylniederalkinyl bedeutet; X_1 für CO oder SO_2 steht; X_2 einen gegebenenfalls durch Hydroxy, C_3-C_7-Cycloalkyl oder C_3-C_7-Cycloalkenyl oder Phenyl oder einen entsprechenden 5- oder 6-gliedrigen und monocyclischen aromatischen Rest, der bis zu vier gleiche oder verschiedene Heteroatome aufweist, substituiertes C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden oder C_3-C_7-Cycloalkylen bedeutet, wobei ein Kohlenstoffatom von C_1-C_{10}-Alkylen bzw. C_2-C_{10}-Alkyliden zusätzlich durch C_2-C_6-Alkylen überbrückt sein kann, und wobei C_3-C_7-Cycloalkylen gegebenenfalls ein- oder mehrfach substituiert sind durch Carboxy, Carboxy, welches durch einen Alkohol verestert ist, der sich von Niederalkyl, Phenylniederalkyl, Niederalkenyl, Niederalkinyl, Niederalkoxyniederalkyl, Niederalkoxyniederalkenyl oder Niederalkoxyniederalkinyl ableitet, Carbamoyl, Carbamoyl, in welchem die Aminogruppe durch Niederalkyl, Niederalkenyl, Niederalkinyl, Phenylniederalkyl, Phenylniederalkenyl oder Phenylniederalkinyl mono- oder unabhängig voneinander disubstituiert oder durch C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden disubstituiert ist, wobei C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden gegebenenfalls durch -O- unterbrochen sind, Formyl, Diniederalkoxymethyl oder Oxyniederalkylenoxymethylen; R_2 Carboxy, Carboxy, welches durch einen Alkohol verestert ist, der sich von Niederalkyl, Phenylniederalkyl, Niederalkenyl, Niederalkinyl, Niederalkoxyniederalkyl, Niederalkoxyniederalkenyl oder Niederalkoxyniederalkinyl ableitet, Carbamoyl, Carbamoyl, in welchem die Aminogruppe durch Niederalkyl, Niederalkenyl, Niederalkinyl, Phenylniederalkyl, Phenylniederalkenyl oder Phenylniederalkinyl mono- oder unabhängig voneinander disubstituiert oder durch C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden disubstituiert ist, wobei C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden gegebenenfalls durch -O- unterbrochen sind, Amino, Amino, welches durch Niederalkyl, Niederalkenyl, Niederalkinyl, Phenylniederalkyl, Phenylniederalkenyl oder Phenylniederalkinyl mono- oder unabhängig voneinander disubstituiert oder durch C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden disubstituiert ist, wobei C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden gegebenenfalls durch -O- unterbrochen sind, Niederalkanoyl-, Phenylniederalkanoyl-, Benzoyl-, Niederalkansulfonyl-, Benzolsulfonyl-amino, Formyl, Diniederalkoxymethyl, Oxynieder-alkylenoxymethylen, Hydroxy, Niederalkoxy, Niederalkenyloxy, Phenylniederalkoxy, Phenoxy, $S(O)_m$-R, wobei m für 0, 1 oder 2 steht und R Wasserstoff, Niederalkyl, Niederalkenyl oder Niederalkinyl bedeutet, Niederalkanoyl, Sulfamoyl, Sulfamoyl, in welchem die Aminogruppe durch Niederalkyl, Niederalkenyl, Niederalkinyl, Phenylniederalkyl, Phenylniederalkenyl oder Phenylniederalkinyl mono- oder unabhängig voneinander disubstituiert oder durch C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden disubstituiert ist, wobei C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden gegebenenfalls durch -O- unterbrochen sind, oder PO_nH_2 bedeutet, wobei n für 2 oder 3 steht; X_3 C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden bedeutet; R_3 Carboxy, 5-Tetrazolyl, SO_3H, PO_2H_2, PO_3H_2 oder Halogenniederalkylsulfamoyl ist; wobei (hetero-)aromatische Reste einschliesslich der Ringe A und B unabhängig voneinander gegebenenfalls substituiert sind durch Substituenten ausgewählt aus der Gruppe bestehend aus: Halogen, Hydroxy, Niederalkoxy, Niederalkenyloxy, Phenylniederalkoxy, Phenoxy, $S(O)_m$-R und gegebenenfalls durch Halogen oder Hydroxy substituiertes Niederalkyl, Niederalkenyl oder Niederalkinyl, wobei Niederalkyl, Niederalkenyl oder Niederalkinyl gegebenenfalls durch -O- unterbrochen sind, sowie, im Falle von (hetero-)aromatischen Resten, gegebenenfalls zusätzlich substituiert sind durch Carboxy, Carboxy, welches durch einen Alkohol verestert ist, der sich von Niederalkyl, Phenylniederalkyl, Niederalkenyl, Niederalkinyl, Niederalkoxyniederalkyl, Niederalkoxyniederalkenyl oder Niederalkoxyniederalkinyl ableitet, durch Carbamoyl, Carbamoyl, in welchem die Aminogruppe durch Niederalkyl, Niederalkenyl, Niederalkinyl, Phenylniederalkyl, Phenylniederalkenyl oder Phenylniederalkinyl mono- oder unabhängig voneinander disubstituiert oder durch C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden disubstituiert ist, wobei C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden gegebenenfalls durch -O- unterbrochen sind, durch Formyl, Diniederalkoxymethyl oder Oxyniederalkylenoxymethylen; in freier Form oder in Salzform.

Die Erfindung betrifft insbesondere Verbindungen der Formel I und ihre Salze, worin R_1 gegebenenfalls durch Halogen oder Hydroxy substituiertes Niederalkyl, Niederalkenyl oder Niederalkinyl oder C_3-C_7-Cycloalkyl oder C_3-C_7-Cycloalkenyl oder Phenylniederalkyl, Phenylniederalkenyl oder Phenylniederalkinyl bedeutet; X_1 für CO oder SO_2 steht; X_2 gegebenenfalls durch Hydroxy, C_3-C_7-Cycloalkyl oder C_3-C_7-Cycloalkenyl oder Phenyl oder einen entsprechenden 5- oder 6-gliedrigen und monocyclischen aromatischen Rest, der bis zu vier gleiche oder verschiedene Heteroatome aufweist, substituiertes C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden bedeutet; R_2 Carboxy, Carboxy, welches durch einen Alkohol verestert ist, der sich von Niederalkyl, Phenylniederalkyl, Niederalkenyl, Niederalkinyl, Niederalkoxyniederalkyl, Niederalkoxyniederalkenyl oder Niederalkoxyniederalkinyl ableitet, Carbamoyl, Carbamoyl, in welchem die Aminogruppe durch Niederalkyl, Niederalkenyl, Niederalkinyl, Phenylniederalkyl, Phenylniederalkenyl oder Phenylniederalkinyl mono- oder unabhängig voneinander disubstituiert oder durch C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden disubstituiert ist, wobei C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden gegebenenfalls durch -O- unterbrochen sind, Amino, Amino, welches durch Niederalkyl, Niederalkenyl, Niederalkinyl, Phenylniederalkyl, Phenylniederalkenyl oder Phenylniederalkinyl mono- oder unabhängig voneinander disubstituiert oder durch C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden disubstituiert ist, wobei C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden gegebenenfalls durch -O- unterbrochen sind, Niederalkanoyl-, Phenylniederalkanoyl-, Benzoyl-, Niederalkansulfonyl-, Benzolsulfonyl-amino, Formyl, Diniederalkoxymethyl, Oxyniederalkylenoxymethylen, Hydroxy, Niederalkoxy, Niederalkenyloxy, Phenylniederalkoxy oder Phenoxy, $S(O)_m$-R, wobei m für 0, 1 oder 2 steht und R Wasserstoff, Niederalkyl, Niederalkenyl oder Niederalkinyl bedeutet, Niederalkanoyl, Sulfamoyl, Sulfamoyl, in welchem die Aminogruppe durch Niederalkyl, Niederalkenyl, Niederalkinyl, Phenylniederalkyl, Phenylniederalkenyl oder Phenylniederalkinyl mono- oder unabhängig voneinander disubstituiert oder durch C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden disubstituiert ist, wobei C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden gegebenenfalls durch -O- unterbrochen sind, oder PO_nH_2 bedeutet, wobei n für 2 oder 3 steht; X_3 -CH_2- bedeutet; R_3 Carboxy, 5-Tetrazolyl, SO_3H, PO_2H_2, PO_3H_2 oder Halogenniederalkylsulfamoyl ist; und wobei (hetero-)aromatische Reste einschliesslich der Ringe A und B unabhängig voneinander gegebenenfalls substituiert sind durch Substituenten ausgewählt aus der Gruppe bestehend aus: Halogen, Hydroxy, Niederalkoxy, Niederalkenyloxy, Phenylniederalkoxy, Phenoxy, $S(O)_m$-R und gegebenenfalls durch Halogen oder Hydroxy substituiertes Niederalkyl, Niederalkenyl oder Niederalkinyl, wobei Niederalkyl, Niederalkenyl oder Niederalkinyl gegebenenfalls durch -O- unterbrochen sind, sowie, im Falle von (hetero-)aromatischen Resten, gegebenenfalls zusätzlich substituiert sind durch Carboxy, Carboxy, welches durch einen Alkohol verestert ist, der sich von Niederalkyl, Phenylniederalkyl, Niederalkenyl, Niederalkinyl, Niederalkoxyniederalkyl, Niederalkoxyniederalkenyl oder Niederalkoxyniederalkinyl ableitet, durch Carbamoyl, Carbamoyl, in welchem die Aminogruppe durch Niederalkyl, Niederalkenyl, Niederalkinyl, Phenylniederalkyl, Phenylniederalkenyl oder Phenylniederalkinyl mono- oder unabhängig voneinander disubstituiert oder durch C_1-C_{10}-Alkylen oder C_1-C_{10}-Alkyliden disubstituiert ist, wobei C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden gegebenenfalls durch -O- unterbrochen sind, durch Formyl, Diniederalkoxymethyl oder Oxyniederalkylenoxymethylen; in freier Form oder in Salzform.

Die Erfindung betrifft insbesondere Verbindungen der Formel I und ihre Salze, worin R_1 Niederalkyl, Niederalkenyl, Niederalkinyl, Halogenniederalkyl, -niederalkenyl, -niederalkinyl, Hydroxyniederalkyl, -niederalkenyl, -niederalkinyl, Cycloalkyl, Cycloalkenyl, Phenylniederalkyl, Phenylniederalkenyl oder Phenylniederalkinyl bedeutet; X_1 für CO oder SO_2 steht; X_2 Alkylen oder Alkyliden bedeutet, die gegebenenfalls durch Hydroxy, einen Cycloalkyl-, Cycloalkenyl-, einen Phenylrest oder einen 5- oder 6-gliedrigen, monocyclischen heteroaromatischen Rest mit bis zu vier gleichen oder verschiedenen Heteroatomen substituiert sind, wobei die cyclischen Reste ihrerseits gegebenenfalls substituiert sind durch Carboxy, welches gegebenenfalls verestert ist mit einem Alkohol, der sich von Niederalkyl, Phenylniederalkyl, Niederalkenyl, Niederalkinyl, Niederalkoxyniederalkyl, -niederalkenyl oder -niederalkinyl ableitet, Carbamoyl, in dem die Aminogruppe gegebenenfalls durch Niederalkyl, Niederalkenyl, Niederalkinyl, Phenylniederalkyl, Phenylniederalkenyl, Phenylniederalkinyl mono- oder unabhängig voneinander disubstituiert oder durch Niederalkylen- oder Niederalkylenoxyniederalkylen disubstituiert ist, Formyl, Diniederalkoxymethyl, Oxyniederalkylenoxymethylen; R_2 Carboxy, welches gegebenenfalls verestert ist mit einem Alkohol, der sich von Niederalkyl, Phenylniederalkyl, Niederalkenyl, Niederalkinyl, Niederalkoxyniederalkyl, -niederalkenyl oder -niederalkinyl ableitet, Carbamoyl, in dem die Aminogruppe gegebenenfalls durch Niederalkyl, Niederalkenyl, Niederalkinyl, Phenylniederalkyl, Phenylniederalkenyl, Phenylniederalkinyl mono- oder unabhängig voneinander disubstituiert oder durch Niederalkylen- oder Niederalkylenoxyniederalkylen disubstituiert ist, Amino, in dem die Aminogruppe gegebenenfalls durch Niederalkyl, Niederalkenyl, Niederalkinyl, Phenylniederalkyl, Phenylniederalkenyl, Phenylniederalkinyl mono- oder unabhängig voneinander disubstituiert oder durch Niederalkylen- oder Niederalkylenoxyniederalkylen disubstituiert ist, Niederalkanoyl-, Phenylniederalkanoyl-, Benzoyl-, Niederalkansulfonyl-, Benzolsulfonyl-amino, Formyl, Diniederalkoxymethyl, Oxyniederalkylenoxymethylen, Hydroxy, Niederalkoxy, Niederalkenyloxy, Phenylniederalkoxy, Phenoxy, $S(O)_m$-R, wobei m für 0, 1 oder 2 und R für Wasserstoff, Niederalkyl, Niederalkenyl oder Niederalkinyl steht, Niederalkanoyl, Sulfamoyl, in dem die Aminogruppe gegebenenfalls durch Niederalkyl, Niederalkenyl, Niederalkinyl, Phenylniederalkyl, Phenylniederalkenyl, Phenylniederalkinyl mono- oder unabhängig voneinander disubstituiert oder durch Niederalkylen- oder Niederalkylenoxyniederalkylen disubstituiert ist, oder PO_nH_2 bedeutet, wobei n für 2 oder 3 steht; X_3 -CH_2- bedeutet; R_3 Carboxy, 5-Tetrazolyl, SO_3H, PO_2H_2, PO_3H_2 oder Halogenniederalkylsulfamoyl bedeutet; wobei (hetero-)aromatische Reste einschliesslich der Ringe A und B unabhängig voneinander jeweils gegebenenfalls substituiert sind durch einen oder mehrere Substituenten ausgewählt aus Halogen,

Hydroxy, Niederalkoxy, Niederalkenyloxy, jeweils gegebenenfalls durch Halogen oder Hydroxy substituiertes Niederalkyl, Niederalkenyl, Niederalkinyl, Niederalkoxyniederalkyl, -niederalkenyl, -niederalkinyl, Niederalkenyloxyniederalkyl, -niederalkenyl und -niederalkinyl.

Die Erfindung betrifft insbesondere Verbindungen der Formel I und ihre Salze, worin X_2 Alkylen oder Alkyliden bedeutet, die gegebenenfalls durch Hydroxy, einen Cycloalkyl-, Cycloalkenyl-, einen Phenylrest oder einen 5- oder 6-gliedrigen, monocyclischen heteroaromatischen Rest mit bis zu vier gleichen oder verschiedenen Heteroatomen substituiert sind, wobei ein C-Atom von Alkylen bzw. Alkyliden durch C_2-C_6-Alkylen überbrückt sein kann und wobei die cyclischen Reste ihrerseits gegebenenfalls substituiert sind durch Carboxy, welches gegebenenfalls verestert ist mit einem Alkohol, der sich von Niederalkyl, Phenylniederalkyl, Niederalkenyl, Niederalkinyl, Niederalkoxyniederalkyl, -niederalkenyl oder -niederalkinyl ableitet, Carbamoyl, in dem die Aminogruppe gegebenenfalls durch Niederalkyl, Niederalkenyl, Niederalkinyl, Phenylniederalkyl, Phenylniederalkenyl, Phenylniederalkinyl mono- oder unabhängig voneinander disubstituiert oder durch Niederalkylen- oder Niederalkylenoxyniederalkylen disubstituiert ist, Formyl, Diniederalkoxymethyl oder durch Oxyniederalkylenoxymethylen, oder X_2 C_3-C_7-Cycloalkylen bedeutet; X_3 Niederalkylen oder Niederalkyliden bedeutet; und die Variablen X_1, R_1, R_2, R_3 die unmittelbar vorstehend angegebenen Bedeutungen haben und die (hetero-)aromatischen Ringe einschliesslich der Ringe A und B wie unmittelbar vorstehend angegeben substituiert sein können.

Die Erfindung betrifft insbesondere Verbindungen der Formel I und ihre Salze, worin R_1 Niederalkyl, Niederalkenyl, Halogenniederalkyl, -niederalkenyl, Hydroxyniederalkyl, 3-bis 7-gliedriges Cycloalkyl oder Phenylniederalkyl bedeutet; X_1 für CO, SO_2 oder -O-C(=O)-, wobei das Kohlenstoffatom der Carbonylgruppe an das in der Formel I eingezeichnete Stickstoffatom gebunden ist, steht; X_2 C_1-C_{10}-Alkylen oder C_1-C_7-Alkyliden, die gegebenenfalls substituiert sind durch Hydroxy, Carboxy, Amino, Guanidino, einen 3- bis 7-gliedrigen Cycloalkyl-, 3- bis 7-gliedrigen Cycloalkenyl-, Phenyl-, Pyrrolyl-, Pyrazolyl-, Imidazolyl-, Triazolyl-, Tetrazolyl-, Furyl-, Thienyl- oder Pyridylrest, welche ihrerseits gegebenenfalls zusätzlich durch Carboxy, Niederalkoxycarbonyl, Phenylniederalkoxycarbonyl, Carbamoyl, in dem die Aminogruppe gegebenenfalls durch Niederalkyl oder Phenylniederalkyl mono- oder unabhängig voneinander disubstituiert ist, Formyl, Diniederalkoxymethyl oder Oxyniederalkylenoxymethylen substituiert sein können; R_2 Carboxy, Niederalkoxy-, Phenylniederalkoxy-, Niederalkenyloxy-, Niederalkoxyniederalkoxy-carbonyl, Carbamoyl, in dem die Aminogruppe gegebenenfalls durch Niederalkyl, Phenylniederalkyl mono- oder unabhängig voneinander disubstituiert oder durch Niederalkylen, das gegebenenfalls an zwei benachbarten Kohlenstoffatomen mit einem Benzolring kondensiert ist, oder Niederalkylenoxyniederalkylen disubstituiert ist, Amino, in dem die Aminogruppe gegebenenfalls durch Niederalkyl, Phenylniederalkyl mono- oder unabhängig voneinander disubstituiert oder durch Niederalkylen- oder Niederalkylenoxyniederalkylen disubstituiert ist, Niederalkanoyl-, Phenylniederalkanoyl-, Benzoyl-, Niederalkansulfonyl-, Benzolsulfonyl-amino, Formyl, Diniederalkoxymethyl, Oxyniederalkylenoxymethylen, Hydroxy, Niederalkoxy, Phenylniederalkoxy, Phenoxy, $S(O)_m$-R, wobei m für 0, 1 oder 2 und R für Niederalkyl steht, Niederalkanoyl, Sulfamoyl, in dem die Aminogruppe gegebenenfalls durch Niederalkyl, Phenylniederalkyl mono- oder unabhängig voneinander disubstituiert ist, oder PO_nH_2 bedeutet, wobei n für 2 oder 3 steht; X_3 Methylen ist; R_3 Carboxy, 5-Tetrazolyl, SO_3H, PO_2H_2, PO_3H_2 oder Halogenniederalkylsulfamoyl bedeutet; (hetero-)aromatische Reste einschliesslich der Ringe A und B jeweils gegebenenfalls zusätzlich substituiert sind durch einen oder mehrere Substituenten ausgewählt aus Halogen, Hydroxy, Niederalkoxy, jeweils gegebenenfalls durch Halogen oder Hydroxy substituiertes Niederalkyl bzw. Niederalkoxyniederalkyl.

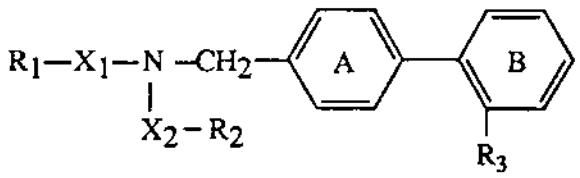
Die Erfindung betrifft insbesondere Verbindungen der Formel I und ihre Salze, worin R_1 Niederalkyl, Niederalkenyl, Halogenniederalkyl, -niederalkenyl, Hydroxyniederalkyl, 3- bis 7-gliedriges Cycloalkyl oder Phenylniederalkyl bedeutet; X_1 für CO oder SO_2 steht; X_2 C_1-C_{10}-Alkylen oder C_1-C_7-Alkyliden, die gegebenenfalls substituiert sind durch Hydroxy, einen 3- bis 7-gliedrigen Cycloalkyl-, 3-bis 7-gliedrigen Cycloalkenyl-, Phenyl-, Pyrrolyl-, Pyrazolyl-, Imidazolyl-, Triazolyl-, Tetrazolyl-, Furyl-, Thienyl- oder Pyridylrest, welche ihrerseits gegebenenfalls zusätzlich durch Carboxy, Niederalkoxycarbonyl, Phenylniederalkoxycarbonyl, Carbamoyl, in dem die Aminogruppe gegebenenfalls durch Niederalkyl oder Phenylniederalkyl mono- oder unabhängig voneinander disubstituiert ist, Formyl, Diniederalkoxymethyl oder Oxyniederalkylenoxymethylen substituiert sein können; R_2 Carboxy, Niederalkoxy-, Phenylniederalkoxy-, Niederalkenyloxy-, Niederalkoxyniederalkoxy-carbonyl, Carbamoyl, in dem die Aminogruppe gegebenenfalls durch Niederalkyl, Phenylniederalkyl mono-oder unabhängig voneinander disubstituiert oder durch Niederalkylen- oder Niederalkylenoxyniederalkylen disubstituiert ist, Amino, in dem die Aminogruppe gegebenenfalls durch Niederalkyl, Phenylniederalkyl mono- oder unabhängig voneinander disubstituiert oder durch Niederalkylen-oder Niederalkylenoxyniederalkylen disubstituiert ist, Niederalkanoyl-, Phenylniederalkanoyl-, Benzoyl-, Niederalkansulfonyl-, Benzolsulfonyl-amino, Formyl, Diniederalkoxymethyl, Oxyniederalkylenoxymethylen, Hydroxy, Niederalkoxy, Phenylniederalkoxy, Phenoxy, $S(O)_m$-R, wobei m für 0, 1 oder 2 und R für Niederalkyl steht, Niederalkanoyl, Sulfamoyl, in dem die Aminogruppe gegebenenfalls durch Niederalkyl, Phenylniederalkyl mono- oder unabhängig voneinander disubstituiert ist, oder PO_nH_2 bedeutet, wobei n für 2 oder 3 steht; X_3 Methylen ist; R_3 Carboxy, 5-Tetrazolyl, SO_3H, PO_2H_2, PO_3H_2 oder Halogenniederalkylsulfamoyl bedeutet; (hetero-)aromatische Reste einschliesslich der Ringe A und B jeweils gegebenenfalls zusätzlich substituiert sind durch einen oder mehrere Substituenten ausgewählt aus Halogen, Hydroxy, Niederalkoxy, jeweils gegebenenfalls durch Halogen oder Hydroxy substituiertes Niederalkyl bzw. Niederalkoxyniederalkyl.

Die Erfindung betrifft insbesondere Verbindungen der Formel I und ihre Salze, worin X_2 C_1-C_{10}-Alkylen oder C_1-C_7-Alkyliden, die gegebenenfalls substituiert sind durch Hydroxy, einen 3- bis 7-gliedrigen Cycloalkyl-, 3- bis 7-gliedrigen Cycloalkenyl-, Phenyl-, Pyrrolyl-, Pyrazolyl-, Imidazolyl-, Triazolyl-, Tetrazolyl-, Furyl-, Thienyl- oder Pyridylrest, welche ihrerseits gegebenenfalls zusätzlich durch Carboxy, Niederalkoxycarbonyl, Phenylniederalkoxycarbonyl, Carbamoyl, in dem die Aminogruppe gegebenenfalls durch Niederalkyl oder Phenylniederalkyl mono- oder unabhängig voneinander disubstituiert ist, Formyl, Diniederalkoxymethyl oder durch Oxyniederalkylenoxymethylen substituiert sein können, wobei ein C-Atom von Alkylen bzw. Alkyliden durch C_2-C_6-Alkylen überbrückt sein kann, oder X_2 C_3-C_7-Cycloalkylen bedeutet; X_3 Niederalkylen oder Niederalkyliden bedeutet und die Variablen X_1, R_1, R_2, R_3 die unmittelbar vorstehend angegebenen Bedeutungen haben und die (hetero-)aromatischen Ringe einschliesslich der Ringe A und B wie unmittelbar vorstehend angegeben substituiert sein können.

Die Erfindung betrifft insbesondere Verbindungen der Formel I und ihre Salze, worin die Variablen R_1, X_1, R_3 die jeweils vorstehend angegebenen Bedeutungen haben; X_2 gegebenenfalls durch Hydroxy, 3- bis 7-gliedriges Cycloalkyl, Phenyl oder Imidazolyl substituiertes Niederalkylen oder Niederalkyliden bedeutet und R_2 Carboxy, Niederalkoxy-, Phenylniederalkoxy-, Niederalkoxyniederalkoxy-carbonyl, Carbamoyl, welches gegebenenfalls durch Niederalkyl, Phenylniederalkyl mono- oder unabhängig voneinander disubstituiert ist, Amino, Niederalkanoyl-, Phenylniederalkanoyl-, Niederalkansulfonylamino, Hydroxy, Niederalkoxy, Phenylniederalkoxy oder Phenoxy bedeutet; X_3-CH_2- bedeutet; wobei (hetero-)aromatische Reste einschliesslich der Ringe A und B jeweils gegebenenfalls durch einen oder mehrere Substituenten ausgewählt aus Halogen, Trifluormethyl, Hydroxy, Niederalkoxy, Niederalkyl, Hydroxyniederalkyl oder Niederalkoxyniederalkyl substituiert sind.

Die Erfindung betrifft insbesondere Verbindungen der Formel I und ihre Salze, worin X_2 gegebenenfalls durch Hydroxy, 3-bis 7-gliedriges Cycloalkyl, 7-gliedriges Cycloalkenyl, Phenyl oder Imidazolyl substituiertes Niederalkylen oder Niederalkyliden bedeutet, wobei ein C-Atom von Niederalkylen bzw. Niederalkyliden durch C_2-C_6-Alkylen überbrückt sein kann, oder X_2 C_3-C_7-Cycloalkylen bedeutet; und die Variablen X_1, X_3, R_1, R_2, R_3 die unmittelbar vorstehend angegebenen Bedeutungen haben, die Ringe A und B wie unmittelbar vorstehend angegeben substituiert sein können.

Die Erfindung betrifft insbesondere Verbindungen der Formel

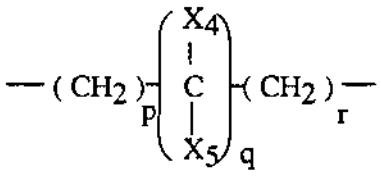


(Ia)

und ihre Salze, worin die Variablen R_1, X_1, X_2, R_2 und R_3 die jeweils vorstehend angegebenen Bedeutungen haben und die Ringe A und B wie unmittelbar vorstehend angegeben substituiert sein können.

Die Erfindung betrifft insbesondere Verbindungen der Formel Ia und ihre Salze, worin X_2 gegebenenfalls durch Hydroxy oder 3-bis 7-gliedriges Cycloalkyl substituiertes Niederalkylen oder Niederalkyliden bedeutet, wobei ein C-Atom von Niederalkylen bzw. Niederalkyliden durch C_2-C_6-Alkylen, insbesondere C_4-C_5-Alkylen, überbrückt sein kann, oder worin X_2 C_3-C_7-Cycloalkylen bedeutet, und die Variablen R_1, X_1, R_2 und R_3 die jeweils vorstehend angegebenen Bedeutungen haben und die Ringe A und B wie unmittelbar vorstehend angegeben substituiert sein können.

Die Erfindung betrifft insbesondere Verbindungen der Formel Ia und ihre Salze, worin X_2 für die Gruppe der Formel



(Ib)

steht, in der p für 0 oder 1, q für 1 und r für 0 oder 1 stehen oder in der p für 1 bis 8 und q sowie r jeweils für 0 stehen; X_4 gegebenenfalls durch Hydroxy, 3- bis 7-gliedriges Cycloalkyl, Phenyl oder Imidazolyl substituiertes Niederalkyl oder Phenyl bedeutet und X_5 Wasserstoff oder Niederalkyl bedeutet; R_2 Carboxy, Niederalkoxycarbonyl, Phenylniederalkoxycarbonyl, Niederalkoxyniederalkoxycarbonyl, Hydroxy, Niederalkoxy, Phenylniederalkoxy, Phenoxy, Amino, Niederalkanoylamino, Phenylniederalkanoylamino oder Niederalkansulfonylamino bedeutet; und die Variablen R_1, X_1 und R_3 die jeweils vorstehend angegebenen Bedeutungen haben; wobei (hetero-)aromatische Reste einschliesslich der Ringe A und B jeweils gegebenenfalls durch Halogen, Trifluormethyl, Hydroxy, Niederalkoxy, Niederalkyl oder Hydroxyniederalkyl substituiert sind.

Die Erfindung betrifft insbesondere Verbindungen der Formel Ia und ihre Salze, worin X_2 für die Gruppe der Formel Ib steht, in der p für 0 oder 1, q für 1 und r für 0 oder 1 stehen oder in der p für 1 bis 8 und q sowie r jeweils für 0 stehen; X_4 gegebenenfalls durch Hydroxy, 3- bis 7-gliedriges Cycloalkyl, Phenyl oder Imidazolyl substituiertes Niederalkyl oder Phenyl bedeutet und X_5 Wasserstoff oder Niederalkyl bedeutet; oder X_4 und X_5 gemeinsam für C_2-C_6-Alkylen, insbesondere C_4-C_5-Alkylen, stehen, oder X_2 C_3-C_7-Cycloalkylen, insbesondere C_5-C_6-Cycloalkylen, bedeutet; R_2 Carboxy, Niederalkoxycarbonyl, Phenylniederalkoxycarbonyl, Niederalkoxyniederalkoxycarbonyl, Hydroxy, Niederalkoxy, Phenylniederalkoxy, Phenoxy, Amino, Niederalkanoylamino, Phenylniederalkanoylamino oder Niederalkansulfonylamino bedeutet; und die Variablen R_1, X_1 und R_3 die jeweils vorstehend angegebenen Bedeutungen haben; wobei (hetero-)aromatische Reste einschliesslich der Ringe A und B jeweils gegebenenfalls durch Halogen, Trifluormethyl, Hydroxy, Niederalkoxy, Niederalkyl oder Hydroxyniederalkyl substituiert sind.

Die Erfindung betrifft insbesondere Verbindungen der Formel Ia und ihre Salze, worin R_1 Niederalkyl, insbesondere C_3-C_5-Alkyl, oder Niederalkenyl, insbesondere C_3-C_5-Alkenyl, bedeutet; X_1 für CO oder ferner SO_2 steht; X_2 für die Gruppe der Formel Ib steht, in der p und r für 0 oder 1 und q für 1 stehen; X_4 gegebenenfalls durch Hydroxy, 3- bis 7-gliedriges Cycloalkyl, wie Cyclohexyl, durch gegebenenfalls durch Halogen oder Hydroxy substituiertes Phenyl oder Imidazolyl, wie 4-Imidazolyl, substituiertes Niederalkyl, insbesondere C_1-C_4-Alkyl, oder Phenyl bedeutet; X_5 Wasserstoff oder Niederalkyl, wie C_1-C_4-Alkyl, bedeutet oder X_4 und X_5 gemeinsam für C_2-C_6-Alkylen, wie C_4-C_5-Alkylen, bedeuten, oder X_2 C_3-C_7-Cycloalkylen, wie C_5-C_6-Cycloalkylen,wie 1,4-Cyclohexylen, bedeutet; R_2 Carboxy, Niederalkoxycarbonyl, wie C_2-C_5-Alkoxycarbonyl, Phenylniederalkoxycarbonyl, wie Phenyl-C_1-C_4-alkoxycarbonyl, Niederalkoxyniederalkoxycarbonyl, wie C_1-C_4-Alkoxy-C_2-C_5-alkoxycarbonyl, Hydroxy oder Niederalkoxy, wie C_1-C_4-Alkoxy, bedeutet; R_3 Carboxy oder 5-Tetrazolyl bedeutet; wobei (hetero-)aromatische Reste einschliesslich der Ringe A und B jeweils gegebenenfalls durch Halogen, Trifluormethyl, Hydroxy, Niederalkoxy, Niederalkyl oder Hydroxyniederalkyl substituiert sind.

Die Erfindung betrifft insbesondere Verbindungen der Formel Ia und ihre Salze, worin R_1 Niederalkyl, insbesondere C_3-C_5-Alkyl, oder Niederalkenyl, insbesondere C_3-C_5-Alkenyl, bedeutet; X_1 für CO oder ferner SO_2 steht; X_2 für die Gruppe der Formel Ib steht, in der p und r für 0 oder 1 und q für 1 stehen; X_4 gegebenenfalls durch Hydroxy, 3- bis 7-gliedriges Cycloalkyl, wie Cyclohexyl, durch gegebenenfalls durch Halogen oder Hydroxy substituiertes Phenyl oder Imidazolyl, wie 4-Imidazolyl, substituiertes Niederalkyl, insbesondere C_1-C_4-Alkyl, oder Phenyl bedeutet; X_5 Wasserstoff oder Niederalkyl, wie C_1-C_4-Alkyl, bedeutet; R_2 Carboxy, Niederalkoxycarbonyl,wie C_2-C_5-Alkoxycarbonyl, Phenylniederalkoxycarbonyl, wie Phenyl-C_1-C_4-alkoxycarbonyl, Niederalkoxyniederalkoxycarbonyl, wie C_1-C_4-Alkoxy-C_2-C_5-alkoxycarbonyl, Hydroxy oder Niederalkoxy, wie C_1-C_4-Alkoxy, bedeutet; R_3 Carboxy oder 5-Tetrazolyl bedeutet; wobei (hetero-)aromatische Reste einschliesslich der Ringe A und B jeweils gegebenenfalls durch Halogen, Trifluormethyl, Hydroxy, Niederalkoxy, Niederalkyl oder Hydroxyniederalkyl substituiert sind.

Die Erfindung betrifft insbesondere Verbindungen der Formel Ia und ihre Salze, worin R_1 Niederalkyl, insbesondere C_3-C_5-Alkyl, oder ferner Niederalkenyl, insbesondere C_3-C_5-Alkenyl, bedeutet; X_1 für CO oder ferner SO_2 steht; X_2 für die Gruppe der Formel Ib steht, in der p für 1-8 und q sowie r für 0 stehen; R_2 Hydroxy, Niederalkoxy, wie C_1-C_4-Alkoxy, Phenylniederalkoxy, wie Phenyl-C_1-C_4-alkoxy, Phenoxy, Niederalkanoylamino, wie C_1-C_4-Alkanoylamino, Phenylniederalkanoylamino, wie Phenyl-C_1-C_4-alkanoylamino, Niederalkansulfonylamino, wie C_1-C_4-Alkansulfonylamino, bedeutet; R_3 Carboxy oder in erster Linie 5-Tetrazolyl bedeutet; wobei (hetero-)aromatische Reste einschliesslich der Ringe A und B jeweils gegebenenfalls durch Halogen, Trifluormethyl, Hydroxy, Niederalkoxy, Niederalkyl oder Hydroxyniederalkyl substituiert sind.

Die Erfindung betrifft in erster Linie Verbindungen der Formel Ia und ihre Salze, worin R_1 C_3-C_5-Alkyl oder in zweiter Linie C_3-C_5-Alkenyl, bedeutet; X_1 für CO, ferner SO_2 steht; X_2 für die Gruppe der Formel Ib steht, in der p und r unabhängig voneinander für 0 oder 1 und q für 1 stehen; X_4 C_1-C_4-Alkyl, wie Methyl, Ethyl, Propyl, Isopropyl, 1- oder 2-Butyl, Hydroxy-C_1-C_4-alkyl, wie Hydroxymethyl, C_3-C_7-Cycloalkyl-C_1-C_4-alkyl, wie Cyclohexylmethyl, Phenyl-C_1-C_4-alkyl, wie Benzyl, oder Imidazolyl-C_1-C_4-alkyl, wie Imidazol-4-yl-methyl, bedeutet; X_5 Wasserstoff oder C_1-C_4-Alkyl, wie Methyl, bedeutet; oder X_4 und X_5 gemeinsam für Tetramethylen, ferner Pentamethylen stehen; R_2 Carboxy oder C_2-C_5-Alkoxycarbonyl, ferner Phenyl-C_1-C_4-alkoxycarbonyl, wie Benzyloxycarbonyl, bedeutet; R_3 Carboxy oder insbesondere 5-Tetrazolyl bedeutet.

Die Erfindung betrifft in erster Linie Verbindungen der Formel Ia und ihre Salze, worin R_1 C_3-C_5-Alkyl oder in zweiter Linie C_3-C_5-Alkenyl, bedeutet; X_1 für CO, ferner SO_2 steht; X_2 für die Gruppe der Formel Ib steht, in der p und r jeweils für 0 oder 1 und q für 1 stehen; X_4 C_1-C_4-Alkyl, wie Methyl, Ethyl, Propyl, Isopropyl, 1- oder 2-Butyl, Hydroxy-C_1-C_4-alkyl, wie Hydroxymethyl, C_3-C_7-Cycloalkyl-C_1-C_4-alkyl, wie Cyclohexylmethyl, Phenyl-C_1-C_4-alkyl, wie Benzyl, oder Imidazolyl-C_1-C_4-alkyl, wie Imidazol-4-yl-methyl, bedeutet; X_5 Wasserstoff bedeutet; R_2 Carboxy oder C_2-C_5-Alkoxycarbonyl, ferner Phenyl-C_1-C_4-alkoxycarbonyl, wie Benzyloxycarbonyl, bedeutet; R_3 Carboxy oder 5-Tetrazolyl bedeutet.

Die Erfindung betrifft in erster Linie Verbindungen der Formel Ia und ihre Salze, worin R_1 C_3-C_5-Alkyl, wie Propyl, Butyl oder Pentyl, bedeutet; X_1 für CO steht; X_2 für die Gruppe der Formel Ib steht, in der q und r für 0 und p für 1 bis 3, insbesondere 2, stehen, oder in der p und q für 1 und r für 0 stehen; X_4 C_1-C_4-Alkyl, wie Methyl, Ethyl, Propyl, Isopropyl, 1- oder 2-Butyl, bedeutet; X_5 Wasserstoff oder C_1-C_4-Alkyl, wie Methyl, bedeutet; R_2 Carboxy, C_2-C_5-Alkoxycarbonyl, wie Methoxy- oder Ethoxycarbonyl, bedeutet; R_3 Carboxy oder 5-Tetrazolyl bedeutet.

Die Erfindung betrifft in erster Linie Verbindungen der Formel Ia und ihre Salze, worin R_1 C_3-C_5-Alkyl, wie Propyl, Butyl oder Pentyl, bedeutet; X_1 für CO steht; X_2 für die Gruppe der Formel Ib steht, in der p für 0 oder 1, r für 0 und q für 1 stehen; X_4 C_1-C_4-Alkyl, wie Methyl, Ethyl, Propyl, Isopropyl, 1- oder 2-Butyl, bedeutet; X_5 Wasserstoff oder C_1-C_4-Alkyl, wie Methyl oder Ethyl, bedeutet oder X_4 und X_5 gemeinsam für Tetramethylen oder Pentamethylen stehen; R_2 Carboxy, C_2-C_5-Alkoxycarbonyl, wie Methoxy- oder Ethoxycarbonyl, bedeutet; R_3 5-Tetrazolyl bedeutet.

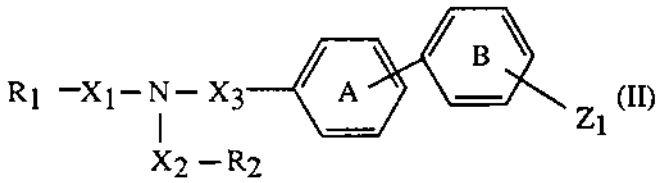
Die Erfindung betrifft in erster Linie Verbindungen der Formel Ia und ihre Salze, worin R_1 C_3-C_5-Alkyl, wie Propyl, Butyl oder Pentyl, bedeutet; X_1 für CO steht; X_2 für die Gruppe der Formel Ib steht, in der p 0 oder 1 und r für 0 und q für 1 stehen; X_4 und X_5 gemeinsam für Tetramethylen, ferner Pentamethylen stehen; R_2 Carboxy oder C_2-C_5-Alkoxycarbonyl, wie Methoxy- oder Ethoxycarbonyl, bedeutet; R_3 5-Tetrazolyl bedeutet.

Die Erfindung betrifft in erster Linie Verbindungen der Formel Ia und ihre Salze, worin R_1 C_3-C_5-Alkyl, wie Propyl, Butyl oder Pentyl, bedeutet; X_1 für CO steht; X_2 für die Gruppe der Formel Ib steht, in der p und r für 0 oder 1 und q für 1 stehen; X_4 C_1-C_4-Alkyl, wie Methyl, Ethyl, Propyl, Isopropyl, 1- oder 2-Butyl, bedeutet; X_5 Wasserstoff bedeutet; R_2 Carboxy, C_2-C_5-Alkoxycarbonyl, wie Methoxy- oder Ethoxycarbonyl, bedeutet; R_3 5-Tetrazolyl bedeutet.

Die Erfindung betrifft insbesondere die in den Beispielen aufgeführten neuen Verbindungen sowie die dort beschriebenen Herstellungsweisen.

Gegenstand der Erfindung sind auch Verfahren zur Herstellung der erfindungsgemässen Verbindungen. Die Herstellung von Verbindungen der Formel I und ihrer Salze erfolgt in an sich bekannter Weise und ist z.B. dadurch gekennzeichnet, dass man

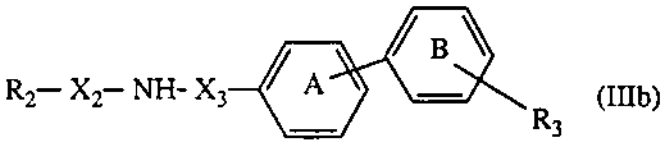
a) in einer Verbindung der Formel



(II)

oder einem Salz davon, worin Z_1 einen in R_3 überführbaren Rest bedeutet, Z_1 in R_3 überführt oder

b) eine Verbindung der Formel R_1-X_1OH (IIIa), ein reaktionsfähiges Derivat davon oder ein Salz davon mit einer Verbindung der Formel



(IIIb)

oder einem Salz davon umsetzt und jeweils, wenn erwünscht, eine verfahrensgemäss oder auf andere Weise erhältliche Verbindung I in freier Form oder in Salzform in eine andere Verbindung I überführt, ein verfahrensgemäss erhältliches Gemisch von Isomeren auftrennt und das gewünschte Isomere isoliert und/oder eine verfahrensgemäss erhältliche freie Verbindung I in ein Salz oder ein verfahrensgemäss erhältliches Salz einer Verbindung I in die freie Verbindung I oder in ein anderes Salz überführt.

Salze von Ausgangsmaterialien, die mindestens ein basisches Zentrum aufweisen, beispielsweise der Formel IIIb, sind entsprechende Säureadditionssalze, während Salze von Ausgangsstoffen, die eine acide Gruppe aufweisen, beispielsweise der Formel (IIIa), als Salze mit Basen vorliegen, jeweils wie in Zusammenhang mit entsprechenden Salzen der Formel I vorstehend aufgeführt.

In die Variable R_3 überführbare Reste Z_1 stellen beispielsweise Cyano, Mercapto, Halogen, die Gruppe $-N_2^+ A^-$, in der A^- ein von einer Säure abgeleitetes Anion bedeutet, Amino sowie von COOH, SO_3H, PO_3H_2 oder PO_2H_2 verschiedene funktionell abgewandelte Formen sowie N-geschütztes 5-Tetrazolyl.

Reaktionsfähige Derivate von Verbindungen der Formel IIIa sind beispielsweise davon abgeleitete aktivierte Ester oder reaktionsfähige Anhydride, ferner reaktionsfähige cyclische Amide.

Die vor- und nachstehend in den Varianten beschriebenen Umsetzungen werden in an sich bekannter Weise durchgeführt, z.B. in Ab- oder üblicherweise in Anwesenheit eines geeigneten Lösungs- oder Verdünnungsmittels oder eines Gemisches derselben, wobei man je nach Bedarf unter Kühlen, bei Raumtemperatur oder unter Erwärmen, z.B. in einem

Temperaturbereich von etwa -80°C bis zur Siedetemperatur des Reaktionsmediums, vorzugsweise von etwa -10° bis etwa +200°C, und, falls erforderlich, in einem geschlossenen Gefäss, unter Druck, in einer Inertgasatmosphäre und/oder unter wasserfreien Bedingungen arbeitet.

Verfahrensvariante a):

In 5-Tetrazolyl R_3 überführbare Reste Z_1 sind beispielsweise Cyano oder geschütztes 5-Tetrazolyl.

Zur Herstellung von Verbindungen der Formel I, worin R_3 5-Tetrazolyl bedeutet, geht man beispielsweise von Ausgangsmaterial der Formel II aus, worin Z_1 Cyano bedeutet, und setzt dieses mit einem Azid, wie HN_3 oder insbesondere einem Salz, wie Alkalimetallsalz, davon oder mit einem Organozinnazid, wie Tri(nieder)alkyl- oder Triarylzinnazid, um. Bevorzugte Azide sind beispielsweise Natrium- und Kaliumazid sowie Tri-C_1-C_4-alkyl-, z.B. Triethyl- oder Tributylzinnazid, und Triphenylzinnazid. Bevorzugt wird die Tetrazol-5-yl-Bildung mit solchen Verbindungen der Formel II durchgeführt, worin R_2 von Carboxy verschieden ist.

Als Schutzgruppen von geschütztem 5-Tetrazolyl kommen die üblicherweise in der Tetrazolchemie verwendeten Schutzgruppen in Frage, insbesondere Triphenylmethyl, gegebenenfalls, z.B. durch Nitro, substituiertes Benzyl, wie 4-Nitrobenzyl, Niederalkoxymethyl, wie Methoxy- und Ethoxymethyl, Niederalkylthiomethyl, wie Methylthiomethyl, Silyl, wie Triniederalkylsilyl,z.B. Dimethyl-tert-butyl- und Triisopropyl-silyl, sowie 2-Cyanoethyl, ferner Niederalkoxyniederalkoxymethyl, wie 2-Methoxyethoxymethyl, Benzyloxymethyl sowie Phenacyl.

Die Abspaltung der Schutzgruppen erfolgt in Anlehnung an bekannte Methoden, beispielsweise wie in J. Green, Protective Groups in Organic Synthesis, Wiley-Interscience (1980) beschrieben. So wird z.B. die Triphenylmethylgruppe üblicherweise durch Hydrolyse, insbesondere in Gegenwart einer Säure, oder Hydrogenolyse in Gegenwart eines Hydrierungskatalysators, 4-Nitrobenzyl z.B. durch Hydrogenolyse in Gegenwart eines Hydrierungskatalysators, Methoxy- oder Ethoxymethyl z.B. durch Behandeln mit einem Triniederalkyl-, wie Triethyl-oder Tributyl-zinn-bromid, Methylthiomethyl z.B. durch Behandeln mit Trifluoressigsäure, Silyreste z.B. durch Behandeln mit Fluoriden, wie Tetraniederalkylammoniumfluoriden, z.B. Tetrabutylammoniumfluorid, oder Alkalimetallfluoriden, z.B. Natriumfluorid, oder 2-Cyanoethyl z.B. durch Hydrolyse, beispielsweise mit Natronlauge, 2-Methoxyethoxymethyl z.B. durch Hydrolyse, z.B. mit Salzsäure, Benzyloxymethyl und Phenacyl z.B. durch Hydrogenolyse in Gegenwart eines Hydrierungskatalysators abgespalten.

Ein in R_3= SO_3H überführbarer Rest ist beispielsweise die Mercaptogruppe. Eine solche Gruppe aufweisende Ausgangsverbindungen der Formel II werden beispielsweise durch an sich bekannte Oxidationsverfahren zu solchen Verbindungen der Formel I oxidiert, worin R_3 SO_3H ist. Als Oxidationsmittel kommen beispielsweise anorganische Persäuren, wie Persäuren von Mineralsäuren, z.B. Periodsäure oder Perschwefelsäure, organische Persäuren, wie entsprechende Percarbon- oder Persulfonsäuren, z.B. Perameisen-, Peressig-, Trifluorperessig- bzw. Perbenzoesäure oder p-Toluolpersulfonsäure, oder Gemische aus Wasserstoffperoxid und Säuren, z.B. Gemisch aus Wasserstoffperoxid mit Essigsäure, in Betracht.

Häufig führt man die Oxidation in Gegenwart von geeigneten Katalysatoren durch, wobei als Katalysatoren geeignete Säuren, wie gegebenenfalls substituierte Carbonsäuren, z.B. Essigsäure oder Trifluoressigsäure, oder Übergangsmetalloxide, wie Oxide von Elementen der VII. Nebengruppe, z.B. Vanadium-, Molybdän- oder Wolframoxid, zu nennen sind. Die Oxidation wird unter milden Bedingungen, z.B. bei Temperaturen von etwa -50° bis etwa +100°C, durchgeführt.

Unter einer in R_3 = PO_3H_2 überführbaren Gruppe ist beispielsweise eine Gruppe N_2^+ A^- zu verstehen, wobei A^- für ein Anion einer Säure, wie Mineralsäure, steht. Derartige Diazoniumverbindungen werden beispielsweise in an sich bekannter Weise mit einem P(III)-Halogenid, wie PCl_3 oder PBr_3, umgesetzt und hydrolytisch aufgearbeitet, wobei solche Verbindungen der Formel I erhältlich sind, worin R_3 PO_3H_2 ist.

Als in Halogenalkylsulphamoyl R_3 überführbarer Rest Z_1 kommt beispielsweise primäres Amino in Frage.

Zur Herstellung von Verbindungen der Formel I, worin R_3 Halogenalkylsulphamoyl bedeutet, setzt man beispielsweise entsprechende Aniline mit einer üblicherweise reaktionsfähig veresterten Halogenalkylsulfonsäure um, wobei gegebenenfalls in Gegenwart einer Base gearbeitet wird. Als bevorzugte reaktionsfähig veresterte Halogensulfonsäure kommt das entsprechende Halogenid, wie Chlorid oder Bromid, in Frage.

Ein in R_3 = COOH überführbarer Rest Z_1 steht beispielsweise für funktionell abgewandeltes Carboxy, wie Cyano, verestertes oder amidiertes Carboxy, Hydroxymethyl oder Formyl.

Verestertes Carboxy ist beispielsweise mit einem gegebenenfalls substituierten aliphatischen, cycloaliphatischen oder aromatischen Alkohol verestertes Carboxy. Ein aliphatischer Alkohol ist beispielsweise ein Niederalkanol, wie Methanol, Ethanol, Propanol, Isopropanol, n-Butanol, sec- oder tert.-Butanol, während als cycloaliphatischer Alkohol beispielsweise ein 3- bis 8-gliedriges Cycloalkanol, wie Cyclopentanol, -hexanol oder -heptanol, in Frage kommt. Ein aromatischer Alkohol ist beispielsweise ein Phenol oder heterocyclischer Alkohol, welche jeweils gegebenenfalls substituiert sein können, insbesondere Hydroxypyridin, z.B. 2-, 3- oder 4-Hydroxypyridin. Carboxy kann ebenfalls mit einem silyliertem Alkohol verestert sein und bedeutet insbesondere Tri-(C_1-C_4-)-alkylsilyl-(C_1-C_4-)alkoxy-carbonyl, insbesondere Trimethylsilylethoxycarbonyl.

Amidiertes Carboxy ist beispielsweise Carbamoyl, durch Hydroxy, Amino oder gegebenenfalls substituiertes Phenyl monosubstituiertes, durch Niederalkyl mono- oder disubstituiertes oder durch 4- bis 7-gliedriges Alkylen bzw. 3-Aza-, 3-Niederalkylaza-, 3-Oxo- oder 3-Thiaalkylen disubstituiertes Carbamoyl. Als Beispiele sind Carbamoyl, N-Mono- oder N,N-Diniederalkylcarbamoyl, wie N-Methyl-, N-Ethyl-, N,N-Dimethyl-, N,N-Diethyl- oder N,N-Dipropylcarbamoyl, Pyrrolidino- oder Piperidinocarbonyl, Morpholino-, Piperazino- bzw. 4-Methylpiperazino- sowie Thiomorpholinocarbonyl, Anilinocarbonyl oder durch Niederalkyl, Niederalkoxy und/oder Halogen substituiertes Anilinocarbonyl zu nennen.

Bevorzugtes funktionell abgewandeltes Carboxy ist beispielsweise Niederalkoxycarbonyl, wie Methoxy- oder Ethoxycarbonyl, Tri-(C_1-C_4-)-alkylsilyl-(C_1-C_4-)alkoxy-carbonyl, insbesondere Trimethylsilylethoxycarbonyl, oder Cyano. Verbindungen der Formel I, worin R_3 Carboxy ist, können beispielsweise ausgehend von Verbindungen der Formel II, worin Z_1 funktionell abgewandeltes Carboxy bedeutet, in an sich bekannter Weise, beispielsweise durch Hydrolyse, insbesondere in Gegenwart einer Base, im Falle von entsprechenden Tri-(C-C-)alkylsilyl-(C-C-)alkoxy-carbonylderivaten z.B. durch Behandeln mit einem Ammoniumfluorid, wie Tetraniederalkylammonium-, z.B. Tetra-n-butyl-ammonium-fluorid, oder im Falle von Benzyloxycarbonylderivaten durch Hydrogenolyse in Gegenwart eines Hydrierungskatalysators, bzw. ausgehend von solchen Verbindungen der Formel II, worin Z_1 Hydroxymethyl oder Formyl bedeutet, unter Verwendung üblicher Oxidationsmittel, durch Oxidation hergestellt werden.

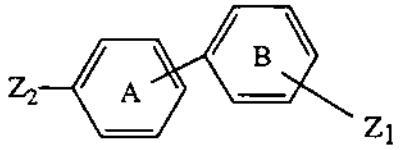
Die Oxidation erfolgt beispielsweise in einem inerten Lösungsmittel, wie einer Niederalkancarbonsäure z.B. Essigsäure, einem Keton, z.B. Aceton, einem Ether, z.B. Tetrahydrofuran, einem heterocyclischen Aromaten, z.B. Pyridin, oder Wasser oder einem Gemisch davon, erforderlichenfalls unter Kühlen oder Erwärmen, z.B. von etwa 0° bis etwa 150°C. Als Oxidationsmittel kommen beispielsweise oxidierende Übergangsmetallverbindungen, insbesondere solche mit Elementen der I., VI., oder VIII. Nebengruppe, in Frage. Als Beispiele seien genannt: Silberverbindungen, wie Silbernitrat, -oxid oder -picolinat, Chromverbindungen, wie Chromtrioxid oder Kaliumdichromat, Manganverbindungen, wie Kaliumpermanganat, Tetrabutylammonium- oder Benzyl(triethyl)ammoniumpermanganat. Weitere Oxidationsmittel sind beispielsweise geeignete Verbindungen mit Elementen der 4. Hauptgruppe, wie Bleidioxid, oder Halogen-Sauerstoff-Verbindungen, wie Natriumiodat oder Kaliumperiodat.

So wird beispielsweise Hydroxymethyl und Formyl zu Carboxy R_3 oxidiert.

Vorzugsweise eignet sich diese Variante zur Herstellung solcher Verbindungen der Formel I, worin die Variablen Bedeutungen haben, die von ungesättigten Resten verschieden sind.

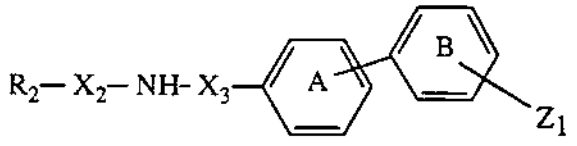
Als Basen kommen beispielsweise Alkalimetall-hydroxide, -hydride, -amide, -alkanolate, -carbonate, -triphenylmethylide, -diniederalkylamide, -aminoalkylamide oder -niederalkylsilylamide, Naphthalinamine, Niederalkylamine, basische Heterocyclen, Ammoniumhydroxide, sowie carbocyclische Amine in Frage. Beispielhaft seien Natriumhydroxid, -hydrid, -amid, Natriummethylat, -ethylat, Kalium-tert-butylat, -carbonat, Lithium-triphenylmethylid, -diisopropylamid, Kalium-3-(aminopropyl)-amid, -bis-(trimethylsilyl)-amid, Dimethylaminonaphthalin, Di- oder Triethylamin, oder Ethyldiisopropylamin, N-Methyl-piperidin, Pyridin, Benzyltrimethyl-ammoniumhydroxid, 1,5-Diazabicyclo[4.3.0]non-5-en (DBN) sowie 1,8-Diaza-bicyclo[5.4.0] undec-7-en (DBU) genannt.

Das Ausgangsmaterial der Formel II ist beispielsweise zugänglich, indem man eine Verbindung der Formel R_2-X_2-NH_2 (IIa) mit einer Verbindung der Formel



(IIb),

worin Z_2 für -X_3-Z_4 und Z_4 für reaktionsfähiges verestertes Hydroxy steht, beispielsweise in Gegenwart einer Base, umsetzt und die so erhältliche Verbindung der Formel



(IIc)

im nächsten Reaktionsschritt mit einer Verbindung der Formel IIIa, z.B. analog Variante b), umsetzt.

Reaktionsfähiges verestertes Hydroxy Z_4 ist insbesondere mit einer starken anorganischen Säure oder organischen Sulfonsäure verestertes Hydroxy, beispielsweise Halogen, wie Chlor, Brom oder Iod, Sulfonyloxy, wie Hydroxysulfony-

loxy, Halogensulfonyloxy, z.B. Fluorsulfonyloxy, gegebenenfalls, z.B. durch Halogen, substituiertes C_1-C_7-Alkansulfonyloxy, z.B. Methan- oder Trifluormethansulfonyloxy, C_5-C_7-Cycloalkansulfonyloxy, z.B. Cyclohexansulfonyloxy, oder gegebenenfalls, z.B. durch C_1-C_7-Alkyl oder Halogen, substituiertes Benzolsulfonyloxy, z.B. p-Brombenzol- oder p-Toluolsulfonyloxy.

Verbindungen der Formel IIb ihrerseits sind beispielsweise aus EP 253,310 bekannt oder können in an sich bekannter Weise hergestellt werden. Verbindungen der Formel (IIa) sind im wesentlichen bekannt oder sind analog an sich bekannter Herstellungsverfahren zugänglich.

Verfahrensvariante b):

Aktivierte Ester von Verbindungen der Formel IIIa sind insbesondere am Verknüpfungskohlenstoffatom des veresterden Restes ungesättigte Ester, z.B. vom Vinylester-Typ, wie Vinylester (erhältlich z.B. durch Umesterung eines entsprechenden Esters mit Vinylacetat; Methode des aktivierten Vinylesters), Carbamoylvinylester (erhältlich z.B. durch Behandeln der entsprechenden Säure mit einem Isoxazoliumreagens; 1,2-Oxazolium- oder Woodward-Methode) oder 1-Niederalkoxyvinylester (erhältlich z.B. durch Behandeln der entsprechenden Säure mit einem Niederalkoxyacetylen; Ethoxyacetylen-Methode), oder Ester vom Amidinotyp, wie N,N'-disubstituierte Amidinoester (erhältlich z.B. durch Behandeln der entsprechenden Säure mit einem geeigneten N,N'-disubstituierten Carbodiimid, z.B. N,N'-Dicyclohexylcarbodiimid; Carbodiimid-Methode) oder N,N-disubstituierte Amidinoester (erhältlich z.B. durch Behandeln der entsprechenden Säure mit einem N,N-disubstituierten Cyanamid; Cyanamid-Methode), geeignete Arylester, insbesondere durch elektronenanziehende Substituenten substituierte Phenylester (erhältlich z.B. durch Behandeln der entsprechenden Säure mit einem geeignet substituierten Phenol, z.B. 4-Nitrophenol, 4-Methylsulfonylphenol, 2,4,5-Trichlorphenol, 2,3,4,5,6-Pentachlorphenol oder 4-Phenyldiazophenol, in Gegenwart eines Kondensationsmittels, wie N,N'-Dicyclohexylcarbodiimid; Methode der aktivierten Arylester), Cyanmethylester (erhältlich z.B. durch Behandeln der entsprechenden Säure mit Chloracetonitril in Gegenwart einer Base; Cyanmethylester-Methode), Thioester, insbesondere gegebenenfalls, z.B. durch Nitro, substituierte Phenylthioester (erhältlich z.B. durch Behandeln der entsprechenden Säure mit gegebenenfalls, z.B. durch Nitro, substituierten Thiophenolen, u.a. mit Hilfe der Anhydrid- oder Carbodiimid-Methode; Methode der aktivierten Thiolester) oder insbesondere Amino- oder Amidoester (erhältlich z.B. durch Behandeln der entsprechenden Säure mit einer N-Hydroxyamino- bzw. N-Hydroxyamido-Verbindung und deren aktivierten Derivaten, z.B. N-Hydroxysuccinimid, N-Hydroxypiperidin, N-Hydroxyphthalimid, N-Hydroxy-5-norbornen- oder norbornan-2,3-dicarbonsäureimid, 1-Hydroxybenzotriazol bzw. Benzotriazol-1-yloxy-phosphoniumsalzen oder Benzotriazol-1-yluroniumsalzen, oder 3-Hydroxy-3,4-dihydro-1,2,3-benzotriazin-4-on, z.B. nach der Anhydrid- oder Carbodiimid-Methode; Methode der aktivierten N-Hydroxyester).

Anhydride von Säuren können symmetrische oder vorzugsweise gemischte Anhydride dieser Säuren sein, z.B. Anhydride mit anorganischen Säuren, wie Säurehalogenide, insbesondere Säurechloride (erhältlich z.B. durch Behandeln der entsprechenden Säure mit Thionylchlorid, Phosphorpentachlorid oder Oxalylchlorid; Säurechloridmethode), Azide (erhältlich z.B. aus einem entsprechenden Säureester über das entsprechende Hydrazid und dessen Behandlung mit salpetriger Säure; Azidmethode), Anhydride mit Kohlensäurehalbestern, z.B. Kohlensäureniederalkylhalbestern (erhältlich z.B. durch Behandeln der entsprechenden Säure mit Chlorameisensäureniederalkylestern oder mit einem 1-Niederalkoxycarbonyl-2-niederalkoxy-1,2-dihydrochinolin, z.B. 1-Ethoxycarbonyl-2-ethoxy-1,2-dihydrochinolin; Methode der gemischten O-Alkylkohlensäureanhydride), Anhydride mit dihalogenierter, insbesondere dichlorierter Phosphorsäure (erhältlich z.B. durch Behandeln der entsprechenden Säure mit Phosphoroxychlorid; Phosphoroxychlorid-methode), Anhydride mit anderen Phosphorsäurederivaten (z.B. solchen, die man mit Phenyl-N-phenylphosphoramidochloridat erhalten kann) oder mit Phosphorigsäurederivaten, oder Anhydride mit organischen Säuren, wie gemischte Anhydride mit organischen Carbonsäuren (erhältlich z.B. durch Behandeln der entsprechenden Säure mit einem gegebenenfalls substituierten Niederalkan- oder Phenylniederalkancarbonsäurehalogenid, z.B. Phenylessigsäure-, Pivalinsäure- oder Trifluoressigsäurechlorid; Methode der gemischten Carbonsäureanhydride) oder mit organischen Sulfonsäuren (erhältlich z.B. durch Behandeln eines Salzes, wie eines Alkalimetallsalzes, der entsprechenden Säure mit einem geeigneten organischen Sulfonsäurehalogenid, wie Niederalkan- oder Aryl-, z.B. Methan- oder p-Toluolsulfonsäurechlorid; Methode der gemischten Sulfonsäureanhydride), sowie symmetrische Anhydride (erhältlich z.B. durch Kondensation der entsprechenden Säure in Gegenwart eines Carbodiimids oder von 1-Diethylaminopropin; Methode der symmetrischen Anhydride).

Geeignete cyclische Amide sind insbesondere Amide mit fünfgliedrigen Diazacyclen aromatischen Charakters, wie Amide mit Imidazolen, z.B. Imidazol (erhältlich z.B. durch Behandeln der entsprechenden Säure mit N,N'-Carbonyldiimidazol; Imidazol-Methode), oder Pyrazolen, z.B. 3,5-Dimethylpyrazol (erhältlich z.B. über das Säurehydrazid durch Behandeln mit Acetylaceton; Pyrazolid-Methode).

Die Kondensation zur Herstellung der Amidbindung kann in an sich bekannter Weise durchgeführt werden, beispielsweise wie in Standardwerken, wie Houben-Weyl, "Methoden der organischen Chemie", 4. Auflage, Band 15/II, Georg Thieme Verlag, Stuttgart 1974, "The Peptides" (Herausg. E. Gross und J. Meienhofer), Band 1 und 2, Academic

Press, London und New York, 1979/1980, oder M. Bodanszky, "Principles of Peptide Synthesis", Springer-Verlag, Berlin 1984, beschrieben.

Die Kondensation kann in Gegenwart eines der üblichen Kondensationsmittel durchgeführt werden. Uebliche Kondensationsmittel sind z.B. Carbodiimide, beispielsweise Diethyl-, Dipropyl-, N-Ethyl-N'-(3-dimethylaminopropyl)-carbodiimid oder insbesondere Dicyclohexylcarbodiimid, ferner geeignete Carbonylverbindungen, beispielsweise Carbonyldiimidazol, 1,2-Oxazoliumverbindungen, z.B. 2-Ethyl-5-phenyl-1,2-oxazolium-3'-sulfonat und 2-tert-Butyl-5-methylisoxazoliumperchlorat, oder eine geeignete Acylaminoverbindung, z.B. 2-Ethoxy-1-ethoxycarbonyl- 1,2-dihydrochinolin, ferner aktivierte Phosphorsäurederivate, z.B. Diphenylphosphorylazid, Diethylphosphorylcyanid, Phenyl-N-phenylphosphoramidochloridat, Bis-(2-oxo-3-oxazolidinyl)-phosphinsäurechlorid oder 1-Benzotriazolyloxy-tris-(dimethylamino)-phosphonium-hexafluorophosp hat.

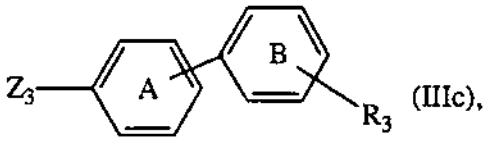
Gewünschtenfalls wird eine organische Base zugegeben, z.B. ein Triniederalkylamin mit voluminösen Resten, z.B. Ethyldiisopropylamin, oder eine heterocyclische Base, z.B. Pyridin, 4-Dimethylaminopyridin oder bevorzugt N-Methylmorpholin.

Die Kondensation von Säureanhydriden mit Aminen kann z.B. in Gegenwart von anorganischen Carbonaten, z.B. Alkalimetallcarbonaten oder -hydrogencarbonaten, wie Natrium- oder Kaliumcarbonat oder -hydrogencarbonat (üblicherweise zusammen mit einem Sulfat), erfolgen.

Die Kondensation wird vorzugsweise in einem inerten, polaren, aprotischen, vorzugsweise wasserfreien, Lösungsmittel oder Lösungsmittelgemisch durchgeführt, beispielsweise in einem Carbonsäureamid, z.B. Formamid oder Dimethylformamid, einem halogenierten Kohlenwasserstoff, z.B. Methylenchlorid, Tetrachlorkohlenstoff oder Chlorbenzol, einem Keton, z.B. Aceton, cyclischen Ether, z.B. Tetrahydrofuran, einem Ester, z.B. Essigsäureethylester, oder einem Nitril, z.B. Acetonitril, oder in Mischungen davon, gegebenenfalls bei erniedrigter oder erhöhter Temperatur, z.B. in einem Temperaturbereich von etwa -40°C bis etwa +100°C, bevorzugt von etwa -10°C bis etwa +50°C, und gegebenenfalls unter Inertgas-, z.B. Stickstoffatmosphäre.

Reaktionsfähige Säurederivate können auch in situ gebildet werden.

Das Ausgangsmaterial der Formel IIIb kann man beispielsweise herstellen, indem man eine Verbindung der Formel IIa mit einer Verbindung der Formel



(IIIc),

worin Z_3 -X_3-Z_4 und Z_4 reaktionsfähiges verestertes Hydroxy bedeutet, insbesondere in Gegenwart einer der vorstehend aufgeführten Basen, umsetzt. Zur Herstellung von Verbindungen der Formel IIIb, worin X_3 -CH_2- bedeutet, geht man z.B. von Verbindungen der Formel IIa aus und setzt diese mit Verbindungen der Formel IIIc um, worin Z_3 Formyl bedeutet. Die so erhältlichen Schiff'schen Basen werden anschliessend mit Hilfe eines Reduktionsmittels, wie Natriumcyanoborhydrid, reduziert.

Reaktionsfähiges verestertes Hydroxy Z_4 ist insbesondere mit einer starken anorganischen Säure oder organischen Sulfonsäure verestertes Hydroxy, beispielsweise Halogen, wie Chlor, Brom oder Iod, Sulfonyloxy, wie Hydroxysulfonyloxy, Halogensulfonyloxy, z.B. Fluorsulfonyloxy, gegebenenfalls, z.B. durch Halogen, substituiertes C_1-C_7-Alkansulfonyloxy, z.B. Methan-oder Trifluormethansulfonyloxy, C_5-C_7-Cycloalkansulfonyloxy, z.B. Cyclohexansulfonyloxy, oder gegebenenfalls, z.B. durch C_1-C_7-Alkyl oder Halogen, substituiertes Benzolsulfonyloxy, z.B. p-Brombenzol- oder p-Toluolsulfonyloxy.

Eine verfahrensgemäss erhältliche erfindungsgemässe Verbindung kann in an sich bekannter Weise in eine andere erfindungsgemässe Verbindung übergeführt werden.

Eine Hydroxy aufweisende erfindungsgemässe Verbindung kann nach an sich bekannten Methoden verethert werden. Die Veretherung kann z.B. mit einem Alkohol, wie gegebenenfalls substituiertem Niederalkanol, oder einem reaktionsfähigen Ester desselben erfolgen. Als reaktionsfähige Ester der gewünschten Alkohole kommen beispielsweise solche mit starken anorganischen oder organischen Säuren in Frage, wie entsprechende Halogenide, Sulfate, Niederalkansulfonate oder gegebenenfalls substituierte Benzolsulfonate, z.B. Chloride, Bromide, Iodide, Methan-, Benzol- oder p-Toluol-sulfonate, in Betracht. Die Veretherung kann z.B. in Gegenwart einer Base, eines Alkalimetallhydrids, -hydroxids, -carbonats oder eines Amins, erfolgen. Umgekehrt können entsprechende Ether, wie Niederalkoxyverbindungen, z.B. mittels starker Säuren, wie Mineralsäuren, z.B. den Halogenwasserstoffsäuren Brom- oder Iodwasserstoffsäure, die vorteilhaft in Form von Pyridiniumhalogeniden vorliegen können, oder mittels Lewissäuren, z.B. Halogeniden von Elementen der 3. Hauptgruppe oder der entsprechenden Nebengruppen, gespalten werden. Diese Umsetzungen können, falls erforderlich, unter Kühlen oder Erwärmen, z.B. einem Temperaturbereich von etwa -20° bis etwa 100°C, in

An- oder Abwesenheit eines Lösungs- oder Verdünnungsmittels, unter Inertgas und/oder unter Druck und gegebenenfalls in einem geschlossenen Gefäss, durchgeführt werden.

Hydroxymethylgruppen aufweisende erfindungsgemässe Verbindungen können beispielsweise ausgehend von entsprechenden Carboxy oder verestertes Carboxy aufweisenden Verbindungen hergestellt werden, wobei entsprechende Verbindungen in an sich bekannter Weise reduziert werden, z.B. durch Reduktion mit einem gegebenenfalls komplexen Hydrid, wie einem Hydrid gebildet aus einem Element der 1. und 3. Hauptgruppe des Periodensystems der Elemente, z.B. Boranat oder Alanat, beispielsweise Lithiumborhydrid, Lithium-, Diisobutylaluminiumhydrid (gegebenenfalls ist ein nachgelagerter Reduktionsschritt unter Verwendung von Alkalimetall-, wie Natriumcyanoborhydrid, erforderlich), ferner Diboran.

Falls ein aromatischer Strukturbestandteil durch (Nieder-)Alkylthio substituiert ist (in $S(O)_m$-R steht m für 0), kann man dieses auf übliche Weise zu entsprechendem (Nieder-)-Alkansulfinyl bzw. - sulfonyl oxidieren. Als geeignetes Oxidationsmittel für die Oxidation zur Sulfoxidstufe kommen beispielsweise anorganische Persäuren, wie Persäuren von Mineralsäuren, z.B. Periodsäure oder Perschwefelsäure, organische Persäuren, wie entsprechende Percarbon- oder Persulfonsäuren, z.B. Perameisen-, Peressig-, Trifluorperessig-bzw. Perbenzoesäure oder p-Toluolpersulfonsäure, oder Gemische aus Wasserstoffperoxid und Säuren, z.B. Gemisch aus Wasserstoffperoxid mit Essigsäure, in Betracht.

Häufig führt man die Oxidation in Gegenwart von geeigneten Katalysatoren durch, wobei als Katalysatoren geeignete Säuren, wie gegebenenfalls substituierte Carbonsäuren, z.B. Essigsäure oder Trifluoressigsäure, oder Übergangsmetalloxide, wie Oxide von Elementen der VII. Nebengruppe, z.B. Vanadium-, Molybdän- oder Wolframoxid, zu nennen sind. Die Oxidation wird unter milden Bedingungen, z.B. bei Temperaturen von etwa -50° bis etwa +100°C, durchgeführt.

Die Oxidation zur Sulfonstufe kann man auch mit Distickstofftetroxid als Katalysator in Gegenwart von Sauerstoff bei tiefen Temperaturen entsprechend durchführen, ebenso wie die direkte Oxidation des (Nieder-)Alkylthio zum (Nieder-)Alkansulfonyl. Jedoch setzt man hierbei üblicherweise das Oxidationsmittel im Überschuss ein.

Weist eine der Variablen Amino auf, können entsprechende Verbindungen der Formel I, ihre Tautomeren oder Salze in an sich bekannter Weise N-alkyliert werden; ebenso können Carbamoyl bzw. Carbamoyl aufweisende Reste N-alkyliert werden. Die (Aryl-)-Alkylierung erfolgt z.B. mit einem reaktiven Ester eines (Aryl-)C_1-C_7-Alkylhalogenids, z.B. -bromid oder -iodid, (Aryl-)C_1-C_7-Alkylsulfonat, z.B. methansulfonat oder -p-toluolsulfonat, oder einem Di-C_1-C_7-alkylsulfat, z.B. Dimethylsulfat, vorzugsweise unter basischen Bedingungen, wie in Gegenwart von Natronlauge oder Kalilauge, und vorteilhaft eines Phasentransfer-Katalysators, wie Tetrabutylammoniumbromid oder Benzyltrimethylammoniumchlorid, wobei indes stärker basische Kondensationsmittel, wie Alkalimetallamide, -hydride oder -alkoholate, z.B. Natriumamid, Natriumhydrid oder Natriumethanolat, erforderlich sein können. Ebenso kann Amino in an sich bekannter Weise, z.B analog Variante b), acyliert werden.

In Verbindungen der Formel I, die als Substituenten eine veresterte oder amidierte Carboxygruppe aufweisen, kann man eine solche Gruppe z.B. mittels Hydrolyse, z.B. in Gegenwart eines basischen Mittels, oder eines sauren Mittels, wie einer Mineralsäure, in eine freie Carboxygruppe überführen. Tert-Butyloxycarbonyl beispielsweise kann weiterhin z.B. in an sich bekannter Weise, wie durch Behandeln mit Trihalogen-, wie Trifluoressigsäure, und Benzyloxycarbonyl z.B. durch katalytische Hydrierung in Gegenwart eines Hydrierungskatakysators, z.B. in der nachstehend beschriebenen Weise, in Carboxy überführt werden.

Ferner kann man in Verbindungen der Formel I, die als Substituenten eine Carboxygruppe aufweisen, insbesondere sofern R_3 von Carboxy verschieden ist, diese z.B. durch Behandeln mit einem Alkohol, wie einem Niederalkanol, in Gegenwart eines geeigneten Veresterungsmittels, wie eines sauren Reagens, z.B. einer anorganischen oder organischen Säure oder einer Lewissäure, z.B. Zinkchlorid, oder eines wasserbindenden Kondensationsmittels, z.B. eines Carbodiimids, wie N,N'-Dicyclohexyl-carbodiimid, oder durch Behandeln mit einem Diazoreagens, wie mit einem Diazoniederalkan, z.B. Diazomethan, in eine veresterte Carboxygruppe überführen. Diese kann man auch erhalten, wenn man Verbindungen der Formel I, worin die Carboxygruppe in freier Form oder in Salz-, wie Ammonium- oder Metall-, z.B. Alkalimetall-, wie Natrium- oder Kaliumsalzform vorliegt, mit einem reaktionsfähigen Ester eines (C_1-C_7-)Alkylhalogenid, z.B. Methyl- oder Ethyl-bromid oder -iodid, oder einem organischen Sulfonsäureester, wie einem entsprechenden (C_1-C_7-)Alkylester, z.B. Methansulfonsäure- oder p-Toluolsulfonsäuremethylester oder -ethylester, behandelt.

Verbindungen der Formel I, die als Substituenten eine veresterte Carboxygruppe aufweisen, kann man durch Umesterung, z.B. durch Behandeln mit einem Alkohol, üblicherweise einem höheren als dem der veresterten Carboxygruppe im Ausgangsmaterial entsprechenden Alkohol, in Gegenwart eines geeigneten Umesterungsmittels, wie eines basischen Mittels, z.B. eines Alkalimetall-(C_1-C_7-)alkanoats, -(C_1-C_7-)alkanolats oder -cyanids, wie Natriumacetat, -methanolat, -ethylat, -tert-butanolat oder -cyanid, oder eines geeigneten sauren Mittels, gegebenenfalls unter Entfernung des entstehenden Alkohols, z.B. durch Destillation, in andere Esterverbindungen der Formel I umestern. Man kann auch von entsprechenden, sogenannten aktivierten Estern der Formel I ausgehen, die als Substituenten eine aktivierte veresterte Carboxygruppe aufweisen (siehe unten), und diese durch Behandeln mit einem (C_1-C_7-)Alkanol, in einen anderen Ester umwandeln.

Man kann in Verbindungen der Formel I, die als Substituenten die Carboxylgruppe enthalten, diese auch zuerst in ein reaktionsfähiges Derivat, wie ein Anhydrid, inkl. ein gemischtes Anhydrid, wie ein Säurehalogenid, z.B. -chlorid (z.B. durch Behandeln mit einem Thionylhalogenid, z.B. -chlorid), oder ein Anyhdrid mit einem Ameisensäureester, z.B. -(C_1-

C_7-) alkylester (z.B. durch Behandeln eines Salzes, wie eines Ammonium- oder Alkalimetallsalzes, mit einem Halogen-, wie Chlorameisensäureester, wie (C_1-C_7-)Alkyl-ester), oder in einen aktivierten Ester, wie Cyanmethyl-, Nitrophenyl-, z.B. 4-Nitrophenyl-, oder Polyhalogenphenyl-, z.B. Pentachlorphenylester (z.B. durch Behandeln mit einer entsprechenden Hydroxyverbindung in Gegenwart eines geeigneten Kondensationsmittels, wie N,N'-Dicyclohexyl-carbodiimid) überführen, und ein solches reaktionsfähiges Derivat dann mit einem Amin umsetzen und so zu Amidverbindungen der Formel I gelangen, die als Substituenten eine amidierte Carboxygruppe aufweisen. Dabei kann man diese direkt oder über Zwischenverbindungen erhalten; so kann man z.B. einen aktivierten Ester, wie einen 4-Nitrophenylester, einer Verbindung der Formel I mit einer Carboxygruppe zuerst mit einem 1-unsubstituierten Imidazol umsetzen und die so entstandene 1-Imidazolylcarbonylverbindung mit einem Amin in Reaktion bringen. Man kann aber auch andere, nicht-aktivierte Ester, wie (C_1-C_7-)Alkylester von Verbindungen der Formel I, die als Substituenten z.B. (C_2-C_8-)Alkoxycarbonyl aufweisen, mit Aminen zur Reaktion bringen.

Weist ein aromatischer Ring als Substituenten ein Wasserstoffatom auf, so kann dieses mit Hilfe eines Halogenierungsmittels in üblicher Weise durch ein Halogenatom ersetzt, z.B. mit Brom, Hypobromsäure, Acylhypobromite oder andere organische Bromverbindungen, z.B. N-Bromsuccinimid, N-Bromacetamid, N-Bromphthalimid, Pyridiniumperbromid, Dioxandibromid, 1,3-Dibrom-5,5-dimethylhydantoin, 2,4,4,6-Tetrabrom-2,5-cyclohexandien-1-on, bromiert bzw. mit elementarem Chlor, z.B. in einem halogenierten Kohlenwasserstoff, wie Chloroform, und unter Kühlen, z.B. bis auf etwa -10° bis etwa +100°C, chloriert werden.

Enthält ein aromatischer Ring in den erfindungsgemässen Verbindungen eine Aminogruppe, so kann diese in üblicher Weise diazotiert werden, z.B. durch Behandeln mit einem Nitrit, z.B. Natriumnitrit, in Gegenwart einer geeigneten Protonsäure, z.B. Mineralsäure, wobei die Reaktionstemperatur vorteilhaft unter etwa 5°C gehalten wird.

Die so erhältliche, in Salzform vorliegende Diazoniumgruppe kann man nach analogen Verfahren beispielsweise wie folgt substituieren: durch die Hydroxygruppe analog der Phenolverkochung in Gegenwart von Wasser, durch eine Alkoxygruppe durch Behandeln mit einem entsprechenden Alkohol, wobei Energie zugeführt werden muss; durch das Fluoratom analog der Schiemann-Reaktion bei der Thermolyse von entsprechenden Diazoniumtetrafluorboraten; durch die Halogenatome Chlor, Brom oder Iod sowie die Cyanogruppe analog der Sandmeyer-Reaktion bei der Umsetzung mit entsprechenden Cu(I)-Salzen, zunächst unter Kühlen, z.B. auf etwa unter 5°C, und anschliessendem Erhitzen, z.B. auf etwa 60° bis etwa 150°C.

Enthalten die Verbindungen der Formel I ungesättigte Reste, wie (Nieder-) Alkenyl oder (Nieder-)Alkinylgruppierungen, können diese in an sich bekannter Weise in gesättigte Reste überführt werden. So erfolgt beispielsweise die Hydrierung von Mehrfachbindungen durch katalytische Hydrierung in Gegenwart von Hydrierungskatalysatoren, wobei hierfür z.B. Nickel, wie Raney-Nickel, sowie Edelmetalle bzw. deren Derivate, z.B. Oxide, geeignet sind, wie Palladium, Platinoxid, die gegebenenfalls auf Trägermaterialien, z.B. auf Kohle oder Calciumcarbonat, aufgezogen sein können. Die Hydrierung kann vorzugsweise bei Drucken zwischen 1 und etwa 100 at und bei Raumtemperatur zwischen etwa -80° bis etwa 200°C, vor allem zwischen Raumtemperatur und etwa 100°C, durchgeführt werden. Die Reaktion erfolgt zweckmässig in einem Lösungsmittel, wie Wasser, einem Niederalkanol, z.B. Ethanol, Isopropanol oder n-Butanol, einem Ether, z.B. Dioxan, oder einer Niederalkancarbonsäure, z.B. Essigsäure.

Weiterhin kann in Verbindungen der Formel I, worin z.B. einer der Reste R_1 und/oder X_2 Halogen, wie Chlor, aufweist, Halogen durch Umsetzung mit einem gegebenenfalls substituierten Amin, einem Alkohol oder Mercaptan ausgetauscht werden.

Die Erfindung betrifft insbesondere die in den Beispielen beschriebenen Verfahren.

Salze von Verbindungen der Formel I können in an sich bekannter Weise hergestellt werden. So erhält man beispielsweise Säureadditionssalze von Verbindungen der Formel I durch Behandeln mit einer Säure oder einem geeigneten Ionenaustauscherreagenz. Salze können in üblicher Weise in die freien Verbindungen überführt werden, Säureadditionssalze z.B. durch Behandeln mit einem geeigneten basischen Mittel.

Je nach Verfahrensweise bzw. Reaktionsbedingungen können die erfindungsgemässen Verbindungen mit salzbildenden, insbesondere basischen Eigenschaften, in freier Form oder bevorzugt in Form von Salzen erhalten werden.

Infolge der engen Beziehung zwischen der neuen Verbindung in freier Form und in Form ihrer Salze sind im Vorausgegangenen und nachfolgend unter der freien Verbindung oder ihren Salzen sinn- und zweckgemäss gegebenenfalls auch die entsprechenden Salze bzw. die freie Verbindung zu verstehen.

Die neuen Verbindungen einschliesslich ihrer Salze von salzbildenden Verbindungen können auch in Form ihrer Hydrate erhalten werden oder andere zur Kristallisation verwendete Lösungsmittel einschliessen.

Die neuen Verbindungen können, je nach der Wahl der Ausgangsstoffe und Arbeitsweisen, in Form eines der möglichen Isomeren oder als Gemische derselben, z.B. je nach der Anzahl der asymmetrischen Kohlenstoffatome, als reine optische Isomere, wie Antipoden, oder als Isomerengemische, wie Racemate, Diastereoisomerengemische oder Racematgemische, vorliegen. Beispielsweise weisen Verbindungen der Formel Ia, worin X_2 für die Gruppe der Formel Ib, in welcher q für 1 steht und X_4 und X_5 unterschiedliche Bedeutungen haben, steht, ein asymmetrisches C-Atom auf. In entsprechenden Verbindungen der Formel I, worin R_2 beispielsweise gegebenenfalls verestertes oder amidiertes Carboxy oder gegebenenfalls verethertes Hydroxy bedeutet, weist das betreffende asymmetrische C-Atom der Partialstruktur der Formel -X_2-R_2 vorzugsweise die S-Konfiguration auf.

Erhaltene Racemate und Diastereomerengemische können auf Grund der physikalischchemischen Unterschiede der Bestandteile in bekannter Weise in die reinen Isomeren oder Racemate aufgetrennt werden, beispielsweise durch fraktionierte Kristallisation. Erhaltene Racemate lassen sich ferner nach bekannten Methoden in die optischen Antipoden zerlegen, beispielsweise durch Umkristallisation aus einem optisch aktiven Lösungsmittel, Chromatographie an chiralen Adsorbentien, mit Hilfe von geeigneten Mikroorganismen, durch Spaltung mit spezifischen, immobilisierten Enzymen, über die Bildung von Einschlussverbindungen, z.B. unter Verwendung chiraler Kronenether, wobei nur ein Enantiomeres komplexiert wird, oder durch Überführung in diastereomere Salze, z.B. durch Umsetzung eines basischen Endstoffracemats mit einer optisch aktiven Säure, wie Carbonsäure, z.B. Wein- oder Apfelsäure, oder Sulfonsäure, z.B. Campher-sulfonsäure, und Trennung des auf diese Weise erhaltenen Diastereomerengemisches, z.B. auf Grund ihrer verschiedenen Löslichkeiten, in die Diastereomeren, aus denen das gewünschte Enantiomere durch Einwirkung geeigneter Mittel freigesetzt werden kann. Vorteilhaft isoliert man das wirksamere Enantiomere.

Die Erfindung betrifft auch diejenigen Ausführungsformen des Verfahrens, nach denen man von einer auf irgendeiner Stufe des Verfahrens als Zwischenprodukt erhältlichen Verbindung ausgeht und die fehlenden Schritte durchführt oder einen Ausgangsstoff in Form eines Derivates bzw. Salzes und/oder seiner Racemate bzw. Antipoden verwendet oder insbesondere unter den Reaktionsbedingungen bildet.

Beim Verfahren der vorliegenden Erfindung werden vorzugsweise solche Ausgangsstoffe verwendet, welche zu den eingangs als besonders wertvoll geschilderten Verbindungen führen. Neue Ausgangsstoffe, die speziell für die Herstellung der erfindungsgemässen Verbindungen entwickelt wurden, ihre Verwendung und Verfahren zu ihrer Herstellung bilden ebenfalls einen Gegenstand der Erfindung, wobei die Variablen R, R_1, R_2, R_3, X_1, X_2, X_3, X_4, X_5, m, p, q, und r die für die jeweils bevorzugten Verbindungsgruppen der Formel I angegebenen Bedeutungen haben. Insbesondere sind Verbindungen der Formel IIa, ihre Tautomeren und Salze, worin Z_1 Cyano bedeutet, als Ausgangsmaterial bevorzugt.

Die Erfindung betrifft ebenfalls die Verwendung der Verbindungen der Formel I oder von pharmazeutisch verwendbaren Salzen von solchen Verbindungen mit salzbildenden Eigenschaften, insbesondere als pharmakologische, in erster Linie Angiotensin-II-antagonisierende Wirksubstanzen. Dabei kann man sie, vorzugsweise in Form von pharmazeutisch verwendbaren Zubereitungen, in einem Verfahren zur prophylaktischen und/oder therapeutischen Behandlung des tierischen oder menschlichen Körpers, insbesondere als Angiotensin-II-Antagonisten, verwenden.

Die Erfindung betrifft gleichfalls pharmazeutische Präparate, die die erfindungsgemässen Verbindungen oder pharmazeutisch verwendbare Salze derselben als Wirkstoffe enthalten, sowie Verfahren zu ihrer Herstellung.

Bei den erfindungsgemässen pharmazeutischen Präparaten, welche die erfindungsgemässe Verbindung oder pharmazeutisch verwendbare Salze davon enthalten, handelt es sich um solche zur enteralen, wie oralen, ferner rektalen, und parenteralen Verabreichung an Warmblüter(n), wobei der pharmakologische Wirkstoff allein oder zusammen mit einem pharmazeutisch anwendbaren Trägermaterial enthalten ist. Die tägliche Dosierung des Wirkstoffes hängt von dem Alter und dem individuellen Zustand sowie von der Applikationsweise ab.

Die neuen pharmazeutischen Präparate enthalten z.B. von etwa 10 % bis etwa 80 %, vorzugsweise von etwa 20 % bis etwa 60 %, des Wirkstoffs. Erfindungsgemässe pharmazeutische Präparate zur enteralen bzw. parenteralen Verabreichung sind z.B. solche in Dosiseinheitsformen, wie Dragées, Tabletten, Kapseln oder Suppositorien, ferner Ampullen. Diese werden in an sich bekannter Weise, z.B. mittels konventioneller Misch-, Granulier-, Dragier-, Lösungs- oder Lyophilisierungsverfahren hergestellt. So kann man pharmazeutische Präparate zur oralen Anwendung erhalten, indem man den Wirkstoff mit festen Trägerstoffen kombiniert, ein erhaltenes Gemisch gegebenenfalls granuliert, und das Gemisch bzw. Granulat, wenn erwünscht oder notwendig, nach Zugabe von geeigneten Hilfsstoffen zu Tabletten oder Dragée-Kernen verarbeitet.

Geeignete Trägerstoffe sind insbesondere Füllstoffe, wie Zucker, z.B. Lactose, Saccharose, Mannit oder Sorbit, Cellulosepräparate und/oder Calciumphosphate, z.B. Tricalciumphosphat oder Calciumhydrogenphosphat, ferner Bindemittel, wie Stärkekleister, unter Verwendung z.B. von Mais-, Weizen-, Reis- oder Kartoffelstärke, Gelatine, Tragakanth, Methylcellulose und/oder Polyvinylpyrrolidon, wenn erwünscht, Sprengmittel, wie die obengenannten Stärken, ferner Carboxymethylstärke, quervernetztes Polyvinylpyrrolidon, Agar, Alginsäure oder ein Salz davon, wie Natriumalginat, Hilfsmittel sind in erster Linie Fliess-, Fliessregulier- und Schmiermittel, z.B. Kieselsäure, Talk, Stearinsäure oder Salze davon, wie Magnesium- oder Calciumstearat, und/oder Polyethylenglykol. Dragée-Kerne werden mit geeigneten, gegebenenfalls Magensaftresistenten Überzügen versehen, wobei man u.a. konzentrierte Zuckerlösungen, welche gegebenenfalls arabischen Gummi, Talk, Polyvinylpyrrolidon, Polyethylenglykol und/oder Titandioxid enthalten, Lacklösungen in geeigneten organischen Lösungsmitteln oder Lösungsmittelgemische oder, zur Herstellung von Magensaft-resistenten Überzügen, Lösungen von geeigneten Celluloseprapäraten, wie Acetylcellulosephthalat oder Hydroxypropylmethylcellulosephthalat, verwendet. Den Tabletten oder Dragée-Überzügen können Farbstoffe oder Pigmente, z.B. zur Identifizierung oder zur Kennzeichnung verschiedener Wirkstoffdosen, beigefügt werden.

Weitere oral anwendbare pharmazeutische Präparate sind Steckkapseln aus Gelatine, sowie weiche, geschlossene Kapseln aus Gelatine und einem Weichmacher, wie Glycerin oder Sorbitol. Die Steckkapseln können den Wirkstoff in Form eines Granulates, z.B. im Gemisch mit Füllstoffen, wie Lactose, Bindemitteln, wie Stärken, und/oder Gleitmitteln, wie Talk oder Magnesiumstearat, und gegebenenfalls Stabilisatoren, enthalten. In weichen Kapseln ist der Wirkstoff

vorzugsweise in geeigneten Flüssigkeiten, wie fetten Ölen, Paraffinöl oder flüssigen Polyethylenglykolen, gelöst oder suspendiert, wobei ebenfalls Stabilisatoren zugefügt sein können.

Als rektal anwendbare pharmazeutische Präparate kommen z.B. Suppositorien in Betracht, welche aus einer Kombination des Wirkstoffs mit einer Suppositoriengrundmasse bestehen. Als Suppositoriengrundmasse eignen sich z.B. natürliche oder synthetisch Triglyceride, Paraffinkohlenwasserstoffe, Polyethylenglyckole oder höhere Alkanole. Ferner können auch Gelatine-Rektalkapseln verwendet werden, die eine Kombination des Wirkstoffs mit einem Grundmassenstoff enthalten. Als Grundmassenstoffe kommen z.B. flüssige Triglyceride, Polyethylenglykole oder Paraffinkohlenwasserstoffe in Frage.

Zur parenteralen Verabreichung eignen sich in erster Linie wässrige Lösungen eines Wirkstoffs in wässerlöslicher Form, z.B. eines wasserlöslichen Salzes, ferner Suspensionen des Wirkstoffs, wie entsprechende ölige Injektionssuspensionen, wobei man geeignete lipophile Lösungsmittel oder Vehikel, wie fette Öle, z.B. Sesamöl, oder synthetische Fettsäureester, z.B. Ethyloleat oder Triglyceride, verwendet oder wässrige Injektionssuspensionen, welche viskositätserhöhende Stoffe, z.B. Natrium-carboxymethylcellulose, Sorbit und/oder Dextran, und gegebenenfalls auch Stabilisatoren enthalten.

Die Dosierung des Wirkstoffes hängt von der Warmblüter-Spezies, dem Alter und dem individuellen Zustand sowie der Applikationsweise ab. Im Normalfall ist für einen etwa 75 kg schweren Patienten bei oraler Applikation eine ungefähre Tagesdosis von etwa 10 mg bis etwa 250 mg zu veranschlagen.

Die nachfolgenden Beispiele illustrieren die oben beschriebene Erfindung. Temperaturen werden in Celsiusgraden angegeben. Folgende Laufmittelsysteme für die Chromatographie werden in den nachfolgenden Beispielen verwendet:

Neutrale Systeme

N1 Ethylacetat/Hexan	2:1
N2 Ethylacetat/Hexan	1:1
N3 Ethylacetat/Hexan	1:2
N4 Ethylacetat/Hexan	1:4
N5 Ethylacetat/Hexan	1:9
N6 CH_2Cl_2/Methanol	95:5
N7 CH_2Cl_2/Methanol	9:1
N8 CH_2Cl_2/Methanol	4:1
N9 CH_2Cl_2/Methanol	2:1
N10 CH_2Cl_2/Methanol	1:1

Basische Systeme

B1 CH_2Cl_2/Methanol/konzentriertes NH_3	40:10:1
B2 CH_2Cl_2/Methanol/konzentriertes NH_3	50:10:1
B3 CH_2Cl_2/Methanol/konzentriertes NH_3	60:10:1
B4 CH_2Cl_2/Methanol/konzentriertes NH_3	80:10:1
B5 CH_2Cl_2/Methanol/konzentriertes NH_3	100:10:1
B6 Ethylacetat/Ethanol/konzentriertes NH_3	24:12:4
B7 Toluol/Isopropanol/konzentriertes NH_3	170:30:2

Saure Systeme

S1 CH_2Cl_2/Methanol/Wasser/Essigsäure	150:50:10:1
S2 Toluol/Isopropanol/Essigsäure	170:30:2

Mit basischen (d. h. konzentriertes Ammoniak enthaltenden) Laufmittelsystemen chromatographierte Produkte mit sauren funktionellen Gruppen werden nach der Chromatographie in einem organischen Lösungsmittel, z. B. in Diethylether, Essigsäureethylester oder Dichlormethan, aufgenommen. Sodann wird dieses organische Gemisch nacheinander mit (ca. 1 N-) Salzsäure, Wasser und gesättigter Natriumchloridlösung gewaschen und die organische Phase getrocknet und eingedampft. Auf diese Weise erhält man das Produkt mit der freigesetzten sauren funktionellen Gruppe.

Beispiel 1: N-Carboxymethyl-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin

1,2 g N-(2'-Cyanobiphenyl-4-yl-methyl)-N-methoxycarbonylmethyl-N-pentanoyl-amin, 2,18 g Tributylzinnazid und 40 ml Xylol werden 24 Stunden unter Rückfluss erhitzt. Dann wird das Reaktionsgemisch eingeengt, der Rückstand mit 1 N-Natronlauge versetzt, dieses Gemisch 10 Stunden bei Raumtemperatur gerührt und dann mit Diethylether extrahiert, die wässrige Phase sauer gestellt und anschliessend mit Diethylether extrahiert, diese zweite etherische Phase mit Sole gewaschen, getrocknet und eingeengt und das Rohprodukt mittels Flashchromatographie (100 g Kieselgel; System B1) gereinigt. Amorphes Produkt [R_f-Wert: 0,29 (CH_2Cl_2/Methanol/konzentriertes Ammoniak = 30:10:1)].

Das Ausgangsmaterial kann beispielsweise wie folgt erhalten werden:

a) 2'-Cyano-4-formyl-biphenyl

250 g 4-Brommethyl-2'-cyano-biphenyl, 150 g Natriumacetat und 2,5l Eisessig werden über Nacht unter Rückfluss erhitzt. Das Gemisch wird anschliessend im Hochvakuum eingeengt und der Rückstand in Ethylacetat aufgenommen. Man extrahiert nacheinander mit Wasser, Natriumhydrogencarbonatlösung und Sole und dampft am Rotationsverdampfer ein. Das Rohprodukt wird in 3,1 l Ethanol gelöst, die Lösung mit 430 ml 2 N-Natronlauge versetzt, das Gemisch über Nacht bei Raumtemperatur gerührt und dann eingeengt und der Rückstand in Ethylacetat aufgenommen. Das Gemisch wird nacheinander mit Wasser und Sodalösung gewaschen und eingeengt. Der Rückstand wird in Hexan suspendiert, die Suspension abgenutscht und der Filterkuchen gewaschen und 20 Stunden bei 60° im Hochvakuum getrocknet. Man erhält so das 2'-Cyano-4-hydroxymethyl-biphenyl in Form eines weissen Pulvers [^{1}H-NMR (DMSO-d_6): 4,58 ppm (d, 2 H); 5,3 ppm (t, 1 H); 7,6 bis 8,0 ppm (m, 8 H)].

Eine Lösung von 53 ml Oxalylchlorid in 2l Dichlormethan wird auf - 60° gekühlt. Bei dieser Temperatur wird eine Lösung von 88 ml Dimethylsulfoxid in 150 ml Dichlormethan zugetropft und das Gemisch 2 Minuten nachgerührt. Dann wird bei - 60° eine Lösung von 117 g 2'-Cyano-4-hydroxymethyl-biphenyl in 1 l Dichlormethan zugetropft. Nach beendeter Zugabe (nach ca. 5 Minuten) wird das Gemisch 15 Minuten nachgerührt. Dann werden 390 ml

Triethylamin zugetropft. Man rührt das Gemisch 2 Minuten bei -60° nach, lässt es dann auf Raumtemperatur erwärmen und giesst es auf Wasser. Das Gemisch wird mit Dichlormethan extrahiert und die organische Phase nacheinander mit verdünnter Salzsäure und Sole gewaschen, getrocknet und eingeengt. Der Rückstand wird in Hexan suspendiert, die Suspension abgenutscht, der Filterkuchen gewaschen und das so erhaltene Produkt im Hochvakuum bei 60° getrocknet (Elementaranalyse: 80,7 % C; 4,5 % H; 6,7 % N; 7,7 % O).

b) N-(2′-Cyanobiphenyl-4-ylmethyl)-N-methoxycarbonylmethyl-amin
Ein Gemisch aus 2,0 g 2′-Cyano-4-formyl-biphenyl, 1,22 g 2-Aminoethansäuremethylesterhydrochlorid, 9,6 g Molekularsieb 5A und 26 ml Tetrahydrofuran wird 36 Stunden bei Raumtemperatur gerührt und dann auf 0 bis 5° abgekühlt. Es werden 680 mg Natriumcyanoborhydrid (90 %), gelöst in 4,8 ml Methanol, zugegeben. Das Gemisch wird 24 Stunden bei Raumtemperatur gerührt und dann im Vakuum eingeengt. Das Rohprodukt wird mittels Flashchromatographie (180 g Kieselgel; Essigsäureethylester/Petrolether = 1:1) gereinigt [^{1}H-NMR (DMSO-d_6): 3,63 ppm (s, 3 H); 3,79 ppm (s, 2 H); 7,4 bis 8,0 ppm (m, 10 H); 2,6 ppm (1 H)].

c) N-(2′-Cyanobiphenyl-4-ylmethyl)-N-methoxycarbonylmethyl-N-pentanoyl-amin
0,96 g N-(2′-Cyanobiphenyl-4-ymethyl)-N-methoxycarbonylmethyl-amin werden in 9 ml Dichlormethan gelöst. Die Lösung wird mit 1,7 ml Triethylamin und anschliessend bei 0° mit 1,5 ml Pentanoylchlorid versetzt. Man rührt bei Raumtemperatur über Nacht und dampft dann zur Trockne ein: Der Rückstand wird in Diethylether aufgenommen und das etherische Gemisch nacheinander mit Natriumhydrogencarbonatlösung und Sole gewaschen. Flashchromatographie (180 g Kieselgel; Essigsäureethylester/Petrolether = 1: 1) liefert das Produkt in Form eines weissen Pulvers [R_f-Wert: 0,68 (System N2)].

Beispiel 2: (S)-N-(1-Carboxyethyl)-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin

Analog Beispiel 1 wird ausgehend von 1,24 g N-Valeryl-N-[(2′-cyanobiphenyl-4-yl)methyl] -(L)-alaninmethylester und 2,73 g Tributylzinnazid wird nach Flashchromatographie (B3) und anschliessendem Umkristallisieren aus Essigester das Produkt als weisses Pulver erhalten. Smp.: 115° (Zers.).
Das Ausgangsmaterial kann beispielsweise wie folgt erhalten werden:

a) N-[(2′-Cyanobiphenyl-4-yl)-methyl]-(L)-alaninmethylester ausgehend von 2,0 g 2′-Cyanobiphenyl-4-carbaldehyd, 1,34 g (L)-Alaninmethylester-Hydrochlorid, 680 mg Natriumcyanoborhydrid und 2,4 g Molekularsieb 5 A und anschliessender Flashchromatographie mit dem System N3. (DC: System N1) R_f-Wert: 0,59.

b) N-Valeryl-N-[(2′-cyanobiphenyl-4-yl)-methyl]-(L)-alaninmethylester ausgehend von 1,65 g N-[(2′-Cyanobiphenyl)-methyl]-(L)-alaninmethylester, 2,7 ml Triethylamin und 2,35 ml n-Valeriansäurechlorid und anschliessender Flashchromatographie (N2). (DC:System N2) R_f-Wert: 0,62.

Beispiel 3: (S)-N-(1-Methoxycarbonylethyl)-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-amin

0,3 g Säure aus Beispiel 2 werden in 5 ml Methylalkohol gelöst, mit 0,5 ml Salzsäure in Methylalkohol versetzt und während 24 Stunden bei Raumtemperatur gerührt. Das Reaktionsgemisch wird darauf eingeengt, in Methylenchlorid aufgenommen, mit Wasser extrahiert, die organische Phase getrocknet und am Rotationsverdampfer eingeengt. Nach Flashchromatographie (B1) erhält man das Produkt. Smp. des amorphen Materials: 57-59°.

Beispiel 4: N-[1-Carboxy-2-(4-fluorphenyl)-ethyl]-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-amin

Ausgehend von 2,3 g N-Valeryl-N-[(2′-cyanobiphenyl-4-yl)-methyl]-(DL)-p-fluorphenylalaninmethylester und 3,25 g Tributylzinnazid wird nach Flashchromatographie (B1) das Produkt nach Lyophilisation aus tert.-Butylalkohol erhalten. FAB-MS: m/e = 502 $(M+H)^+$.
Das Ausgangsmaterial kann beispielsweise wie folgt erhalten werden:
N-[(2′-Cyanobiphenyl-4-yl)-methyl]-(DL)-p-fluorphenylalaninmethylester ausgehend von 2,33 g 2′-Cyanobiphenyl-4-carbaldehyd, 2,63 g (DL)-p-Fluorphenylalaninmethylester, 790 mg Natriumcyanoborhydrid und 11,0 g Molekularsieb 5 A und anschliessender Flashchromatographie mit System N3. (DC: System N2) R_f-Wert: 0,36.
N-Valeryl-N-[(2′-cyanobiphenyl-4-yl)-methyl]-(DL)-p-fluorphenylalaninmethylester ausgehend von 2,1 g N-[(2′-Cyanobiphenyl-4-yl)-methyl]-(DL)-p-fluorphenylalaninmethylester, 1,0 ml Triethylamin und 0,85 ml n-Valeriansäurechlorid und anschliessender Flashchromatographie (N3). (DC: System N2) R_f-Wert: 0,64.

Beispiel 5: N-[2-(4-Fluorphenyl)-1-methoxycarbonyl-ethyl]-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin

Analog Beispiel 3 ausgehend von 1,29 g N-Valeryl-N-[(2′-(1H-tetrazol-5-yl)-biphenyl-4-yl)-methyl]-(DL)-p-fluorphenylalanin gemäss Beispiel 4. FAB-MS: m/e = 516 $(M+H)^+$.

Beispiel 6: N-[2-(4-Fluorphenyl)-1-hydroxymethyl-ethyl]-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin

0,5 g N-Valeryl-N-[(2′-(1H-tetrazol-5-yl)biphenyl-4-yl)-methyl]-(DL)-p-fluorphenylalanin-methylester aus Beispiel 5 werden in 5 ml Tetrahydrofuran bei -70° mit 1,9 ml Diisobutylaluminiumhydrid versetzt. Nach 20 Minuten gibt man 0,2 ml Methylalkohol zu und lässt auf Raumtemperatur aufwärmen. Das Reaktionsgemisch wird mit Ether und Wasser versetzt, die organische Phase abgetrennt, mit Sole gewaschen, getrocknet und eingeengt. Flashchromatographie (B2) liefert den entsprechenden Aldehyd. Dieser wird bei 0° in 5 ml Ethylalkohol mit 27 mg Natriumborhydrid versetzt und während 3,5 Stunden bei dieser Temperatur gerührt. Nach Abfiltrieren und Einengen wird das Produkt durch Flashchromatographie (N8) und Lyophilisieren aus tert.-Butylalkohol erhalten. FAB-MS: m/e= 488 $(M+H)^+$.

Beispiel 7: N-(2′-Carboxybiphenyl-4-ylmethyl)-N-[1-carboxy-2-(4-fluorphenyl)-ethyl]-N-pentanoyl-amin

N-Valeryl-N-[(2′-carboxybiphenyl-4-yl)-methyl]-(DL)-p-fluorphenylalanin-methylester werden in 10 ml Methylalkohol und 3 ml Wasser mit 0,45 ml 2N NaOH versetzt. Man rührt über Nacht bei Raumtemperatur und neutralisiert anschliessend mit 0,45 ml 2N Salzsäure. Nach Flashchromatographie (B1) und Lyophilisieren aus tert.-Butanol erhält man das amorphe Produkt. FAB-MS: m/e= 478 $(M+H)^+$.

Beispiel 8: N-(2′-Carboxybiphenyl-4-ylmethyl)-N-[2-(4-fluorphenyl)-1-methoxy-carbonyl-ethyl]-N-pentanoyl-amin

840 mg N-Valeryl-N-[(2′-(trimethylsilylethoxycarbonyl)biphenyl-4-yl)-methyl]-(DL)-p-fluorphenylalanin-methylester werden in 10 ml Dimethylformamid mit 15,6 ml einer 0,5 M Lösung von Tetrabutylammoniumfluorid in Tetrahydrofuran versetzt und über Nacht bei Raumtemperatur gerührt. Das Reaktionsgemisch wird eingeengt, in Essigester aufgenommen, mit Wasser und Sole gewaschen, getrocknet und eingeengt. Nach Flashchromatographie (B4) und Lyophilisieren aus tert.-Butanol erhält man das Produkt. FAB-MS: m/e= 492 $(M+H)^+$.

Das Ausgangsmaterial kann beipielsweise wie folgt erhalten werden:

14,2 g 4-Methyl-2′-carboxybiphenyl (EP 253,310) werden in 60 ml Acetonitril und 10,7 ml Pyridin gelöst und 11,4 ml Trimethylsilylethanol zugegeben. Man versetzt mit bei 0° 15,1 g Dicyclohexylcarbodiimid und rührt bei dieser Temperatur während 3 Stunden. Darauf wird das Reaktionsgemisch im Hochvakuum eingedampft, mit Ether versetzt und Dicyclohexylharnstoff abfiltriert. Nach Flashchromatographie (Essigester/Hexan 95:5) erhält man das 4-Methyl-2′-(trimethylsilylethoxycarbonyl)biphenyl als leicht gelbliches Oel. (DC: Essigester/Hexan 95:5) R_f-Wert: 0.42.

312 mg 4-Methyl-2′-(trimethylsilylethoxycarbonyl)biphenyl, 178 mg N-Bromsucciniimid, 5 mg Azoisobutyronitril und 15 ml Tetrachlorkohlenstoff werden eine Stunde zum Rückfluss erhitzt. Nach Abkühlen wird das Gemisch eingedampft. Flashchromatographie (Essigester/Hexan 95:5) liefert 4-Brommethyl-2′-(trimethylsilylethoxycarbonyl)biphenyl als leicht gelbliches Oel. ^{1}H-NMR ($CFCl_3$): 0 ppm (s, 9 H), 0,7 ppm (t, 2 H), 4,5 ppm (s, 2 H), 7,1-8 ppm Aromaten.

2,8 g 4-Brommethyl-2′-(trimethylsilylethoxycarbonyl)biphenyl und 1,17 g wasserfreies Natriumacetat werden in Eisessig über Nacht bei 65° gerührt und anschliessend 3 Stunden unter Rückfluss gekocht. Das Reaktionsgemisch wird eingedampft, der Rückstand in Essigester aufgenommen, mit Wasser und Natriumhydrogencarbonat gewaschen, die organische Phase getrocknet und eingeengt. Der Rückstand wird in 25 ml Ethanol vorgelegt, 6,3 ml 1N NaOH zugegeben und 30 Minuten bei Raumtemperatur gerührt. Das Gemisch wird im Vakuum eingedampft, mit Essigester versetzt, mit Wasser und Sole gewaschen, getrocknet und eingedampft. Flashchromatographie (N4) liefert 4-Hydroxymethyl-2-(trimethylsilylethoxycarbonyl)biphenyl als farbloses Oel. ^{1}H-NMR (DMSO): 0 ppm (s, 9 H), 0,75 ppm (t, 2 H), 4,1 ppm (t, 2 H), 4,73 ppm (d, 2 H), 5,27 ppm (t, 1H), 7,2-7,7 ppm Aromaten.

2′-(Trimethylsilylethoxycarbonyl)biphenyl-4-carbaldehyd wird analog Beispiel 1 a) erhalten ausgehend von 6,5 g 4-Hydroxymethyl-2′-(trimethylsilylethoxycarbonyl)-biphenyl, 1,87 ml Oxalylchlorid, 3,1 ml Dimethylsulfoxid und 13,8 ml Triethylamin und anschliessender Flashchromatographie mit Methylenchlorid. ^{1}H-NMR ($CDCl_3$): 0 ppm (s, 9 H), 0,8 ppm (t, 2 H), 4,2 ppm (t, 2 H), 7,2-8,1 ppm Aromaten, 10,1 ppm (s, 1 H).

Analog Beispiel 1 b) erhält man ausgehend von 1,0 g 2′-(Trimethylsilylethoxycarbonyl)-biphenyl-4-carbaldehyd, 3,0 g Molekularsieb 5 A, 0,715 g (D,L)-p-Fluorphenylalaninmethylester-Hydrochlorid und 215 mg Natriumcyanoborhydrid und anschliessender Flashchromatographie (N3) N-[(2′-(Trimethylsilylethoxy-carbonyl)biphenyl-4-yl)-methyl]-(D,L)-p-fluorphenylalanin-methylester. (DC: N3) R_f-Wert: 0,64.

Analog Beispiel 1 c) erhält man ausgehend von 0,8 g N-[(2′-(Trimethylsilylethoxycarbonyl)biphenyl-4-yl)-methyl]-(D,L)-p-fluorphenylalanin-methylester, 0,29 ml Triethylamin und 0,25 ml Valerylchlorid nach Flashchromatographie (N3)

N-Valeryl-N-[(2′-(trimethylsilylethoxycarbonyl)biphenyl-4-yl)-methyl] -(D,L)-p-fluorphenylalaninmethylester. (DC: N3) R_f-Wert = 0,65.

Beispiel 9: (S)-N-(2′-Carboxybiphenyl-4-ylmethyl)-N-(1-hydroxymethyl-2-phenylethyl)-N-pentanoyl-amin

290 mg N-[3-(p-Fluorphenyl)-1-hydroxy-2-propyl]-N-[2′-(trimethylsilylethoxycarbonyl)-4-yl-methyl]-valeriansäureamid werden in 3 ml Dimethylformamid während 20 Stunden bei Raumtemperatur mit 5,82 ml einer 0,5 molaren Lösung von Tetrabutylammoniumfluorid in Tetrahydrofuran behandelt. Das Gemisch wird im Vakuum eingeengt, in Essigester aufgenommen, mit Wasser und Sole gewaschen und eingeengt. Nach Flashchromatographie (N7) und Lyophilisation erhält man das Produkt als weisses Pulver. FAB-MS: m/e= 446 $(M+H)^+$.

Das Ausgangsmaterial kann beispielsweise wie folgt erhalten werden:
Analog Beispiel 1 b) erhält man ausgehend von 1,5 g 2′-(Trimethylsilylethoxycarbonyl)-biphenyl-4-carbaldehyd, 4,5 g Molekularsieb 5 A, 0,694 g (D,L)-3-Phenyl-2-amino-propan-1-ol und 321 mg Natriumcyanoborhydrid nach Flashchromatographie (B5) N-[(2′-(Trimethylsilylethoxycarbonyl)biphenyl-4-yl)-methyl] -3-(p-fluorphenyl)-2-aminopropan-1-ol. ^{1}H-NMR (DMSO): 0 ppm (2 s, 9 H), 0,73 ppm (2 t, 2 H), 2 ppm (b, 1 H), 2,73 ppm (m, 3 H), 3,3 ppm (m, 2 H), 3,83 ppm (s, 2 H), 4,1 ppm (2 t, 2 H), 4,6 ppm (t, 1 H), 7,15-7,8 ppm, m (8 H).

Analog Beispiel 1 c) erhält man ausgehend von 365 mg N-[(2′-(Trimethylsilylethoxycarbonyl)biphenyl-4-yl)-methyl]-3-(phenyl)-2-amino-propan-1-ol, 0,136 ml Triethylamin, 0,112 ml Valerylchlorid und anschliessender Flashchromatographie (N3) N-[3-(Phenyl)-1-hydroxy-2-propyl]-N-[(2′-(trimethylsilylethoxycarbonyl)-4-yl-methyl]-valeriansäureamid. FAB-MS: m/e= 546 $(M+H)^+$.

Beispiel 10: (S)-N-(2′-Carboxybiphenyl-4-ylmethyl)-N-(1-hydroxymethyl-2-imidazol-4-yl-ethyl)-N-pentanoyl-amin

Analog Beispiel 9 erhält man das Produkt ausgehend von 272 mg N-[3-(Imidazol-4-yl)-1-hydroxy-2-propyl]-N-[(2′-(trimethylsilylethoxycarbonyl)biphenyl-4-yl)-methyl]-valeriansäureamid und 5,54 ml Tetrabutylammoniumfluoridlösung nach Flashchromatographie (B1). FAB-MS $(M+H)^+$=436.

Das Ausgangsmaterial kann beispielsweise analog Beispiel 9 wie folgt erhalten werden:
Umsetzung von 1,5 g 2′-(Trimethylsilylethoxycarbonyl)biphenyl-4-carbaldehyd, 0,984 g 3-(Imidazol-4-yl)-2-(S)-amino-propan-1-ol-dihydrochlorid, 321 mg Natriumcyanoborhydrid und 4,5 g Molekularsieb 5 A liefert nach Flashchromatographie (B5) N-[(2′-(Trimethylsilylethoxycarbonyl)biphenyl-4-yl)-methyl]-3-(imidazol-4-yl)-2-aminopropan-1-ol. (DC) R_f-Wert (0,36).

Umsetzung von 0,45 g N-[(2′-(Trimethylsilylethoxycarbonyl)biphenyl-4-yl)-methyl]-3-(imidazol-4-yl)-2-(S)-amino-propan-1-ol, 0,152 ml Triethylamin und 0,132 ml Valerylchlorid liefert nach Flashchromatographie (Methylenchlorid-Methanol-conc. Ammoniak: 120-10-1) N-[3-(Imidazol-4-yl)-1-hydroxy-2-propyl]-N-[(2′-(trimethylsilylethoxycarbonyl)biphenyl-4-yl)-methyl]-valeriansäureamid. Bei der Aufarbeitung wird die wässrige Phase leicht basisch gestellt. FAB-MS: m/e= 536 $(M+H)^+$.

Beispiel 11: (R)-N-(1-Carboxyethyl)-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin

Analog Beispiel 1 wird das Produkt hergestellt ausgehend von 0,84 g N-Valeryl-N-[(2′-cyano-biphenyl-4-yl)-methyl]-(D)-alanin-methylester und 731 mg Tributylzinnazid und anschliessender Flashchromatographie (B1). FAB-MS: m/e = 408 $(M+H)^+$.

Das Ausgangsmaterial kann beispielsweise analog Beispiel 1 b) erhalten werden:
Umsetzung von 2,0 g 2′-Cyanobiphenyl-4-carbaldehyd, 9,6 g Molekularsieb 5 A, 1,34 g (D)-Alaninmethylester-Hydrochlorid und 680 mg Natriumcyanoborhydrid liefert nach Flashchromatographie (N3) N-[(2′-Cyanobiphenyl-4-yl)-methyl]-(D)-alaninmethylester. ^{1}H-NMR (DMSO): 1,21 ppm (d, 3 H), 3,63 ppm (s, 3 H), 3,75 ppm (dd, 1 H), 4,56 ppm (d, 2 H), 4,58 ppm (d, 2 H), 5,31 ppm (t, 1 H), 7,4-8 ppm Aromaten.

Umsetzung analog Beispiel 1 c) von 1,25 g N-[(2′-Cyanobiphenyl-4-yl)-methyl]-(D)-alaninmethylester, 2,1 ml Triethylamin und 1,8 ml n-Valeriansäurechlorid liefert nach Flashchromatographie (N3) N-Valeryl-N-[(2′-cyano-biphenyl-4-yl)-methyl]-(D)-alaninmethylester (DC: N2) R_f-Wert: 0,61.

Beispiel 12: (1S),(2S)-N-(1-Carboxy-2-methyl-but-1-yl)-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin

Das Produkt kann ausgehend von 2,0 g N-Valeryl-N-[(2′-cyanobiphenyl-4-yl)-methyl]-(L)-isoleucinmethylester und 3,19 g Tributylzinnazid und anschliessender Flashchromatographie (B1) hergestellt werden. FAB-MS $(M+H)^+$ = 450.

Das Ausgangsmaterial kann beispielsweise analog Beispiel 1 b) erhalten werden:
Die Umsetzung von 2,0 g 2′-Cyanobiphenyl-4-carbaldehyd, 9,6 g Molekularsieb 5 A, 1,76 g (L)-Isoleucinmethylester-Hydrochlorid und 680 mg Natriumcyanoborhydrid liefert nach Flashchromatographie (Essigester-Hexan 1:3) den N-[(2′-

Cyanobiphenyl-4-yl)-methyl]-(L)-isoleucinmethylester. ^{1}H-NMR (DMSO): 1,21 ppm (d, 3 H), 3,63 ppm (s, 3 H), 3,75 (dd, 1 H), 4,56 ppm (d, 2 H), 4,58 ppm (d, 2 H), 5,31 ppm (t, 1 H), 7,4-8 ppm Aromaten.

Die Umsetzung analog Beispiel 1 c) von 1,80 g N-[(2′-Cyanobiphenyl)-4-yl-methyl]-(L)-isoleucinmethylester, 2,7 ml Triethylamin und 2,35 ml n-Valeriansäurechlorid liefert nach Flashchromatographie (N4) den N-Valeryl-N-[(2′-cyanobiphenyl-4-yl)-methyl]-(L)-isoleucinmethylester. (DC: N3) R_f-Wert: 0,43.

Beispiel 13: (1S),(2S)-N-(1-Methoxycarbonyl-2-methyl-but-1-yl)-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin

Das Produkt kann erhalten werden analog Beispiel 3 ausgehend von 200 mg N-Valeryl-N-[(2′-(1H-tetrazol-5-yl)biphenyl-4-yl)-methyl]-(L)-isoleucin und anschliessender Flashchromatographie (B1). FAB-MS: m/e= 464 $(M+H)^+$.

Beispiel 14: (S)-N-(1-Carboxybut-1-yl)-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin

Das Produkt kann analog Beispiel 1 ausgehend von 0,30 g N-Valeryl-N-[(2′-cyano-biphenyl-4-yl)-methyl]-(L)-norvalin-methylester und 490 mg Tributylzinnazid und anschliessender Flashchromatographie (B1) hergestellt werden. FAB-MS $(M+H)^+$ = 436.

Das Ausgangsmaterial kann beispielsweise analog Beispiel 1 b) erhalten werden:
Die Umsetzung von 2,0 g 2′-Cyanobiphenyl-4-carbaldehyd, 9,6 g Molekularsieb 5 A, 1,34 g (L)-Norvalinmethylester-Hydrochlorid und 680 mg Natriumcyanoborhydrid liefert nach Flashchromatographie (N3) den N-[(2′-Cyanobiphenyl-4-yl)-methyl]-(L)-norvalin-methyl-ester. ^{1}H-NMR (DMSO): 0,83 ppm (t, 3 H), 1,33 ppm (m, 2 H), 1,55 ppm (m, 2 H), 3,62 ppm (s, 3 H), 3,1 ppm (m, 1 H), 7,3-8 ppm Aromaten.

Die Umsetzung analog Beispiel 1 c) von 1,5 g N-[(2′-Cyanobiphenyl)-4-yl)-methyl]-(L)-norvalinmethylester, 2,35 ml Triethylamin und 2, 15 ml n-Valeriansäurechlorid liefert nach Flashchromatographie (Essigester-Hexan: 1-3) den N-Valeryl-N-[(2′-cyanobiphenyl-4-yl)-methyl]-(L)-norvalinmethylester (DC:B1) R_f-Wert: 0,9.

Beispiel 15: (S)-N-(1-Methoxycarbonylbut-1-yl)-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-amin

Das Produkt kann analog Beispiel 3 erhalten werden ausgehend von 200 mg der Verbindung gemäss Beispiel 14 und anschliessender Flashchromatographie (B1). FAB-MS: m/e=464 $(M+H)^+$.

Beispiel 16: (S)-N-(1-Carboxy-2-methyl-prop-1-yl)-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-amin

Das Produkt kann hergestellt werden ausgehend von 1,40 g N-Valeryl-N-[(2′-cyanobiphenyl-4-yl)-methyl]-(L)-valinmethylester und 2,25 g Tributylzinnazid und anschliessender Flashchromatographie (B1). FAB-MS $(M+H)^+$ = 436, Schmelzintervall 105-115° (aus Ethylacetat).

Das Ausgangsmaterial kann beispielsweise analog Beispiel 1 b) erhalten werden:
Umsetzung von 0,5 g 2′-Cyanobiphenyl-4-carbaldehyd, 2,5 g Molekularsieb 5 A, 0,815 g (L)-Valinmethylester-Hydrochlorid und 180 mg Natriumcyanoborhydrid liefert nach Flashchromatographie (N3) den N-[(2′-Cyanobiphenyl-4-yl)-methyl]-(L)-valinmethylester. (DC: N3) R_f-Wert: 0,5.

Umsetzung analog Beispiel 1 c) von 1,15 g N-[(2′-Cyanobiphenyl-4-yl)-methyl]-(L)-valinmethylester, 0,625 ml Triethylamin und 0,56 ml n-Valeriansäurechlorid liefert nach Flashchromatographie (N3) den N-Valeryl-N-[(2′-cyanobiphenyl-4-yl)-methyl]-(L)-valinmethylester. (DC: N2) R_f-Wert: 0,63.

Beispiel 17: (S)-N-(1-Carboxyethyl)-N-hexanoyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin

Das Produkt kann hergestellt werden ausgehend von 2,4 g N-Caproyl-N-[(2′-cyanobiphenyl-4-yl)-methyl]-(L)-alaninmethylester und 4,05 g Tributylzinnazid und anschliessender Flashchromatographie (B1). FAB-MS: m/e= 422 $(M+H)^+$.

Das Ausgangsmaterial kann beispielsweise analog Beispiel 2 erhalten werden:
Umsetzung von 2,0 g N-[(2′-Cyanobiphenyl)-4-yl-methyl]-(L)-alaninmethylester, 1,23 ml Triethylamin, und 1,22 ml n-Caproylchlorid liefert den N-Caproyl-ageN- [(2′-cyanobiphenyl-4-yl)-methyl]-(L)-alanin-methylester. (DC: N2) R_f-Wert: 0,5.

Beispiel 18: (S)-N-Butanoyl-N-(1-carboxyethyl)-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin

Das Produkt kann hergestellt werden ausgehend von 2,25 g N-Butyryl-N-[(2′-cyanobiphenyl-4-yl)-methyl]-(L)-alaninmethylester und 4,11 g Tributylzinnazid und anschliessender Flashchromatographie (B1). FAB-MS: m/e = 394 $(M+H)^+$.

Das Ausgangsmaterial kann beispielsweise analog Beispiel 2 erhalten werden:
Umsetzung von 2,0 g N-[(2′-Cyanobiphenyl-4-yl)-methyl]-(L)-alaninmethylester, 1,23 ml Triethylamin und 0,92 ml n-Buttersäurechlorid liefert den N-Butyryl-N-[(2′-cyanobiphenyl-4-yl)-methyl]-(L)-alanin-methylester. (DC: N2) R_f-Wert: 0,5.

Beispiel 19: (S)-N-(1-Carboxyprop-1-yl)-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin

Das Produkt kann hergestellt werden ausgehend von 0,68 g N-Valeryl-N-[(2′-cyanobiphenyl-4-yl)-methyl]-(L)-2-aminobuttersäuremethylester und 1,15 g Tributylzinnazid. Kristallisation aus Ether. Smp.: 102- 104°. FAB-MS $(M+H)^+$ = 422.
Das Ausgangsmaterial kann beispielsweise analog Beispiel 1 b) erhalten werden:
Umsetzung von 3,0 g 2′-Cyanobiphenyl-4-carbaldehyd, 14,5 g Molekularsieb 5 A, 2,23 g (L)-2-Aminobuttersäure-Hydrochlorid und 1075 mg Natriumcyanoborhydrid liefert nach Flashchromatographie (N3) den N-[(2′-cyanobiphenyl-4-yl)-methyl]-(L)-2-aminobuttersäuremethylester. ^{1}H-NMR (DMSO): 0,88 ppm (t, 3 H), 1,62 ppm (m, 2 H), 2,53 ppm (b, 1 H), 3,15 ppm (m, 1 H), 3,63 ppm (s, 3 H), 3,62 ppm (d, 2 H), 3,81 ppm (d, 1 H).
Umsetzung analog Beispiel 1 c) von 0,54 g N-[(2′-Cyanobiphenyl-4-yl)-methyl]-(L)-2Aminobuttersäuremethylester, 0,33 ml Triethylamin und 0,29 ml N-Valeriansäurechlorid liefert den N-Valeryl-N-[(2′-cyano-biphenyl-4-yl)-methyl]-(L)-2-aminobuttersäuremethylester. (DC: N2) R_f-Wert: 0,52.

Beispiel 20: (S)-N-(1-Carboxy-2-cyclohexyl-ethyl)-N-pentanoyl-N-(2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin

Das Produkt kann hergestellt werden ausgehend von 4,0 g N-Valeryl-N-[(2′-cyanobiphenyl-4-yl)-methyl]-(L)-cyclohexylalaninmethylester und 5,8 g Tributylzinnazid und anschliessender Flashchromatographie (B1). FAB-MS $(M+H)^+$ = 490.
Das Ausgangsmaterial kann beispielsweise analog Beispiel 1 b) erhalten werden:
Umsetzung von 9,35 g 2′-Cyanobiphenyl-4-carbaldehyd, 46 g Molekularsieb 5 A, 10,0 g (L)-Cyclohexylalaninmethylester-Hydrochlorid und 3,3 g Natriumcyanoborhydrid liefert nach Flashchromatographie (N3) den N-[(2′-Cyanobiphenyl-4-yl)-methyl]-(L)-cyclohexylalaninmethylester. (DC: N3) R_f-Wert: 0,45.
Umsetzung analog Beispiel 1 c) von 9,0 g N-(2′-Cyanobiphenyl-4-ylmethyl)-(L)-cyclohexylalaninmethylester, 4,33 g Triethylamin und 3,75 ml n-Valeriansäurechlorid liefert nach Flashchromatographie (N3) den N-Valeryl-N-[(2′-cyanobiphenyl-4-yl)-methyl](L)-cyclohexylalanin-ester-methylester. (DC: N3) R_f-Wert: 0,55.

Beispiel 21: (S)-N-(2-Cyclohexyl-1-methoxycarbonyl-ethyl)-N-pentanoyl-N-[2′-(1-H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin

Das Produkt kann erhalten werden analog Beispiel 3 ausgehend von 1,02 g der Verbindung aus Beispiel 20. FAB-MS: m/e= 504 $(M+H)^+$.

Beispiel 22: (R)-N-(1-Carboxy-2-methyl-prop-1-yl)-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin

Das Produkt kann hergestellt werden analog Beispiel 11 ausgehend von 3,8 g N-Valeryl-N-[(2′-cyano-biphenyl-4-yl)-methyl]-(D)-valinmethylester und 6,17 g Tributylzinnazid und anschliessender Flashchromatographie (N8). FAB-MS $(M+H)^+$ = 436.
Das Augangsmaterial kann beispielsweise analog Beispiel 1 b) erhalten werden:
Umsetzung von 4,0 g 2′-Cyanobiphenyl-4-carbaldehyd, 19,3 g Molekularsieb 5 A, 3,8 g (D)-Valinmethylester-Hydrochlorid und 1,43 g Natriumcyanoborhydrid liefert nach Flashchromatographie (N3) den N-[(2′-cyanobiphenyl-4-yl)-methyl]-(D)-Valinmethylester. (DC: N2) R_f-Wert: 0,56.
Umsetzung analog Beispiel 1 c) von 3,2 g N-[(2′-Cyanobiphenyl)-4-yl-methyl]-(D)-valinmethylester, 1,82 ml Triethylamin und 1,6 ml N-Valeriansäurechlorid liefert nach Flashchromatographie (N2) den N-Valeryl-N- [(2′-cyano-biphenyl-4-yl)methyl]-(D)-valinmethylester. FAB-MS: m/e= 407 $(M+H)^+$.

Beispiel 23: N-(2-Methoxyethyl)-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin

Unter Ueberleiten eines schwachen Stickstoffstromes wird eine Lösung von 1,6 g (4,5 mMol) rohem N-[(2′-Cyanobiphenyl-4-yl)-methyl]-N-(2-methoxyethyl)-valeriansäureamid und 1,8 g (5,5 mMol) Tri-n-butylzinnazid in 15 ml o-Xylol während 20-24 Stunden unter Rückfluss erhitzt. Nach dem Abkühlen wird die Lösung mit ca. 30 ml Toluol verdünnt, mit 15 ml 1N wässriger Natronlauge versetzt und während 2 Stunden intensiv gerührt. Die wässrige Phase wird abgetrennt und mit 16 ml 1N wässriger Salzsäure sauer gestellt. Das ausgefällte Produkte wird durch Extraktion mit Aethylacetat isoliert. Man erhält so die rohe Titelverbindung als Oel, das aus wenig Ethylacetat kristallisiert, Smp. 120-122°.
Das Ausgangsmaterial kann beispielsweise wie folgt hergestellt werden:

a) 4-[N-(2-Methoxyethyl)-aminomethyl]-2′-cyanobiphenyl
Eine Lösung von 5,45 g (20 mMol) 4-Brommethyl-2′-cyanobiphenyl in 40 ml 1,4-Dioxan wird mit 7,5 g (100 mMol) 2-Methoxyethylamin versetzt und hierauf 8-10 Stunden unter Rückfluss zum Sieden erhitzt. Nach dem gründlichen Eindampfen im Wasserstrahlvakuum wird der Eindampfrückstand in 60 ml 2N Salzsäure gelöst und mit 60 ml Ether extrahiert. Die salzsaure Lösung wird abgetrennt und mit conc. Natronlauge alkalisch gestellt. Das ausgefallene Oel wird mit Ether extrahiert, die Etherlösung mit Wasser gewaschen, über Magnesiumsulfat getrocknet und eingedampft. Man erhält so die rohe Titelverbindung als Oel, das in wenig Ether gelöst und mit einer methanolischen Lösung von Salzsäure-Gas versetzt wird. Das so erhaltene kristalline Hydrochlorid wird aus 2-Propanol umkristallisiert und schmilzt bei 174-176°.

b) N-[(2′-Cyanobiphenyl-4-yl)methyl]-N-(2-methoxyethyl)-n-valeri ansäureamid
Zu einem Gemisch von 3,7 g (12,2 mMol) 4-[N-(2-Methoxyethyl)-aminomethyl]2′-cyanobiphenyl-Hydrochlorid und 3,1 g (31 mMol) Triethylamin in 50 ml 1,4-Dioxan werden unter Rühren und Kühlen mit Eiswasser 1,5 g (15 mMol) n-Valerylchlorid getropft. Die Suspension wird 4-6 Stunden bei Raumtemperatur gerührt. Nach dem Eindampfen im Wasserstrahlvakuum wird das Reaktionsgemisch zwischen 20 ml Wasser und 200 ml Ethylacetat verteilt. Die organische Phase wird nacheinander mit je 10 ml 2N Salzsäure, gesättigter $NaHCO_3$-Lösung und Sole gewaschen, über Magnesiumsulfat getrocknet und im Vakuum eingedampft. Die so erhaltene Titelverbindung wird als Oel erhalten (R_f-Wert: 0,51 im System B7) und kann roh weiter umgesetzt werden.

Beispiel 24: N-(2-Benzyloxyethyl)-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin

6,5 g (15,2 mMol) rohes N-(2-Benzyloxyethyl)-N-[(2′-cyanobiphenyl-4-yl)-methyl]n-valeriansäureamid und 6,1 g Tri-n-butylzinnazid werden analog Beispiel 23 umgesetzt und aufgearbeitet. Man erhält so die rohe Titelverbindung, die nach Umkristallisation aus wenig Ethylacetat bei 109-110° schmilzt.
Das Ausgangsmaterial kann beispielsweise auf folgende Weise hergestellt werden:

a) 4-[N-(2-Benzyloxyethyl)-aminomethyl]-2′-cyanobiphenyl
Analog Beispiel 23 a) erhält man aus 2-Benzyloxyethylamin (J. Am. Pharm. Assoc., Sci. Ed. 1952, 41, 257) die Titelverbindung nach flash-chromatographischer Reinigung (Silicagel; Toluol-Methanol 19:1) als gelbliches Oel, das im DC im System B7 einen R_f-Wert von 0,48 aufweist.

b) N-(2-Benzyloxyethyl)-N-[(2′-cyanobiphenyl-4-yl)methyl]-n-vale riansäureamid
Analog Beispiel 26 b) erhält man aus 4-[N-(2-Benzyloxyethyl)-aminomethyl]-2′-cyanobiphenyl die Titelverbindung. Sie weist im DC-System B7 einen R_f-Wert von 0,71 auf und kann roh weiterverwendet werden.

Beispiel 25: N-(3-Methoxyprop-1-yl)-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin

Analog Beispiel 23 erhält man aus 2,1 g (5,8 mMol) rohem N-[(2′-Cyanobiphenyl-4-yl)methyl]-N-(3-methoxypropyl)-n-valeriansäureamid und 2,3 g (6,9 mMol) Tri-n-butylzinnazid in 20 ml o-Xylol und flash-chromatographischer Reinigung die Titelverbindung als dickflüssiges Oel mit einem R_f-Wert von 0,33 im DC-System B6.
Das Ausgangsmaterial kann beispielsweise auf folgende Weise hergestellt werden:

a) 4-[N-(3-Methoxypropyl)-aminomethyl]-2′-cyanobiphenyl
Analog Beispiel 23 a) erhält man aus 3-Methoxypropylamin die Titelverbindung, die ein Hydrochlorid vom Smp. 183-184° bildet (aus 2-Propanol-Ether).

b) N-[(2′-Cyanobiphenyl-4-yl)-methyl]-N-(3-methoxypropyl)-n-vale riansäureamid
Analog Beispiel 23 b) erhält man aus 25 a) die Titelverbindung. Sie weist im DC-System B7 einen R_f-Wert von 0,55 auf und kann roh weiter umgesetzt werden.

Beispiel 26: N-(3-Benzyloxyprop-1-yl)-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin

5,8 g (13 mMol) der Verbindung 26 b) und 5,3 g (16 mMol) Tri-n-butylzinnazid werden analog Beispiel 23 umgesetzt und aufgearbeitet. Man erhält so die rohe Titelverbindung als Oel, das aus wenig 2-Propanol-Ether zur Kristallisation gebracht wird und dann bei 112-115° schmilzt.
Das Ausgangsmaterial kann beispielsweise auf folgende Weise hergestellt werden:

a) 4-[N-(3-Benzyloxypropyl)-aminomethyl]-2′-cyanobiphenyl
Eine Lösung von 6,0 g (22 mMol) 4-Brommethyl-2′-cyanobiphenyl, 5,8 g (35 mMol) 3-Benzyloxypropylamin und 3,6

g Triethylamin in 50 ml 1,4-Dioxan wird 18 Stunden unter Rückfluss zum Sieden erhitzt. Nach Aufarbeitung analog Beispiel 23 a) erhält man ein Oel, das nach flashchromatographischer Reinigung (Ethanol:Ethylacetat: 1:4) die Titelverbindung ergibt (DC-System B7; Rf-Wert 0,39).

b) N-(3-Benzyloxypropyl)-N-[(2′-cyanobiphenyl-4-yl)methyl]-n-val eriansäureamid
2,0 g (16,7 mMol) n-Valerylchlorid werden unter Kühlung mit einem Wasserbad unter Rühren in eine Lösung von 5,5 g (15,4 mMol) der Verbindung 26 a) und 4,0 g Triethylamin in 40 ml 1,4-Dioxan getropft. Das Reaktionsgemisch wird 5-10 Stunden bei Raumtemperatur gerührt und wie in Beispiel 23 b) aufgearbeitet. Man erhält so die Titelverbindung als Oel (R_f im System B7: 0,51), das für die weitere Umsetzung genügend rein ist.

Beispiel 27: N-(2-Hydroxyethyl)-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin

Eine Lösung von 2,6 g (5,5 mMol) der in Beispiel 24 beschriebenen Verbindung in 90 ml 1,4-Dioxan wird unter Zusatz von insgesamt 2,0 g Palladium-auf-Kohle-Katalysator (5 %) bei Raumtemperatur solange hydriert, bis in einer DC-Kontrolle (System B6) keine Ausgangsverbindung mehr festzustellen ist (ca. 70 Stunden). Der Katalysator wird abfiltriert, das Filtrat im Vakuum eingedampft und der Rückstand in Ethylacetat gelöst. Durch Waschen der Ethylacetat-Lösung mit Wasser, Trocknen und Eindampfen im Vakuum erhält man einen farblosen Schaum, dessen ^{1}H-NMR-Spektrum mit der Struktur der Titelverbindung übereinstimmt und der einen R_f-Wert von 0,60 aufweist (DC-System B6).

Beispiel 28: N-(3-Hydroxyprop-1-yl)-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin

2,7 g (5,5 mMol) der in Beispiel 26 beschriebenen Verbindung werden analog Beispiel 27 hydriert und aufgearbeitet. Man erhält ein gelbliches Oel, das nach flashchromatographischer Reinigung (System S2) die Titelverbindung als farblosen Schaum ergibt, die einen R_f-Wert von 0,26 aufweist (System S2).

Beispiel 29: N-(1-Methoxycarbonyl-1-methyl-ethyl)-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin

Eine Lösung von 9,4 g (24 mMol) rohem 2-Amino-N- [(2′-cyanobiphenyl-4-yl)methyl]-2-methyl-N-valeryl-propansäure-methylester und 9,7 g (29 mMol) Tri-n-butylzinnazid in 120 ml o-Xylol wird 30 Stunden unter Rückfluss zum Sieden erhitzt und dann analog Beispiel 23 aufgearbeitet. Die so als Oel erhaltene, rohe Titelverbindung wird zur Reinigung mit dem System B6 flashchromatographiert. Die so erhaltene Titelverbindung bildet einen Schaum und zeigt einen R_f-Wert von 0,39 (System B6).
Das Ausgangsprodukt kann beispielsweise auf folgende Weise erhalten werden:

a) 2-Amino-N-[(2′-cyanobiphenyl-4-yl)methyl]-2-methyl-propansäur e-methylester
Ein Gemisch von 10,9 g (40 mMol) 4-Brommethyl-2′-cyanobiphenyl, 18,4 g (120 mMol) 2-Amino-2-methyl-propansäuremethylester-hydrochlorid (D. Leibfritz et al., Tetrahedron 1982, 38, 2165) und 22 g Kaliumcarbonat in 100 ml Dimethylformamid wird 18-20 Stunden unter Rühren in einem Bad von 80° erwärmt. Die Suspension wird filtriert, das Filtrat im Vakuum eingedampft und der Rückstand zwischen 200 ml Ethylacetat und 50 ml Wasser verteilt. Die organische Phase wird abgetrennt, mit je 30 ml Wasser und Sole gewaschen, getrocknet und eingedampft. Man erhält so die rohe Titelverbindung. Sie bildet ein Hydrochlorid vom Smp. 170-175° (aus 2-Propanol).

b) 2-Amino-N-[(2′-cyanobiphenyl-4-yl)methyl]-2-methyl-N-valerylp ropionsäuremethylester
Eine Lösung von 7,4 g (24 mMol) der Verbindung 29 a) (als Base) und 3,7 g (29 mMol) Ethyldiisopropylamin in 100 ml Methylenchlorid wird unter Rühren tropfenweise mit 3,5 g (29 mMol) Valerylchlorid versetzt. Das Reaktionsgemisch wird 20-25 Stunden bei Raumtemperatur gerührt, bis kein Ausgangsamin mehr im DC festzustellen ist (System B7). Aufarbeitung analog Beispiel 23 b) ergibt die rohe Titelverbindung als gelbliches Oel mit R_f 0,40 (System B7), welches roh weiterverwendet wird.

Beispiel 30: N-(2-Carboxyethyl)-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin

393 mg N-[(2′-Cyano-biphenyl-4-yl)methyl]-N-valeryl-3-amino-propansäureethylester werden analog Beispiel 1 umgesetzt. Das Rohprodukt wird an Kieselgel 60 (40-63 µm) mit CH_2Cl_2-MeOH 95:5 gereinigt, R_f = 0,15 (System N8).
Das Ausgangsmaterial kann beispielsweise folgendermassen hergestellt werden:

a) 3-[(2′-Cyano-biphenyl-4-yl)methylamino]-propansäureethylester
wird analog Beispiel 1 b) aus 4,145 g 2′-Cyanobiphenyl-4-carbaldehyd und 3,135 g 3-Amino-propansäure-ethylester-hydrochlorid erhalten und an Kieselgel 60 (40-63 µm) mit CH_2Cl_2-MeOH 95:5 gereinigt, R_f = 0,21 (System N6).

b) N-[(2′-Cyano-biphenyl-4-yl)methyl]-N-valeryl-3-amino-propansä ure-ethylester
wird analog Beispiel 1 c) aus 1,542 g 3-[(2′-Cyano-biphenyl-4-yl)methylamino]-propansäureethylester erhalten, R_f = 0,66 (System N6).

Beispiel 31: N-(2-Carboxyprop-1-yl)-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin

785 mg rac-N-[(2′-Cyano-biphenyl-4-yl)methyl]-N-valeryl-3-amino-2-methyl-propansäuremethylester werden analog Beispiel 1 umgesetzt und extraktiv gereinigt, R_f = 0,29 (Sytem N8).
Das Ausgangsmaterial kann beispielsweise folgendermassen hergestellt werden:

a) rac-3-Amino-2-methyl-propansäure-methylester-hydrochlorid
wird aus 10,312 g rac-3-Amino-2-methylpropansäure in 100 ml Methanol durch tropfenweise Zugabe von 7,3 ml Thionylchlorid erhalten, R_f = 0,30 (System N8).

b) rac-3-[(2′-Cyano-biphenyl-4-yl)methylamino]-2-methyl-propansäuremethylester
wird analog Beispiel 1 b) aus 4,145 g 2′-Cyanobiphenyl-4-carbaldehyd und 3,072 g rac-3-Amino-2-methyl-propansäuremethylester-hydrochlorid erhalten und an Kieselgel 60 (40-63 µm) mit CH_2Cl_2-MeOH 97:3 gereinigt, R_f = 0,31 (System N6).

c) rac-N-[(2′-Cyano-biphenyl-4-yl)methyl]-N-valeryl-3-amino-2-me thyl-propansäuremethylester
wird analog Beispiel 1 c) aus 1,542 g rac-3-[(2′-Cyano-biphenyl-4-yl)methylamino]-2-methyl-propansäuremethylester erhalten und an Kieselgel 60 (40-63 µm) mit CH_2Cl_2-MeOH 98:2 gereinigt, R_f = 0,66 (System N6).

Beispiel 32: N-(1-Carboxy-1-methyl-ethyl)-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-amin

Eine Lösung von 2,6 g (6 mMol) des in Beispiel 29 beschriebenen Esters in 30 ml Methanol wird mit 35 ml wässriger Natronlauge (20 %) versetzt und solange unter Rückfluss und Rühren zum Sieden erhitzt (ca. 35-40 Std.), bis der Ausgangsester im DC (System B6) nicht mehr nachzuweisen ist. Die Lösung wird klar filtriert, das Methanol wird im Vakuum abgedampft und die verbleibende wässrige Lösung mit conc. Salzsäure auf pH 1-2 gebracht. Das ausgefallene Produkt wird mit 200 ml Ethylacetat extrahiert, die organische Phase abgetrennt, mit Sole gewaschen und über $MgSO_4$ getrocknet. Das nach dem Abdampfen des Lösungsmittels isolierte Rohprodukt wird mittels eines Gemisches Methylenchlorid 360 ml, Methanol 40 ml, Wasser 4 ml, Essigsäure 2 ml flashchromatographisch gereinigt. Die einheitlich nur das Produkt enthaltenden Fraktionen werden vereinigt eingedampft und ergeben die Titelverbindung als farblosen Schaum, der im DC (System wie oben erwähnt) einen R_f-Wert von 0,33 aufweist.

Beispiel 33: N-(5-Hydroxypent-1-yl)-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin

Eine Lösung von 6,5 g (17 mMol) rohem N-[(2′-Cyanobiphenyl-4-yl)methyl]-N-(5hydroxypentyl)-n-valeriansäureamid und 6,8 g (20,4 mMol) Tri-n-butylzinnazid in 70 ml o-Xylol wird analog Beispiel 23 umgesetzt und aufgearbeitet. Das so erhaltene Rohprodukt wird durch Flash-Chromatographie (System B6) gereinigt. Die das Produkt (R_f-Wert 0,20) enthaltenden Fraktionen werden eingedampft. Aus dem so isolierten Ammoniumsalz der Titelverbindung wird das freie Tetrazol mittels 1N Salzsäure freigesetzt und mit Aethylacetat extrahiert. Man erhält so die Titelverbindung als gelblichen, glasartigen Feststoff vom R_f-Wert 0,20 (System B6), der aus Ethylacetat kristallin erhalten wird, Smp. 117-118°.
Das Ausgangsmaterial kann beispielsweise auf folgende Weise hergestellt werden:

a) 4-[N-(5-Hydroxypentyl)-aminomethyl]-2′-cyanobiphenyl
Eine Lösung von 6,8 g (25 mMol) 4-Brommethyl-2′-cyanobiphenyl und 12,9 g (125 mMol) 5-Amino-1-pentanol in 50 ml 1,4-Dioxan wird 2-3 Stunden unter Rückfluss zum Sieden erhitzt. Aufarbeitung analog Beispiel 23 a) unter Verwendung von Ethylacetat als Lösungsmittel ergibt die Titelverbindung als Hydrochlorid vom Smp. 189-190° (aus 2-Propanol).

b) N-[(2′-Cyanobiphenyl-4-yl)methyl]-N-(5-hydroxypentyl)-n-valer iansäureamid
Aus 5,1 g (17,3 mMol) der Verbindung 33 a) und 2,3 g (19 mMol) n-Valerylchlorid erhält man unter Verwendung von 9 ml Ethyldiisopropylamin und 50 ml Methylenchlorid analog Beispiel 26b) die Titelverbindung als Oel vom R_f 0,36 (System B7), welches ohne weitere Reinigung weiter umgesetzt wird.

Beispiel 34: N-(1-Carboxyprop-2-yl)-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin

3,390 g rac-N-[(2′-Cyano-biphenyl-4-yl)methyl]-N-valeryl-3-amino-butansäureethylester werden analog Beispiel 1 umgesetzt und extraktiv gereinigt, R_f = 0,30 (System N8).

Das Ausgangsmaterial kann beispielsweise folgendermassen hergestellt werden:

a) rac-3-[(2′-Cyano-biphenyl-4-yl)methylamino]-butansäure-ethyle ster
wird analog Beispiel 1 b) aus 4,145 g 2′-Cyanobiphenyl-4-carbaldehyd und 4,634 ml rac-3-Amino-butansäure-ethylester erhalten und an Kieselgel 60 (40-63 µm) mit CH_2Cl_2-MeOH 98:2 gereinigt, R_f = 0,25 (System N6).

b) rac-N-[(2′-Cyano-biphenyl-4-yl)methyl]-N-valeryl-3-amino-buta nsäure-ethylester
wird analog Beispiel 1 c) aus 7,070 g rac-3-[(2′-Cyano-biphenyl-4-yl)methylamino]butansäure-ethylester erhalten und an Kieselgel 60 (40-63 µm) mit CH_2Cl_2-MeOH 99: 1 gereinigt, R_f = 0,36 (System N6).

Beispiel 35: N-(2-Ethoxycarbonyl-3-methyl-but-1-yl)-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin

2,194 g rac-N- [(2′-Cyano-biphenyl-4-yl)methyl] -N-valeryl-2-(aminomethyl)-3-methylbutansäure-ethylester werden analog Beispiel 1 umgesetzt und an Kieselgel 60 (40-63 µm) mit CH_2Cl_2-MeOH gereinigt, R_f = 0,48 (System N8).

Das Ausgangsmaterial kann beispielsweise folgendermassen hergestellt werden:

a) rac-2-[(2′-Cyano-biphenyl-4-yl)methylaminomethyl]-3-methyl-bu tansäure-ethylester
wird analog Beispiel 1 b) aus 4,145 g 2′-Cyanobiphenyl-4-carbaldehyd und 3,180 g rac-2-Aminomethyl-3-methyl-butansäure-ethylester (Miyazaki et al. J. pharm. Soc. Jpn. 77, 415 (1957)) erhalten und an Kieselgel 60 (40-63 µm) mit CH_2Cl_2-MeOH 97:3 gereinigt, R_f = 0,48 (System N6).

b) rac-N-[(2′-Cyano-biphenyl-4-yl)methyl]-N-valeryl-2-(aminomethyl)-3-methyl-butansäure-ethylester
wird analog Beispiel 1 c) aus 2,519 g rac-2-[(2′-Cyano-biphenyl-4-yl)methylaminomethyl]-3-methyl-butansäureethylester erhalten und an Kieselgel 60 (40-63 µm) mit CH_2Cl_2-MeOH 99: 1 gereinigt, R_f = 0,67 (System N6).

Beispiel 36: N-(2-Carboxy-3-methyl-but-1-yl)-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin

980 mg rac-N-[(2′-(1H-Tetrazol-5-yl)biphenyl-4-yl)methyl]-N-valeryl-2-(aminomethyl)-3-methyl-bütansäureethylester werden in 3,1 ml 2N NaOH während 72 Stunden auf 100° erhitzt. Neutralisieren mit 3,1 ml 2N HCl und extrahieren mit CH_2Cl_2 liefert das Produkt, R_f = 0,30 (System N8).

Beispiel 37: (S)-N-(1-Carboxy-2-methyl-prop-1-yl)-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin

4,2 g N-Valeryl-N-[(2′-cyanobiphenyl-4-yl)methyl]-(L)-valinbenzylester werden in 40 ml Xylol mit 5,7 g Tri-n-butylzinnazid während 24 Stunden zum Rückfluss erhitzt. Darauf wird zur Trockene eingedampft. Das Rohprodukt wird anschliessend in 40 ml Dioxan aufgenommen, mit 400 mg Palladiumkohle (5%) versetzt und unter Normaldruck bis zur Sättigung hydriert. Es wird vom Katalysator abfiltriert, eingedampft, in Ether aufgenommen und das Produkt mit 18 ml 1N NaOH und 100 ml Wasser extrahiert. Die wässrige Phase wird mit Ether gewaschen und nach Ansäuern mit einem Ueberschuss an 1N Salzsäure mit Essigester extrahiert. Umkristallisieren aus Diisopropylether liefert das reine Produkt vom Smp. 116-117°.

Das Ausgangsmaterial kann beispielsweise folgendermassen hergestellt werden:

a) N-(2′-Cyanobiphenyl-4-yl)methyl]-(L)-valinbenzylester
4,38 g 2′-Cyanobiphenyl-4-carbaldehyd, 8,03 g (L)-Valinbenzylester-Toluolsulfonsäuresalz und 25 g Molekularsieb 5A werden in 80 ml Tetrahydrofuran während 36 Stunden bei Raumtemperatur gerührt und dann auf 0° abgekühlt. Es werden 2, 19 g Natriumcyanoborhydrid (90%), gelöst in 10 ml Methanol, zugegeben, 24 Stunden bei Raumtemperatur gerührt und dann im Vakuum eingeengt. Das Reaktionsgemisch wird darauf filtriert, das Filtrat eingeengt, der Rückstand in Methylenchlorid aufgenommen, dreimal mit Wasser gewaschen, getrocknet und eingeengt. Der Rückstand wird in Wasser aufgenommen und mit einem Ueberschuss konzentrierter Salzsäure versetzt. Das Produkt wird als Hydrochlorid ausgefällt und abfiltriert. Nach Umkristallisieren aus Essigester/Hexan 1:1 erhält man das reine Produkt vom Smp. 153-155°.

b) N-Valeryl-N-[(2′cyanobiphenyl-4-yl)methyl]-(L)-valinbenzylest er
5,5 g N-[(2′-Cyanobiphenyl-4-yl)methyl]-(L)-valinbenzylester-Hydrochlorid, 4,33 g Diisopropylethylamin und 3 ml Valerylchlorid werden bei Raumtemperatur während 36 Stunden gerührt und anschliessend zur Trockene einge-

dampft. Der Rückstand wird in Ether aufgenommen, Mit Natriumbicarbonat und Sole gewaschen. Das Rohprodukt wird ohne Reinigung weiterverarbeitet.

Beispiel 38:

In analoger Weise wie vorstehend beschrieben kann man auch die folgenden Verbindungen herstellen:

1. N-(3-Phenoxyprop-1-yl)-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amin;
2. N-[2-(4-Hydroxyphenyl)ethyl]-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin;
3. N-[3-(4-Hydroxyphenyl)prop-1-yl]-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin;
4. N-(8-Hydroxyokt-1-yl)-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amin;
5. N-(2-Methansulfonylaminoethyl)-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin;
6. N-(3-Acetylaminoprop-1-yl)-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin;
7. N-(2-Methoxy-2-oxo-1-phenyl-ethyl)-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin;
8. N-(4-Hydroxybut-2-yl)-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amin;
9. N-(2-Hydroxy-1-phenyl-ethyl)-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin; und
10. N-[3-(4-Hydroxybenzylcarbonylamino)prop-1-yl]-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin.

Beispiel 39: N-(2-Ethoxycarbonyl-2,2-tetramethylen-ethyl)-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin

3.75 g N-[(2′-Cyano-biphenyl-4-yl)-methyl]-N-valeryl-1-aminomethyl-c yclopentan-1-carbonsäure-ethylester werden in 200 ml Xylol mit 10.4 g Tri-n-butylzinnazid versetzt und während 41 h zum Rückfluss erhitzt. Darauf wird im Vakuum eingedampft, der Rückstand in 50 ml 2N NaOH-Lösung aufgenommen und 3 mal mit Ether extrahiert. Die wässrige Phase wird sodann mit 30 ml 4N Salzsäure angesäuert und mit Dichlormethan extrahiert. Das Produkt wird durch Eindampfen der zuvor über Na_2SO_4 getrockneten organischen Phase als farbloser Schaum erhalten, R_f= 0.53 (System N 8). MS (FAB): m/e 490 (M^++H).

Das Ausgangsmaterial kann beispielsweise folgendermassen hergestellt werden:

a) 1-Aminomethyl-cyclopentan-1-carbonsäure-ethylester wird erhalten durch hydrieren von 33 g 1-Cyano-cyclopentan-1-carbonsäure-ethylester (Alfred Bader Chemicals) in 330 ml Ethanol, der ca. 4% Ammoniak enthält, in Gegenwart von 10 g Raney-Nickel bei 45°C und unter Normaldruck. Nach Abfiltrieren vom Katalysator und Entfemen der Lösungsmittel im Vakuum wird das Produkt durch Destillation erhalten, Sdp. 71-74°C bei 0.75 mbar.

b) N-[(2′-Cyano-biphenyl-4-yl)-methyl]-1-aminomethyl-cyclopentan-1-carbonsäure-äthylester wird analog Beispiel 1 b) aus 4.15 g 2′-Cyanobiphenyl-4-carbaldehyd und 4.15 g 1-Aminomethyl-cyclopentan-1-carbonsäure-ethylester erhalten und an Kieselgel 60 (40-63 µm) mit CH_2Cl_2/-MeOH (99.5:0.5) gereinigt, R_f = 0.38 (System N 6).

c) N-[(2′-cyano-biphenyl-4-yl)-methyl]-N-valeryl-1-aminomethyl-cyclopentan-1-carbonsäure-äthylester wird analog Beispiel 1 c) aus 4.70 g N-[(2′-Cyano-biphenyl-4-yl)methyl]-1-aminomethyl-cyclopentan-1-carbonsäure-ethylester erhalten und an Kieselgel 60 (40-63 µm) mit CH_2Cl_2-MeOH 99.5:0.5 gereinigt, R_f = 0.69 (System N 6).

Beispiel 40: N-(2-Carboxy-2,2-tetramethylen-ethyl)-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin

0.979 g N-[(2′-(1H-Tetrazol-5-yl)biphenyl-4-yl)methyl]-N-valeryl-1-am inomethyl-cyclopentan-1-carbonsäure-ethylester werden in 10 ml Ethanol gelöst, mit 4 ml 2 N NaOH-Lösung versetzt und während 23 h zum Rückfluss erhitzt. Nach Abkühlen auf Raumtemperatur und Zugabe von 4.5 ml 2N Salzsäure wird eingedampft und das Produkt durch Chromatographie an Kieselgel 60 (40-63 µm) mit CH_2Cl_2-MeOH 95:5 isoliert, R_f = 0.35 (System N 8). MS (FAB): m/e 462 (M^++H).

Beispiel 41: N-(3-Ethoxycarbonylcyclohexyl)-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin und N-(3-Carboxycyclohexyl)-N-pentanoyl-N-(2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin

0.661 g N-[(2′-Cyano-biphenyl-4-yl)methyl]-N-valeryl-3-amin o-cyclohexan-1-carbonsäure-ethylester werden analog Beispiel 1 umgesetzt und extraktiv gereinigt. Das Rohprodukt wird an Kieselgel 60 (40-63 µm) mit CH_2Cl_2-MeOH 95:5 gereinigt, R_f = 0.33 (System N 8) für die Säure und R_f = 0.67 (System N 8) für den Ester. MS (FAB): m/e 462 (M^++H), 484 (M^++Na) bzw. m/e 490 (M^+ +H), 512 (M^++Na).

Das Ausgangsmaterial kann beispielsweise folgendermassen hergestellt werden:

a) rac-3-[2′-Cyano-biphenyl-4-yl)methylamino]-cyclohex an-1-carbonsäure-ethylester wird aus 2.711 g 4-Brommethyl-2′-cyano-biphenyl und 2.055 g 3-Amino-cyclohexan-1-carbonsäure-ethylester in Gegenwart von N-Methylmorpholin bei 10 minütigem Erhitzen auf 160°C erhalten. Das Rohprodukt wird an Kieselgel 60 (40-63 µm) mit CH_2Cl_2-MeOH 9: 1 gereinigt, R_f = 0.73 (System N 8).

b) rac-N-[(2′-Cyano-biphenyl-4-yl)methyl]-N-valeryl-3- amino-cyclohexan-1-carbonsäure-ethylester wird analog Beispiel 1 c) aus 0.766 g rac-3-[(2′-Cyano-biphenyl-4-yl)methylamino]-cyclohexan-1-carbonsäure-eth ylester erhalten und an Kieselgel 60 (40-63 µm) mit CH_2Cl_2-MeOH 99.5:0.5 gereinigt, R_f = 0.56 (System N 6).

Beispiel 42: cis-N-(4-Carboxycyclohexyl)-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin

2.700 g cis-N-[(2′-Cyano-biphenyl-4-yl)methyl]-N-valeryl-4-amino-cycl ohexan-1carbonsäure-ethylester werden analog Beispiel 1 umgesetzt und extraktiv gereinigt. R_f = 0.40 (System N 8). MS (FAB): m/e 462 (M^++H).

Das Ausgangsmaterial kann beispielsweise folgendermassen hergestellt werden:

a) cis-4-[(2′-Cyano-biphenyl-4-yl)methylamino]-cyclohexan-1-carb onsäure-ethylester wird analog Beispiel 1 b) aus 4.145 g 2′-Cyanobiphenyl-4-carbaldehyd und 5.137 g 4-Amino-cyclohexan-1-carbonsäure-ethylester erhalten und an Kieselgel 60 (40-63 µm) mit CH_2Cl_2-MeOH 99.5:0.5 gereinigt, R_f = 0.18 (System N 6).

b) cis-N-[(2′-Cyano-biphenyl-4-yl)methyl]-N-valeryl-4-amino-cycl ohexan-1-carbonsäure-ethylester wird analog Beispiel 1c aus 2.540 g cis-4-[(2′-Cyano-biphenyl-4-yl)methylamino]-cyclohexan-1-carbonsäure-ethylester erhalten und an Kieselgel 60 (40-63 µm) mit CH_2Cl_2-MeOH 98:2 gereinigt, R_f = 0.32 (System N 6).

Beispiel 43: cis-N-(2-Ethoxycarbonylcyclohexyl)-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin

1.350 g rac-cis-N-[(2′-Cyano-biphenyl-4-yl)methyl]-N-valeryl-2-amino-cyclohexan-1-carbonsäure-ethylester werden analog Beispiel 1 umgesetzt. Das Rohprodukt wird an Kieselgel 60 (40-63 µm) mit CH_2Cl_2-MeOH 95:5 gereinigt, R_f = 0.53 (System N 8). MS (FAB): m/e 490 (M^++H).

Das Ausgangsmaterial kann beispielsweise folgendermassen hergestellt werden:

a) rac-cis-2-[(2′-Cyano-biphenyl-4-yl)methylamino]-cyclohexan-1- carbonsäure-ethylester wird analog Beispiel 1 b) aus 4.145 g 2′-Cyanobiphenyl-4-carbaldehyd und 5.137 g rac-cis-2-Amino-cyclohexan-1-carbonsäure-ethylester erhalten und an Kieselgel 60 (40-63 µm) mit CH_2Cl_2-MeOH 99:1 gereinigt, R_f = 0.24 (System N 6).

b) rac-cis-N-[(2′-Cyano-biphenyl-4-yl)methyl]-N-valeryl-2-amino-cyclohexan-1-carbonsäure-ethylester wird analog Beispiel lc) aus 2.110 g rac-cis-2-[(2′-Cyano-biphenyl-4-yl)methylamino]-cyclohexan-1-carbonsäure-äthylester erhalten und an Kieselgel 60 (40-63 µm) mit CH_2Cl_2-MeOH 98:2 gereinigt, R_f = 0.35 (System N 6).

Beispiel 44: cis-N-(2-Carboxycyclohexyl)-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin

649 mg rac-cis-N-[(2′-(1H-Tetrazol-5-yl)biphenyl-4-yl)methyl]-N-valeryl-2-aminocyclohexan-1-carbonsäure-ethylester werden zusammen mit 10 ml Ethanol und 2 ml 2 N NaOH während 18 Std. auf 80° erhitzt. Die Mischung wird mit 2 ml 2 N HCl neutralisiert und eingedampft. Das Rohprodukt wird an Kieselgel 60 (40-63 µm) mit CH_2Cl_2-MeOH (95:5) gereinigt, R_f = 0.30 (System N 8). MS (FAB): m/e 462 (M^++H), 484 (M^++Na).

Beispiel 45: N-(2-Ethoxycarbonyl-2-ethyl-but-1-yl)-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin

3.28 g N-[(2′-Cyano-biphenyl-4-yl)methyl]-N-valeryl-2-aminomethyl-2- ethyl-buttersäure-ethylester werden analog Beispiel 1 umgesetzt und extraktiv gereinigt. R_f=0.52 (System N 8). MS (FAB): m/e 492 (M^++H), 514 (M^++Na).

Das Ausgangsmaterial kann beispielsweise folgendermassen hergestellt werden:

a) 2-Aminomethyl-2-ethyl-buttersäure-ethylester wird erhalten durch hydrieren von 12.83 g 2-Ethyl-2-cyano-buttersäure-ethylester (Pfaltz . Bauer Inc.) in 130 ml Ethanol, der 4% Ammoniak enthält, in Gegenwert von 4 g Raney-Nickel bei 44°C und unter Normaldruck. Nach Abtrennen vom Katalysator wird im Vakuum eingedampft und die dabei zurückbleibende Flüssigkeit im Vakuum destilliert. Sdp. 60-61°C bei 0.70 mbar.

b) N-[(2′-Cyano-biphenyl-4-yl)methyl]-2-aminomethyl-2-ethyl-butt ersäure-ethylester wird aus 2.711 g 4-Brommethyl-2′-cyano-biphenyl und 4.332 g 2-Aminomethyl-2-ethyl-buttersäure-ethylester analog Beispiel 41 a) erhalten und an Kieselgel 60 (40-63 µm) mit CH_2Cl_2-MeOH 97:3 gereinigt, R_f = 0.54 (System N 6).

c) N-[(2′-Cyano-biphenyl-4-yl)methyl]-N-valeryl-2-aminomethyl-2- ethyl-buttersäure-ethylester wird analog Beispiel 1c) aus 3.256 g N-[(2′-Cyano-biphenyl-4-yl) methyl]-2-aminomethyl-2-ethyl-buttersäure-ethylester erhalten und an Kieselgel 60 (40-63 µm) mit CH_2Cl_2-MeOH 99: 1 gereinigt, R_f = 0.67 (System N 6).

Beispiel 46: N-(2-Ethoxycarbonyl-2-methyl-prop-1-yl)-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin

4.21 g N-[(2′-Cyano-biphenyl-4-yl)methyl]-N-valeryl-3-amino-2,2-dime thylpropionsäure-ethylester werden analog Beispiel 1 umgesetzt. Das Rohprodukt wird an Kieselgel 60 (40-63 µm) mit CH_2Cl_2-MeOH 9: 1 gereinigt, R_f = 0.60 (System N 8). MS (FAB): m/e 464 (M^++H), 486 (M^++Na).

Das Ausgangsmaterial kann beispielsweise folgendermassen hergestellt werden:

a) N-[(2′-Cyano-biphenyl-4-yl)methyl]-3-amino-2,2-dimethyl-propi onsäure-ethylester wird aus 2.711 g 4-Brom-methyl-2′-cyano-biphenyl und 3.630 g 3-Amino-2,2-dimethylpropionsäure-ethylester analog Beispiel 41a) erhalten und als Rohprodukt weiterverwendet, R_f = 0.54 (System N 6).

b) N-[(2′-Cyano-biphenyl-4-yl)methyl]-N-valeryl-3-amino-2,2-dime thyl-propionsäure-ethylester wird analog Beispiel 1c) aus 3.36 g N-[(2′-Cyano-biphenyl-4-yl)methyl]3-amino-2,2-dimethyl-propionsäure-ethylester erhalten und extraktiv gereinigt, R_f = 0.63 (System N 6).

Beispiel 47: N-[2-[2-(4-Hydroxyphenyl)ethylaminocarbonyl]-2,2-tetramethylen-ethyl]N-pentanoyl-N-(2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin

0.507 g N-[(2′-(1H-Tetrazol-5-yl)biphenyl-4-yl)methyl]-N-valeryl-1-am inomethylcyclopentan-1-carbonsäure wird in 4 ml DMF gelöst und mit 0.210 g Tyramin-hydrochlorid, 0.225 ml Hünig-Base und 0.164 g HOBT versetzt. Das Gemisch wird auf O°C gekühlt und es werden 0.274 g EDCI hinzugefügt. Nach 48 stündigem Rühren bei Raumtemperatur wird im Vakuum eingedampft, der Rückstand in 75 ml Essigester aufgenommen und mit 25 ml 1 N Salzsäure gewaschen. Die organische Phase wird über Na_2SO_4 getrocknet und im Vakuum von den Lösungsmittel befreit. Das so erhaltene Rohprodukt wird an Kieselgel 60 (40-63 µm) mit CH_2Cl_2-MeOH 95:5 gereinigt, R_f = 0.43 (System N 8). MS (FAB): m/e 581 (M^++H), 603 (M^++Na).

Beispiel 48: (S)-N-[1-[2-(4-Hydroxyphenyl)ethylaminocarbonyl]-2-methyl-prop-1-yl]-N-pentanoyl-N-(2′-(1H-tetrazol-5-yl)bi-phenyl-4-ylmethyl]-amin

0,5 g der Verbindung aus Beispiel 16, 0,21 g Tyramin Hydrochlorid, 0,225 ml N-Aethyldiisopropylamin, 0,164 g 1-Hydroxybenzotriazol und 0,296 g Dicyclohexylcarbodiimid werden während 48 h in 4 ml DMF bei Raumtemperatur gerührt. Nach Abdampfen des Lösungsmittels im Vakuum wird der Rückstand während 1 h in einem Gemisch von 4 ml CH_2Cl_2-MeOH-AcOH 94:3:3 verrührt. Nach Eindampfen wird mittels Flashchromatographie aufgetrennt (100 g, System N6). Nach Lyophilisieren aus tert.-Butanol erhält man das Produkt als amorphes Pulver. FAB-MS: m/e = 555 $(M+H)^+$.

Beispiel 49: (S)-N-(1-Carboxy-2,2-dimethyl-prop-1-yl)-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin

Ausgehend von 240 mg N-Valeryl-N-[(2′-cyanobiphenyl-4-yl)-methyl]-(L)-tert.-leuci nmethylester und 399 mg Tributylzinnazid wird nach Flashchromatographie (B2) das Produkt erhalten. Smp. 122-124°.

Das Ausgangsmaterial kann beispielsweise wie folgt erhalten werden:

a) N-(2′-Cyanobiphenyl-4-yl)-methyl]-(L)-tert.-leucinmethylester ausgehend von 2,5 g 2′-Cyanbiphenyl-4-carbaldehyd, 4,39 g (L)-tert.-Leucinmethylester Hydrochlorid, 895 mg Natriumcyanoborhydrid (85 %) und 12,5 g Molekularsieb 5A und anschliessender Flashchromatographie mit System N3. (DC-System N2) R_f-Wert: 0,58.

b) N-Valeryl-N-[(2′-cyanobiphenyl-4-yl)-methyl]-(L)-tert.-leucinmethylester ausgehend von 1,2 g N-(2′-Cyanobiphenyl-4-yl)-methyl]-(L)-tert.-leucinmethylester, 0,65 ml Triethylamin und 0,565 ml n-Valeriansäurechlorid und anschliessender Flashchromatographie (N4). (DC-System N3) R_f-Wert: 0,56.

Beispiel 50: (S)-N-(1-Methoxycarbonyl-2-methyl-prop-1-yl)-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin

0,8 g N-Valeryl-N-[(2′-(1H-tetrazol-5-yl)biphenyl-4-yl)-methyl]-(L)-valinmethylester wird erhalten analog Beispiel 3 ausgehend von 4,4 g N-Valeryl-N-[(2′-(1H-tetrazol-5-yl)biphenyl-4-yl)-methyl]-(L)-valin die in MeOH/HCl verestert werden. Flashchromatographie (Essigester/Hexan 1:3). FAB-MS: m/e = 450 $(M+H)^+$.

Beispiel 51: (S)-N-(1-Hydroxymethyl-2-methyl-prop-1-yl)-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin

0,8 g N-Valeryl-N-[(2′-(1H-tetrazol-5-yl)biphenyl-4-yl)-methyl]-(L) - valinmethylester werden in 30 ml THF gelöst, bei 5°C mit 83 mg Lithiumborhydrid versetzt und während 24 h bei Raumtemperatur gerührt. Das Reaktionsgemisch wird darauf eingeengt, mit Wasser versetzt, mit Salzsäure auf pH 2 gestellt, wobei eine weisse Fällung eintritt. Es wird mit Essigester extrahiert, mit Wasser und Sole gewaschen, getrocknet und schliesslich mittels Flashchromatographie aufgetrennt (CH_2Cl_2-MeOH 5: 1). FAB-MS:m/e = 422 $(M+H)^+$.

Beispiel 52: N-(4-Phenoxybut-1-yl)-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin

3,3 g (7,5 mMol) rohes N-[(2′-Cyanobiphenyl-4-yl)-methyl]-N-(4-phenoxybutyl)-n-valeriansäureamid und 3,0 g (9 mMol) Tri-n-butylzinnazid werden analog Beispiel 23 umgesetzt und aufgearbeitet. Man erhält so die Titelverbindung, die durch Flashchromatographie (Toluol-Methanol 4: 1) noch gereinigt wird, als dickflüssiges Oel, R_f 0,50 (System B6).

Das Ausgangsmaterial kann beispielsweise auf folgende Weise hergestellt werden:

a) 4-[N-(4-Phenoxybutyl)-aminomethyl]-2′-cyanobiphenyl.
Analog Beispiel 23a erhält man aus 4-Phenoxybutylamin die Titelverbindung, deren Hydrochlorid bei 103-104° schmilzt (aus Isopropanol-Aethylacetat).

b) N-[(2′-Cyanobiphenyl-4-yl)-methyl]-N-(4-phenoxybutyl)-n-valer iansäureamid.
Analog Beispiel 23b erhält man aus der unter a) beschriebenen Verbindung die Titelverbindung als gelbes Oel vom R_f-Wert 0,71 (System B7), das roh weiterverwendet wird.

Beispiel 52: N-(2-Hydroxy-1-phenyl-2-oxo-ethyl)-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin

Analog Beispiel 1 werden 11,0 g (21 mMol) N-[(2′-Cyanobiphenyl-4-yl)-methyl]-N-valeryl-phenylglycin-benzylester mit 8,5 g (25,5 mMol) Tri-n-butylzinnazid in 60 ml o-Xylol umgesetzt und anschliessend 3 Stunden mit 100 ml 2-n.KOH hydrolysiert. Durch Ansäuern der wässrigen Phase mit 2-n.Salzsäure und Extraktion mit Toluol erhält man die rohe Titelverbindung, die aus wenig Toluol kristallin erhalten wird. Die so erhaltenen Kristalle vom Smp. 145-148 ° enthalten 1/3 Mol-Aequivalent Toluol.

Das Ausgangsmaterial kann beispielsweise wie folgt hergestellt werden:

a) rac. N-[(2′-Cyanobiphenyl-4-yl)-methyl]-phenylglycin-benzylester
24,8 g (60 mMol) rac. Phenylglycin-benzylester-tosylat und 8,2 g (30 mMol) 4-Brommethyl-2′-cyanobiphenyl werden zusammen mit 15,5 g Diisopropylethylamin (Hünigbase) in 60 ml DMF 2 Stunden unter Rühren bei 80° gehalten. Das Reaktionsgemisch wird dann auf Eiswasser gegossen und mit Aethylacetat extrahiert. Das Aethylacetat wird abgetrennt und mit 2-n.Salzsäure verrührt. Das ölig ausfallende Hydrochlorid der Titelverbindung wird abgetrennt, mit Sodalösung in die Base übergeführt und roh weiterverwendet (R_f 0,65 in System B7).

b) N-[(2′-Cyanobiphenyl-4-yl)-methyl]-N-valeryl-phenylglycin-ben zylester
9,4 g (21,7 mMol) der rohen, unter a) beschriebenen Verbindung wird zusammen mit 5,7 g (44 mMol) Hünigbase in 45 ml Methylenchlorid gelöst und mit 3,14 g (26 mMol) Valeriansäurechlorid versetzt. Die Lösung wird 30-40 Stunden stehen gelassen. Aufarbeitung analog Beispiel Ic ergibt die rohe Titelverbindung als dickflüssiges Oel mit Rf-Wert 0,73 (System B7), welches roh weiterverwendet wird.

Beispiel 54: (S)-N-(1-Carboxy-2-methyl-prop-1-yl)-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-amin

Eine Lösung von 21,1 g (40 mMol) N-[(2′-(1H-Tetrazol-5-yl)biphenyl-4-yl)methyl]-N-valeryl-(L)-valinbenzylester in 210 ml Methanol wird unter Zusatz von 4 g Pd/C (10 %) bis zur Aufnahme der berechneten Menge Wasserstoff bei Raumtemperatur hydriert (24 Stunden). Durch Filtration und Eindampfen der Lösung erhält man die rohe Säure. Sie wird zwischen 80 ml 2-n.Kalilauge und 50 ml Aether verteilt. Die wässrige Phase wird abgetrennt, sauer gestellt und die Titelverbindung durch Extraktion mit Ethylacetat isoliert. Sie wird aus Ethylacetat kristallin erhalten und zeigt einen Schmelzintervall von 105-115 ° und eine optische Drehung $[\alpha]_D^{20}$ -69,95°±0,05° (c = 1 % in Methanol).

Das Ausgangsmaterial kann beispielsweise wie folgt hergestellt werden:

a) N-[(2′-Cyanobiphenyl-4-yl)-methyl] -(L)-valinbenzylester
Eine Lösung von 13,6 g (50 mMol) 4-Brommethyl-2′-cyanobiphenyl, 22,8 g (60 mMol) (L)-ValOBz-Tosylat und 34 ml Hünigbase in 100 ml DMF wird 1 Stunde bei 80° gerührt. Das Reaktionsgemisch wird dann abgekühlt, auf 300 ml Eiswasser gegossen und mit 150 ml Ethylacetat extrahiert. Durch Waschen des Extraktes mit wässriger Kalium-

bicarbonatlösung, Trocknen und Eindampfen erhält man die rohe Titelverbindung als Oel, das ein Hydrochlorid vom Smp. 172-173° bildet.

b) N-[(2′-Cyanobiphenyl-4-yl)-methyl]-N-valeryl-(L)-valinbenzyle ster

6,2 g (15,5 mMol) N-[(2′-Cyanobiphenyl-4-yl)-methyl] -(L)-valinbenzylester und 8,0 ml Hünigbase, gelöst in 50 ml Methylenchlorid werden unter Rühren mit 2,3 ml Valeriansäurechlorid versetzt und analog Beispiel 29b weiterbearbeitet. Man erhält so die Titelverbindung als gelbes Oel, das roh weiterverarbeitet wird (R_f-Wert 0,51, Toluol-Methanol 19: 1)

c) (S)-N-(1-Benzyloxycarbonyl-2-methyl-prop-1-yl)-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin 6,6 g (13,6 mMol) roher N-[(2′-Cyanobiphenyl-4-yl)-methyl]-N-valeryl-(L)-valinbenzylester und 6,0 g (18 mMol) Tributylzinnazid werden in 75 ml o-Xylol 48 Stunden unter Rühren zum Sieden erhitzt. Nach 24 Stunden erfolgt ein Zusatz von 2,0 g Tributylzinnazid. Aufarbeitung analog Beispiel 23 unter Verwendung von 110 ml 1-n.Kalilauge während 20 Minuten ergibt die Titelverbindung als gelbliches Oel, das einen R_f-Wert von 0,40 (System S2) und eine optische Drehung $[\alpha]_D^{20}$ - 36,6° (c = 1 % in Methanol) aufweist.

Beispiel 55: (S)-N-(1-Benzyloxycarbonyl-2-methyl-prop-1-yl)-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin

Eine Lösung von 91 g (ca. 100 mMol) rohem N-[(2′-(1-Triphenylmethyl-tetrazol-5-yl)biphenyl-4-yl)methyl]-N-valeryl-(L)-valinbenzylester in 300 ml Dioxan wird bei 60° mit 300 ml 1-n.Salzsäure versetzt und 2 Stunden bei 60° gehalten. Das Dioxan wird hierauf im Vakuum abgedampft und die wässrige Phase mit 2-n.Kalilauge alkalisch gestellt. Neutrale Teile werden mit Aether extrahiert. Die Wasserphase ergibt durch Ansäuern und Extraktion mit Ethylacetat die rohe Titelverbindung als Oel (R_f 0,40 im System S2).

Das Ausgangsmaterial kann beispielsweise wie folgt hergestellt werden:

a) N-[(2′-(1-Triphenylmethyl-tetrazol-5-yl)biphenyl-4-yl)methyl] - (L)-valinbenzylester
Analog Beispiel 57a erhält man aus 4-Brommethyl-2′-(1-triphenylmethyl-tetrazol-5-yl)biphenyl die Titelverbindung (R_f 0,78 im System B6), die roh weiterverwendet wird.

b) N-[(2′-(1-Triphenylmethyl-tetrazol-5-yl)biphenyl-4-yl)methyl]-N-valeryl-(L)-valinbenzylester
Die unter a) erwähnte Verbindung wird mit 2,5 Aequivalenten Valeriansäurechlorid und 5 Aequivalenten Hünigbase in Methylenchlorid analog Beispiel 29b umgesetzt und aufgearbeitet. Die so erhaltene Titelverbindung wird roh weiterumgesetzt.

Beispiel 56: N-Butanoyl-N-(1-carboxy-1-methyl-ethyl)-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin

Eine Lösung von 2,1 g (4,2 mMol) 2-Amino-N-butyryl-2-methyl-N-[(2′-(1H-tetrazol-5-yl) biphenyl-4-yl)methyl]-propansäurebenzylester in 20 ml Methanol wird unter Zusatz von 0,2 g Pd/C (10 %) bei 5 bar Anfangsdruck hydriert, bis der Ausgangsbenzylester im DC (System B6, S2) nicht mehr nachzuweisen ist. Durch Filtrarion, Abdampfen des Lösungsmittels und Umkristallisation des Rückstandes aus CH_3CN erhält man die Titelverbindung vom Smp. 187-189°.

Das Ausgangsmaterial kann beispielsweise wie folgt hergestellt werden:

a) 2-Amino-N-(2′-cyanobiphenyl-4-ylmethyl)-2-methyl-propansäure-benzylester
Analog Beispiel 29a erhält man unter Verwendung von 2-Amino-2-methyl-propansäurebenzylester-tosylat die Titelverbindung, die ein Hydrochlorid vom Smp. 200-202° (Ethylacetat-4-n.HCl in absolutem Ethanol) bildet.

b) 2-Amino-N-butyryl-N-(2′-cyanobiphenyl-4-ylmethyl)-2-methylpropansäure-benzylester
Eine Lösung von 6,3 g (15 mMol) des Hydrochlorids der unter a) beschriebenen Verbindung und 10,2 ml (60 mMol) Hünigbase in 60 ml Methylenchlorid wird mit 1,8 g (16 mMol) Buttersäurechlorid versetzt und über Nacht gerührt. Durch weitere Zusätze von Säurechlorid und Hünigbase wird die Reaktion vervollständigt. Aufarbeitung analog Beispiel 23b ergibt die Titelverbindung, die roh weiterumgesetzt wird.

c) 2-Amino-N-butyryl-2-methyl-N-[(2′-(1H-tetrazol-5-yl)biphenyl 4-yl)-methyl]-propansäure-benzylester
Aus der unter b) beschriebenen Verbindung (6 g, roh) und 5,2 g Tributylzinnazid in 50 ml o-Xylol erhält man analog Beispiel 23 die Titelverbindung vom Smp. 203-204° (aus Ethylacetat).

Beispiel 57: N-(4-Hydroxybut-1-yl)-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin

Analog Beispiel 33 erhält man aus N-[(2′-Cyanobiphenyl-4-yl)methyl]-N-(4-hydroxybutyl)-n-valeriansäureamid die Titelverbindung vom Smp. 110-111° (aus Ethylacetat).

Das Ausgangsmaterial kann beispielsweise wie folgt hergestellt werden:

a) 4-[N-(4-Hydroxybutyl)-aminomethyl]-2′-cyanobiphenyl
Analog Beispiel 33a) erhält man unter Verwendung von 4-Aminobutanol die Titelverbindung als Oel (R_f 0,18 in System B7), das roh weiterverwendet wird.

b) N-[(2′-Cyanobiphenyl-4-yl)-methyl]-N-(4-hydroxybutyl)-n-valeriansäureamid
Analog Beispiel 33b) erhält man aus der unter a) beschriebenen Verbindung die Titelverbindung als Oel (R_f 0,37) das roh weiter umgesetzt wird.

Beispiel 58: (S)-N-(1-Benzyloxycarbonyl-2-methyl-prop-1-yl)-N-[3-brom-2′-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-N-pentanoyl-amin

Eine Lösung von 4,5 g (8 mMol) N-[(3-Brom-2′-cyanobiphenyl-4-yl)methyl]-N-valeryl(L)-valinbenzylester und 3,4 g (10,4 mMol) Tributylzinnazid in 50 ml Xylol wird 20 Stunden unter Rückfluss zum Sieden erhitzt. Aufarbeitung analog Beispiel 54 und "flash"-Chromatographische Reinigung (Toluol-Methanol 4: 1) ergibt die Titelverbindung als farblosen Schaum (R_f-Wert 0,57, System S2).

Das Ausgangsmaterial kann beispielsweise wie folgt hergestellt werden:

a) 3′-Brom-4′-methyl- 1,1′-biphenyl-2-carbonitril
Eine Suspension von 21,0 g (0,157 Mol) wasserfreiem Aluminiumchlorid in 800 ml Tetrachloräthan wird mit 25,0 g (0,129 Mol) 4′-Methyl-1,1′-biphenyl-2-carbonitril versetzt und unter Rühren auf 60° Innentemperatur gebracht. Sobald das Aluminiumchlorid in Lösung gegangen ist, wird bei 60° Innentemperatur eine Lösung von 20,7 g (0,129 Mol) Brom in 100 ml Tetrachloräthan zugetropft. Das Reaktionsgemisch wird 24 Stunden bei 60° gerührt. Nach Zusatz von weiteren 6,2 g Aluminiumchlorid und Erwärmen auf 60-70° lässt sich in DC (Toluol) kein Ausgangsmaterial mehr feststellen. Das Reaktionsgemisch wird hierauf unter Eiskühlung mit 20 ml conc. Salzsäure zersetzt, die organische Phase abgetrennt und im Vakuum eingedampft. Der dunkle Rückstand wird in Aethylacetat gelöst, mit Wasser und Natriumcarbonat-Lösung gewaschen, getrocknet ($MgSO_4$) und eingedampft. Das Rohprodukt wird flash-chromatographisch gereinigt, wodurch 22,0 g (62 % d. Th.) der Titelverbindung erhalten werden, Smp. 104-106° (aus Cyclohexan).

b) 3′-Brom-4′-brommethyl-1,1′-biphenyl-2-carbonitril
In eine Lösung von 8,9 g (0,033 Mol) 3′-Brom-4′-methyl-1,1′-biphenyl-2-carbonitril in 900 ml Tetrachloräthan werden nach Zugabe von 0,1 g Benzoylperoxid unter UV-Bestrahlung bei 100-110° 5,6 g (0,035 Mol) Brom, gelöst in 20 ml Tetrachloräthan, getropft. Nach 30 Minuten wird das Reaktionsgemisch abgekühlt und im Vakuum eingedampft. Der kristalline Rückstand wird aus Aethylacetat umkristallisiert und ergibt 4,1 g der Titelverbindung vom Smp. 152-153°.

c) N-[(3-Brom-2′-cyanobiphenyl-4-yl)methyl]-(L)-valin-benzyleste r
Eine Lösung von 4,63 g (12,2 mMol) (L)-Valinbenzylester-tosylat und 4,8 ml Hünig-Base in 20 ml DMF wird mit einer Lösung von 3,3 g (9,4 mMol) der unter b) beschriebenen Verbindung versetzt und 4 Stunden bei 100° gerührt. Aufarbeitung analog Beispiel 54a und "flash"-chromatographische Reinigung (n-Hexan-Ethylacetat 4: 1) führen zur Titelverbindung als rotbraunem Oel mit R_f 0,21 (n-Hexan-Ethylacetat 4: 1).

d) N-[(3-Brom-2′-cyanobiphenyl-4-yl)methyl]-N-valeryl-(L)-valin benzylester
Aus der unter c) erwähnten Verbindung erhält man analog Beispiel 54b die Titelverbindung als gelbes Oel mit R_f 0,17 (n-Hexan-Ethylacetat).

Beispiel 59: (S)-N-[3-Brom-2′-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-N-(1-carboxy-2-methyl-prop-1-yl)-N-pentanoyl-amin

Eine Lösung von 2,4 g (4 mmol) N-[(3-Brom-2′-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]-N-valeryl-(L)-valinbenzylester in 90 ml Dioxan wird unter Zusatz von 1,2 g Pd/C (10 %) bei 5 bar und Zimmertemperatur bis zur Aufnahme der berechneten Menge Wasserstoff hydriert. Nach dem Eindampfen der filtrierten Lösung wird der Eindampfrückstand in 2-n.Natronlauge gelöst, mit Aether extrahiert und die Wasserphase mit 2-n.Salzsäure sauer gestellt. Durch Extraktion mit

Ethylacetat, Trocknen und Eindampfen erhält man die Titelverbindung als farblosen Schaum (R_f 0,40, System S2), FAB-MS: m/e = 514 $(M+H)^+$.

Beispiel 60: N-(2-Acetylaminoethyl)-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin

9,9 g (22 mMol) rohes N-(2-Acetylamino-ethyl)-N-[2′-cyanobiphenyl-4-yl)methyl]-n-valeriansäureamid und 12,3 g (37 mMol) Tributylzinnazid werden in 100 ml Xylolgemisch 30 Stunden unter Rückfluss erhitzt. Der sich abscheidende Niederschlag wird nach dem Abkühlen durch Dekantieren isoliert und anschliessend durch Verrühren zwischen 100 ml Ether und 100 ml 1-n.Kalilauge in Lösung gebracht (3-4 Stunden). Aus der wässrigen, alkalischen Phase wird die Titelverbindung durch Ansäuern mit 2-n.HCl und Extraktion mit viel Ethylacetat isoliert und durch "flash"-Chromatographie (System S2) gereinigt. Man erhält so die Titelverbindung als Feststoff mit einem Schmelzintervall von 74-80°.

Das Ausgangsmaterial kann beispielsweise wie folgt hergestellt werden:

a) N-[2-2′-Cyanobiphenyl-4-yl)methylamino)ethyl]-acetamid

Aus 9,2 g (90 mMol) 2-Aminoethylacetamid und 8,1 g (30 mMol) 4-Brommethyl-2′-cyanobiphenyl in 100 ml Dioxan erhält man analog Beispiel 23a die Titelverbindung als Oel, das roh weiterverwendet wird.

b) N-[(2-Acetylamino-ethyl)-N-[(2′-cyanobiphenyl-4-yl)methyl]-n-valeriansäureamid

Eine Lösung von 4,2 g (8,8 mMol) der unter a) erwähnten Verbindung und 5,0 ml Hünig-Base in 40 ml Methylenchlorid wird mit 2,4 g (20 mMol) Valeriansäurechlorid versetzt und 24 Stunden unter Rückfluss zum Sieden erhitzt. Aufarbeitung analog Beispiel 23b und "flash"-chromatographische Reinigung (n-Hexan-Ethylacetat 4:1)ergeben die Titelverbindung als gelbes Oel mit R_f 0,17 (n-Hexan-Ethylacetat 4:1).

Beispiel 61: N-[2-(n-Butoxycarbonyl)-2,2-tetramethylen-ethyl]-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin

0,490 g N-[(2′-(1H-Tetrazol-5-yl)biphenyl-4-yl)methyl]-N-valeryl-1-aminomethyl-cyclopentan-1-carbonsäure wird in 20 ml 1-Butanol gelöst, mit Molekularsieb 4Å sowie 0,5 ml 4N Salzsäure versetzt und 48 Stunden zum Rückfluss erhitzt. Das Reaktionsgemisch wird im Vakuum eingedampft und an Kieselgel 60 (40-63 µm) mit CH_2Cl_2-MeOH 95:5 gereinigt, R_f = 0,73 (System N8). MS(FAB): $^m/_e$ 518 (M^+H), 540 (M^+Na).

Beispiel 62: N-(2-Ethoxycarbonyl-2,2-pentamethylen-ethyl)-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin

8,70 g N-[(2′-Cyano-biphenyl-4-yl)methyl]-N-valeryl-1-aminomethyl-cyclohexan-1carbonsäureethylester werden analog Beispiel 1 umgesetzt. Das Rohprodukt wird an Kieselgel 60 (40-63 µm) mit CH_2Cl_2-MeOH 95:5 gereinigt, R_f = 0,66 (System N8). MS (FAB): $^m/_e$ 504 (M^+H), 526 (M^+Na), 542 (M^+K).

Das Ausgangsmaterial kann beispielsweise folgendermassen hergestellt werden:

a) 1-Aminomethyl-cyclohexan-1-carbonsäureethylester wird erhalten durch hydrieren von 72,08g 1-Cyano-cyclohexan-1-carbonsäureethylester (T. Kurihara et al. Tet. Lett. 1976, 2455) in 600 ml Aethanol, der ca. 4 % Ammoniak enthält, in Gegenwart von 20 g Raney-Nickel bei 45°C und unter Normaldruck. Nach Entfernen des Katalysators und Lösungsmittels wird das Produkt durch Destillation erhalten, Siedepunkt 72-75°C bei 0,3 mbar.

b) N-[(2′-Cyano-biphenyl-4-yl)methyl]-1-aminomethyl-cyclohexan-1-carbonsäureethylester wird analog Beispiel 41a) aus 5,422 g 4-Brommethyl-2′-cyano-biphenyl und 9,264 g 1-Aminomethyl-cyclohexan-1-carbonsäureethylester erhalten und an Kieselgel 60 (40-63 µm) mit CH_2Cl_2-MeOH 97,5:2,5 gereinigt, R_f = 0,67 (System N6).

c) N-[(2′-Cyano-biphenyl-4-yl)methyl]-N-valeryl-1-aminomethyl-1 - carbonsäureethylester wird analog Beispiel 1c) aus 7,12 g N-[(2′-Cyano-biphenyl-4-yl)methyl]-1-aminomethylcyclohexan-1-carbonsäureethylester erhalten und extraktiv gereinigt, R_f = 0,68 (System N6).

Beispiel 63: N-(2-Benzylaminocarbonyl-2,2-tetramethylen-ethyl)-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin

0,507 g N-[(2′-(1H-Tetrazol-5-yl)biphenyl-4-yl)methyl]-N-valeryl-1-aminomethyl-cyclopentan-1-carbonsäure wird analog Beispiel 48 mit 0,214 g Benzylamin umgesetzt und das Rohprodukt wird an Kieselgel 60 (40-63 µm) mit CH_2Cl_2-MeOH 95:5 gereinigt, R_f = 0,49 (System N8). MS (FAB): $^m/_e$ 551 (M^+H), 573 (M^+Na).

Beispiel 64: N-(2-Carboxy-2-ethyl-but-1-yl)-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin

1,146 g N-[(2′-(1H-Tetrazol-5-yl)biphenyl-4-yl)methyl]-N-valeryl-2-aminomethyl-2-ethyl-buttersäure-ethylester werden in 10 ml Ethanol gelöst, mit 4,66 ml 2N NaOH-Lösung versetzt und 20 Stunden zum Rückfluss erhitzt. Nach Abkühlen auf Raumtemperatur und Zugabe von 4,66 ml 2N Salzsäure wird eingedampft. Das Produkt wird durch Chromatographie an Kieselgel 60 (40-63 µm) mit CH_2Cl_2-MeOH 80:20 isoliert, R_f = 0,38 (System N8). MS (FAB): $^m/_e$ 486 (M^++Na), 502 (M^++K).

Beispiel 65: (S)-N-(1-Carboxy-2-methyl-prop-1-yl)-N-ethoxycarbonyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin

0.34 g N-Carboethoxy-N-[(2′-(1H-tetrazol-5-yl)biphenyl-4-yl)-methyl] - (L)-valin-benzylester und 0.17 g Palladiumkohle (10%) werden in 10 ml Tetrahydrofuran unter Normaldruck 20 Stunden bis zur Sättigung hydriert. Es wird vom Katalysator abfiltriert und das Rohprodukt wird mittels Flashchromatographie (25 g Kieselgel, Fliessmittel B1) gereinigt. Amorphes Produkt FAB-MS:m/e = 424 ($M+H^+$).

Das Ausgangsmaterial kann beispielsweise wie folgt erhalten werden:

a) N-Carboethoxy-N-[(2′-Cyanobiphenyl-4-yl)methyl]-(L)-valin-ben zylester

10.0 g N-[(2′-Cyanobiphenyl-4-yl)methyl]-(L)-valin-benzylester werden in 150 ml Chloroform gelöst und bei 0° mit 8.2 ml Diisopropylethylamin versetzt. Man gibt 2.4 ml Chlorameisensäureethylester zu und erhitzt während 3 Stunden zum Rückfluss. Das Reaktionsgemisch wird mit 0.1 M-Salzsäure und Sole gewaschen, getrocknet und eingeengt. Amorphes Produkt. DC (System N3) R_f-Wert: 0.45.

b) N-Carboethoxy-N-[(2′-(1H-tetrazol-5-yl)biphenyl-4-yl)methy l]-(L)-valin-benzylester

10.0 g N-Carboethoxy-N-[(2′-Cyanobiphenyl-4-yl)methyl]-(L)-valin-ben zylester und 9.2 g Tributylzinnazid werden in 150 ml Xylol 18 Stunden zum Rückfluss erhitzt. Das Reaktionsgemisch wird eingeengt und der Rückstand während 15 Minuten in 5M etherischer Salzsäure verrührt. Man engt wieder ein, löst den Rückstand in Ether und extrahiert mit kalter 4M Kalilauge. Die Wasserphase wird sauer gestellt und mit Essigester extrahiert. Diese Essigesterphase wird mit Sole gewaschen, über Magnesiumsulfat getrocknet und eingeengt. Das Rohprodukt wird mittels Flashchromatographie (250 g Kieselgel, Fliessmittel N6) gereinigt. Amorphes Produkt, DC (System N6) R_f-Wert: 0.22.

Beispiel 66: (S)-N-(1-Carboxy-2-methyl-prop-1-yl)-N-propyloxycarbonyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin

Analog Beispiel 1 ausgehend von 0.14 g N-Carbopropoxy-N-[(2′-(1H-tetrazol-5-yl)biphenyl-4-yl)-methyl]-(L)-valin und 0.07 g Palladiumkohle wird nach Flashchromatographie (B1) das amorphe Produkt erhalten. FAB-MS: m/e = 438 ($M+H^+$).

Das Ausgangsmaterial kann beispielsweise wie folgt erhalten werden:

a) N-Carbopropoxy-N-[(2′-Cyanobiphenyl-4-yl)methyl]-(L)-valin -benzylester ausgehend von 1.0 g N-[(2′-Cyanobiphenyl-4-yl)methyl]-(L)-valin-benzylester 0.8 ml Diisopropylethylamin und 0.34 ml Chlorameisensäurepropylester und anschliessender Flashchromatographie mit System N3. Amorphes Produkt. DC (System N2) R_f-Wert: 0.38.

b) N-Carbopropoxy-N-[(2′-(1H-tetrazol-5-yl)biphenyl-4-yl)methy l]-(L)-valin-benzylester ausgehend von 1.04 g N-Carbopropoxy-N-[(2′-Cyanobiphenyl-4-yl)methyl]-(L)-valin-benzylester und 1.1 g Tributylzinnazid und anschliessender Flashchromatographie mit dem System N6. Amorphes Produkt, DC (System N6) R_f-Wert: 0.21.

Beispiel 67: (S)-N-Butyloxycarbonyl-N-(1-Carboxy-2-methyl-prop-1-yl)-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin

Analog Beispiel 1 ausgehend von 0.40 g N-Carbobutoxy-N-[(2′-(1H-tetrazol-5-yl)biphenyl-4-yl)-methyl]-(L)-valin und 0.20 g Palladiumkohle wird nach Flashchromatographie (B1) das amorphe Produkt erhalten. FAB-MS: m/e = 452 ($M+H^+$).

Das Ausgangsmaterial kann beispielsweise wie folgt erhalten werden:

a) N-Carbobutoxy-N-[(2′-Cyanobiphenyl-4-yl)methyl]-(L)-valin -benzylester ausgehend von 1.0 g N-[(2′-Cyanobiphenyl-4-yl)methyl]-(L)-valin-benzylester 0.8 ml Diisopropylethylamin und 0.34 ml Chlorameisensäurebutylester und anschliessender Flashchromatographie mit System N3. Amorphes Produkt. DC (System N2) R_f-Wert: 0.41.

b) N-Carbobutoxy-N-[(2′-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]- (L)-valin-benzylester ausgehend von 1.05 g N-Carbobutoxy-N-[(2′-Cyanobiphenyl-4-yl)methyl]-(L)-valin-benzylester und 1.05 g Tributylzinnazid und anschliessender Flashchromatographie mit dem System N6. Amorphes Produkt, DC (System N6) R_f-Wert: 0.17.

Beispiel 68: (S)-N-(1-Carboxy-2-methyl-prop-1-yl)-N-methoxycarbonyl-N-[(2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin

Analog Beispiel 1 ausgehend von 2.40 g N-Carbomethoxy-N-[(2′-(1H-tetrazol-5-yl) biphenyl-4-yl)-methyl]-(L)-valin und 0.50 g Palladiumkohle wird nach Flashchromatographie (B1) das amorphe Produkt erhalten. FAB-MS: m/e = 410 (M+H⁺).

Das Ausgangsmaterial kann beispielsweise wie folgt erhalten werden:

a) N-Carbomethoxy-N-[(2′-Cyanobiphenyl-4-yl)methyl]-(L)-valin -benzylester ausgehend von 4.0 g N-[(2′-Cyanobiphenyl-4-yl)methyl]-(L)-valin-benzylester 3.3 ml Diisopropylethylamin und 0.78 ml Chlorameisensäuremethylester und anschliessender Flashchromatographie mit System N3. Amorphes Produkt. DC (System N3) R_f-Wert: 0.34.

b) N-Carbomethoxy-N-[(2′-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl] -(L)-valin-benzylester ausgehend von 3.21 g N-Carbomethoxy-N-[(2′-Cyanobiphenyl-4-yl) methyl]-(L)-valin-benzylester und 3.50 g Tributylzinnazid und anschliessender Flashchromatographie mit dem System N6. Amorphes Produkt, DC (System N6) R_f-Wert: 0.26.

Beispiel 69:

In analoger Weise wie in Beispiel 47 beschrieben kann man auch das N-(2-Diethylaminocarbonyl-2,2-tetramethylen-ethyl)-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin [R_f-Wert: 0,47 (System N8)] herstellen.

Beispiel 70:

In analoger Weise wie in Beispiel 47 beschrieben kann man auch das N-(2-Methyl-2-morpholin-4-ylcarbonyl-propyl)-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin [R_f-Wert: 0,61 (System N8)] herstellen.

Beispiel 71:

In analoger Weise wie in Beispiel 64 beschrieben kann man auch das N-(2-Carboxy-2-methyl-propyl)-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin [R_f-Wert: 0,39 (System N8)] herstellen.

Beispiel 72:

In analoger Weise wie in Beispiel 40 beschrieben kann man auch das N-(2-Carboxy-2,2-pentamethylen-ethyl)-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl] -amin [R_f-Wert: 0,33 (System N8)] herstellen.

Beispiel 73:

Eine Lösung von 1,5 g (2,8 mmol) N-(1-Benzyloxycarbonylcyclopentyl)-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin in 20 ml Dioxan wird unter Zusatz von 0,3 g Pd/C (10%) in analoger Weise wie in Beispiel 56 beschrieben hydriert. Nach Reinigung durch Flash-Chromatographie (Kieselgel; System S2) erhält man das N-(1-Carboxycyclopentyl)-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin in Form eines Schaumes [R_f-Wert: 0,29 (System S2)].

Das Ausgangsmaterial kann z. B. wie folgt hergestellt werden:

a) Ein Gemisch aus 2,72 g (10 mmol) 4-Brommethyl-2′-cyano-biphenyl, 2,63 g (12 mmol) 1-Aminocyclopentancarbonsäurebenzylester, 3,4 ml (20 mmol) Hünigbase und 10 ml N,N-Dimethylformamid wird unter Rühren 2 Stunden auf 130 bis 140° (Badtemperatur) erhitzt. Nach dem Abkühlen wird das Reaktionsgemisch auf 50 ml Eiswasser gegossen. Durch Extraktion mit Ethylacetat erhält man das rohe N-(1-Benzyloxycarbonylcyclopentyl)-N-(2′-cyanobiphenyl-4-ylmethyl)-amin, das ein zwischen 180 und 182° (Ethanol/Diethylether) schmelzendes Hydrochlorid bildet.

b) Eine Lösung von 2,9 g (6,5 mmol) N-(1-Benzyloxycarbonylcyclopentyl)-N-(2′-cyanobiphenyl-4-ylmethyl)-amin-hydrochlorid und 4,4 ml (26 mmol) Hünigbase in 50 ml Ethylacetat wird mit 1,1 g (9 mmol) Pentanoylchlorid versetzt und das Gemisch 15 Stunden bei 25 bis 30° gerührt. Nach Zusatz von weiteren 0,5 g Pentanoylchlorid wird weitere

8 Stunden gerührt. Das Reaktionsgemisch wird dann mit 10 ml wässriger Ammoniaklösung (5%) versetzt und 0,5 Stunden gerührt. Die Ethylacetatphase wird abgetrennt, nacheinander mit 2 N-Salzsäure, Wasser und Natriumhydrogencarbonatlösung gewaschen, getrocknet und eingedampft. Man erhält so das N-(1-Benzyloxycarbonylcyclopentyl)-N-(2′-cyanobiphenyl-4-ylmethyl)-N-pentanoyl-amin in Form eines braunen Oels [R_f-Wert: 0,53 (System B7)], das in roher Form weiterumgesetzt wird.

c) Ein Gemisch aus 3,2 g (6,5 mmol) N-(1-Benzyloxycarbonylcyclopentyl)-N-(2′-cyanobiphenyl-4-ylmethyl)-N-pentanoyl-amin, 3,3 g (9,8 mmol) Tributylzinnazid und 35 ml o-Xylol wird 24 Stunden unter Rückfluss erhitzt. Aufarbeitung des Gemisches in analoger Weise wie in Beispiel 23 beschrieben ergibt das N-(1-Benzyloxycarbonylcyclopentyl)-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin in Form eines gelben Oels [R_f-Wert: 0,37 (System S2)], das in roher Form weiterumgesetzt werden kann.

Beispiel 74:

Eine Lösung von 2,4 g (4,3 mmol) N-(1-Benzyloxycarbonylcyclohexyl)-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin in 40 ml Dioxan wird unter Zusatz von 0,5 g Pd/C (10%) in analoger Weise wie in Beispiel 73 beschrieben hydriert und aufgearbeitet. Man erhält so das N-(1-Carboxycyclohexyl)-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin in Form von farblosen Kristallen (aus Ethylacetat), die zwischen 134 und 136° schmelzen.

Das Ausgangsmaterial kann z. B. wie folgt hergestellt werden:

a) Das N-(1-Benzyloxycarbonylcyclohexyl)-N-(2′-cyanobiphenyl-4-ylmethyl)-amin, das ein zwischen 164 und 166° (Isopropanol) schmelzendes Hydrochlorid bildet, erhält man in analoger Weise wie in Beispiel 73a) beschrieben.

b) Eine Lösung von 2,9 g (6,8 mmol) N-(1-Benzyloxycarbonylcyclohexyl)-N-(2′-cyanobiphenyl-4-ylmethyl)-amin und 4,4 ml (26 mmol) Hünigbase in 50 ml Ethylacetat wird mit 1,1 g (9 mmol) Pentanoylchlorid versetzt und das Gemisch 24 Stunden unter Rückfluss erhitzt. Nach dem Abkühlen wird das Reaktionsgemisch mit 20 ml wässriger Ammoniaklösung (2 N) versetzt und 1 Stunde gerührt. Die organische Phase wird abgetrennt, nacheinander mit 2 N-Salzsäure, gesättigter Natriumhydrogencarbonatlösung und Sole gewaschen, getrocknet und eingedampft. Man erhält so das N-(1-Benzyloxycarbonylcyclohexyl)-N-(2′-cyanobiphenyl-4-ylmethyl)-N-pentanoyl-amin in Form eines braunen Oels [R_f-Wert: 0,44 (Toluol/Methanol = 19:1)], das in roher Form weiterumgesetzt wird.

c) Ein Gemisch aus 3,3 g (6,5 mmol) N-(1-Benzyloxycarbonylcyclohexyl)-N-(2′-cyanobiphenyl-4-ylmethyl)-N-pentanoyl-amin, 4,1 g (12,3 mmol) Tributylzinnazid und 30 ml o-Xylol wird 44 Stunden unter Rückfluss erhitzt. Aufarbeitung des Gemisches in analoger Weise wie in Beispiel 23 beschrieben ergibt das N-(1-Benzyloxycarbonylcyclohexyl)-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin in Form von hellbraunen Kristallen, die zwischen 189 und 190° (aus Ethylacetat/Diethylether) schmelzen.

Beispiel 75:

In analoger Weise wie in Beispiel 74 beschrieben kann man auch das N-(1-Carboxy-1-ethyl-prop-1-yl)-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin [heller Schaum; R_f-Wert: 0,35 (System S2)] herstellen.

Beispiel 76:

170 mg (S)-N-(1-Benzyloxycarbonyl-5-benzyloxycarbonylamino-pent-1-yl)N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin werden in 5 ml Methanol gelöst. Die Lösung wird mit 170 mg Palladium/Kohle (10%) versetzt und das Gemisch unter Normaldruck und bei Raumtemperatur bis zur Sättigung hydriert. Das Gemisch wird über Hyflo filtriert und das Filtrat eingedampft, wodurch das reine (S)-N-(5-Amino-1-carboxy-pent-1-yl)-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin in Form eines weissen Schaumes erhalten wird [MS (FAB): m/z = 465, $(M + H)^+$].

Das Ausgangsmaterial kann z. B. wie folgt hergestellt werden:

a) 5,0 g (S)-2-Amino-6-benzyloxycarbonylamino-hexansäwebenzylester werden in 250 ml N,N-Dimethylformamid gelöst. Die Lösung wird mit 4,33 ml N,N-Diisopropyl-N-ethyl-amin versetzt und das Gemisch auf 80° erwärmt, 30 Minuten gerührt, mit 4,44 g 4-Brommethyl-2′-(1-triphenylmethyl-1H-tetrazol-5-yl)-biphenyl versetzt, 16 Stunden bei 80° gerührt und dann eingedampft. Der Rückstand wird mit Wasser und Ethylacetat aufgearbeitet. Die organische Phase wird getrocknet und mittels Flashchromatographie gereinigt (200 g Kieselgel; System N4). Das (S)-N-(1-Benzyloxycarbonyl-5-benzyloxycarbonylamino-pent-1-yl)-N-[2′-(1-triphenylmethyl-1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin wird in Form eines braunen Oels erhalten [R_f-Wert: 0,18 (System N3)].

b) 1,1 g (S)-N-(1-Benzyloxycarbonyl-5-benzyloxycarbonylamino-pent-1-yl)-N-[2′-(1-triphenylmethyl-1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin werden in 20 ml CH_2Cl_2 gelöst. Die Lösung wird auf 0° gekühlt und mit 0,408 ml N,N-Diisopropyl-N-ethyl-amin und anschliessend mit 0,29 ml Pentanoylchlorid versetzt. Man rührt das Gemisch 15 Minuten in einem Eisbad und dann 16 Stunden bei Raumtemperatur. Das Gemisch wird dann mit CH_2Cl_2 verdünnt, nacheinander mit 1 N-Natronlauge, 1 N-Salzsäure, Wasser und Sole gewaschen und über $MgSO_4$ getrocknet. Nach Reinigung mittels Flashchromatographie (200 g Kieselgel; System N3) erhält man das (S)-N-(1-Benzyloxycarbonyl-5-benzyloxycarbonylamino-pent-1-yl)-N-pentanoyl-N-[2′-(1-triphenylmethyl-1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin in Form eines bräunlichen Oels [R_f-Wert: 0,34 (System N2)].

c) 1,07 g (S)-N-(1-Benzyloxycarbonyl-5-benzyloxycarbonylamino-pent-1-yl)-N-pentanoyl-N-[2′-(1-triphenylmethyl-1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin werden in 15 ml Dioxan gelöst. Diese Lösung wird mit 1,5 ml einer Lösung von Chlorwasserstoff in Dioxan (7 N) versetzt und das Gemisch 4,5 Stunden bei 40° gerührt, eingedampft und mittels Flashchromatographie gereinigt (200 g Kieselgel; System N6). Man erhält so das (S)-N-(1 -Benzyloxycarbonyl-5-benzyloxycarbonylamino-pent-1-yl)-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin [R_f-Wert: 0,42 (System N7)].

Beispiel 77:

Ein Gemisch aus 3,64 g N-Butansulfonyl-N-(2′-cyanobiphenyl-4-ylmethyl)-N-(2-ethoxycarbonyl-2,2-pentamethylen-ethyl)-amin, 5,0 g Tributylzinnazid und 20 ml o-Xylol wird 15 Stunden unter Rückfluss erhitzt. Nach dem Abkühlen wird das Gemisch eingedampft. Der Rückstand wird mit 20 ml methanolischer Salzsäure (3 N) versetzt und das Gemisch 1 Stunde gerührt und dann eingedampft. Der Rückstand wird in Diethylether aufgenommen. Die Etherlösung wird mit 1 N-Natronlauge extrahiert. Die wässrige Phase wird mit konzentrierter Salzsäure auf pH 3 angesäuert und mit CH_2Cl_2 extrahiert. Die vereinigten organischen Phasen werden über $MgSO_4$ getrocknet und eingeengt. Der Rückstand wird durch Flashchromatographie gereinigt (220 g Kieselgel; CH_2Cl_2/Aceton = 9:1). Kristallisation aus Pentan liefert das N-Butansulfonyl-N-(2-ethoxycarbonyl-2,2-pentamethylen-ethyl)-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin [Smp.: 121° (Zersetzung)].

Das Ausgangsmaterial kann z. B. wie folgt hergestellt werden:

a) 3,0 g 1-Aminomethyl-1-ethoxycarbonyl-cyclohexan werden in 25 ml $CHCl_3$ gelöst. Die Lösung wird bei Raumtemperatur mit 0,7 ml Butansulfonylchlorid versetzt. Das Gemisch wird 5 Stunden unter Rückfluss erhitzt und nach dem Abkühlen eingedampft. Der Rückstand wird in Diethylether aufgenommen. Die etherische Phase wird nacheinander mit 1 N-Salzsäure und Wasser extrahiert, über $MgSO_4$ getrocknet und eingedampft. Der gelbe harzige Rückstand, das rohe N-Butansulfonyl-N-(2-ethoxycarbonyl-2,2-pentamethylen-ethyl)-amin [R_f-Wert: 0,64 (System N2)], kann ohne weitere Reinigung weiterumgesetzt werden.

b) 3,75 g N-Butansulfonyl-N-(2-ethoxycarbonyl-2,2-pentamethylen-ethyl)-amin werden in 30 ml Tetrahydrofuran gelöst. Die Lösung wird mit einem Eisbad gekühlt und mit 309 mg Natriumhydrid-Dispersion (80% in Oel) versetzt. Nach dem Erwärmen auf Raumtemperatur werden 3,5 g 4-Brommethyl-2′-cyano-biphenyl zugegeben. Das Gemisch wird 30 Stunden bei Raumtemperatur und dann 4 Stunden bei 60° gerührt und nach dem Abkühlen eingeengt. Der Rückstand wird in Diethylether aufgenommen. Die etherische Phase wird nacheinander mit 1 N-Salzsäure und Wasser extrahiert, getrocknet und eingeengt. Flashchromatographie des Rückstands (300 g Kieselgel; Hexan/tert.-Butylmethylether = 4:1) liefert das reine N-Butansulfonyl-N-(2′-cyanobiphenyl-4-ylmethyl)-N-(2-ethoxycarbonyl-2,2-pentamethylen-ethyl)-amin in Form eines gelben Harzes [R_f-Wert: 0,46 (Hexan/tert.-Butylmethylether = 1:1)].

Beispiel 78:

1,8 g N-Butansulfonyl-N-(2-ethoxycarbonyl-2,2-pentamethylen-ethyl)-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin werden in 50 ml Methanol/Wasser (1:1) aufgenommen. Das Gemisch wird mit 5,0 g Natriumhydroxid versetzt, 20 Stunden unter Rückfluss erhitzt, auf Raumtemperatur abgekühlt, mit Wasser verdünnt und mit Ethylacetat extrahiert. Die wässrige Phase wird mit konzentrierter Salzsäure auf pH 3 angesäuert, mit NaCl gesättigt und mit CH_2Cl_2 extrahiert. Die vereinigten organischen Phasen werden getrocknet und eingedampft. Umkristallisation aus Diethylether/Hexan liefert das reine N-Butansulfonyl-N-(2-carboxy-2,2-pentamethylen-ethyl)-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin [Smp.: 123° (Zersetzung)].

Beispiel 79:

In analoger Weise wie in Beispiel 77 beschrieben kann man auch das N-Butansulfonyl-N-(2-ethoxycarbonyl-2-methyl-prop-1 -yl)-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin (Smp.: 104°) herstellen.

Beispiel 80:

In analoger Weise wie in Beispiel 78 beschrieben kann man auch das N-Bufansulfonyl-N-(2-carboxy-2-methyl-prop-1-yl)-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin (Smp.: 137°) herstellen.

Beispiel 81:

In analoger Weise wie in Beispiel 77 beschrieben kann man auch das (S)-N-Butansulfonyl-N-(1-tert.-butoxycarbonylethyl)-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin herstellen, ausgehend von (S)-2-Aminopropansäure-tert.-butylester.

Beispiel 82:

750 mg (S)-N-Butansulfonyl-N-(1-tert.-butoxycarbonylethyl)-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin werden 24 Stunden bei 0° mit salzsaurem Eisessig (1,9 N) behandelt. Eindampfen des Gemisches und Flashchromatographie des Rückstands (100 g Kieselgel; CH_2Cl_2/Ethylacetat/Toluol/Ameisensäure = 40:40:20:4) liefert das (S)-N-Butansulfonyl-N-(1-carboxyethyl)-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin in Form eines weissen amorphen Pulvers [Smp.: 90° (Zersetzung bei 127°)].

Beispiel 83:

In analoger Weise wie in den Beispielen 77 und 37 beschrieben kann man auch das (S)-N-Butansulfonyl-N-(1-carboxy-2-methyl-prop-1-yl)-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin [Smp.: 103° (Zersetzung)] herstellen, ausgehend von (S)-2-Amino-3-methyl-butansäurebenzylester-p-toluolsulfonat.

Beispiel 84:

In analoger Weise wie in Beispiel 48 beschrieben kann man auch das (S)-N-(1-Aminocarbonyl-2-methyl-prop-1-yl)-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin (Smp.: 177 bis 178°) herstellen.

Beispiel 85:

In analoger Weise wie in Beispiel 48 beschrieben kann man auch das (S)-N-(2-Methyl-1-methylaminocarbonyl-prop-1-yl)-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin (Smp.: 183 bis 184°) herstellen.

Beispiel 83:

In analoger Weise wie in Beispiel 48 beschrieben kann man auch das (S)-N-(1-Dimethylaminocarbonyl-2-methyl-prop-1-yl)-N-pentanoyl-N-[2′-(1H-tetrazol1-5-yl)biphenyl-4-ylmethyl] -amin (Smp.: 179 bis 180°) herstellen.

Beispiel 87:

In analoger Weise wie in Beispiel 48 beschrieben kann man auch das (S)-N-(2-Methyl-1-morpholin-4-ylcarbonyl-prop-1-yl)-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin [Smp.: 130° (Zersetzung)] herstellen.

Beispiel 83:

In analoger Weise wie in Beispiel 8 beschrieben kann man auch das (S)-N-(2′-Carboxybiphenyl-4-ylmethyl)-N-(1-carboxy-2-methyl-prop-1-yl)-N-pentanoylamin (Smp.: 66 bis 68°) herstellen.

Beispiel 89:

In analoger Weise wie in Beispiel 16 beschrieben kann man auch das (S)-N-(1,2-Dicarboxyethyl)-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin (Smp.: 303 bis 305°) herstellen.

Beispiel 90:

In analoger Weise wie in Beispiel 16 beschrieben kann man auch das (S)-N-(1-Carboxy-2-methyl-prop-1-yl)-N-(5-oxopent-1-en-5-yl)-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin (Smp.: 108 bis 109°) herstellen.

Beispiel 91:

In analoger Weise wie vorstehend beschrieben kann man auch die folgenden Verbindungen herstellen:

1. (S)-N-(1-Carboxy-3-phenyl-prop-1-yl)-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin (Smp.: 124 bis 125°);
2. (S)-N-(2-Cyclohexyl-1-hydroxymethyl-ethyl)-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin (Smp.: 86 bis 87°);
3. (R)-N-(1-Methoxycarbonyl-2-methyl-prop-1-yl)-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin (Smp.: 77 bis 78°);
4. (S)-N-(2-Hydroxy-1-methoxycarbonyl-ethyl)-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin;
5. N-Pentanoyl-N-(1H-tetrazol-5-ylmethyl)-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin;
6. N-Pentanoyl-N-pyrid-3-ylmethyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin;
7. (S)-N-(1-Carboxy-4-guanidino-but-1-yl)-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl] -amin-hydrochlorid [R_f-Wert: 0,34 (CH_2Cl_2/CH_3OH/konzentriertes Ammoniak = 20:10:1)];
8. N-(2-Hydroxy-1-methoxycarbonyl-prop-1-yl)-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin;
9. N-(1-Benzyloxycarbonyl-1-methyl-ethyl)-N-butanoyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin (Smp.: 203 bis 204°);
10. (S)-N-(1-Carboxy-3-methyl-but-1-yl)-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin (Smp.: >300°);
11. N-(1-Carboxy-2-hydroxy-ethyl)-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin;
12. (S)-N-(1-Carboxy-2-hydroxy-ethyl)-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin;
13. (S)-N-[2-Methyl-1-(2-phenylethylaminocarbonyl)-prop-1-yl]-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin (Smp.: 109 bis 111 °);
14. (S)-N-(2-Benzyloxy-1-hydroxymethyl-ethyl)-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl] -amin;
15. (S)-N-(1-Carboxy-2-methyl-prop-1-yl)-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-3-ylmethyl]-amin (Smp.: 78 bis 79°);
16. (S)-N-(1-Carboxy-2-methyl-prop-1-yl)-N-pentanoyl-N-[3′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin (Smp.: 97 bis 98°);
17. (S)-N-[2-Methyl-1-(1,2,3,4-tetrahydrochinol-1-ylcarbonyl)-prop-1 - yl] -N-pentanoylN-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin (Smp.: 100 bis 110°);
18. (S)-N-(2-Methyl-1-piperidin-1-ylcarbonyl-prop-1-yl)-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin (Smp.: 100°);
19. (S)-N-[2-Methyl-1-(1,2,3,4-tetrahydroisochinol-2-ylcarbonyl)-prop-1-yl]-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin (Smp.: 122°):
20. N-(2-Hydroxymethyl-2-methyl-prop-1-yl)-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl] -amin [R_f-Wert: 0,45 (CH_2Cl_2/CH_3OH = 4:1)];
21. N-Ethoxycarbonyl-N-(2-ethoxycarbonyl-2-methyl-prop-1-yl)-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl] -amin [R_f-Wert: 0,64 (CH_2Cl_2/CH_3OH = 4:1)]; und
22. N-(2-Carboxy-2-methyl-prop-1-yl)-N-ethoxycarbonyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin [R_f-Wert: 0,32 (CH_2Cl_2/CH_3OH = 4:1)].

Beispiel 92:

Tabletten, enthaltend je 50 mg Wirkstoff, z.B. (S)-N-(1-Carboxy-2-methylprop-1-yl)-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin, können wie folgt hergestellt werden:

Zusammensetzung (für 10000 Tabletten):

Wirkstoff	500,0 g
Lactose	500,0 g
Kartoffelstärke	352,0 g
Gelatine	8,0 g
Talk	60,0 g
Magnesiumstearat	10,0 g
Siliciumdioxid (hochdispers)	20,0 g
Ethanol	q.s.

Der Wirkstoff wird mit der Lactose und 292 g Kartoffelstärke vermischt, die Mischung mit einer alkoholischen Lösung der Gelatine befeuchtet und durch ein Sieb granuliert. Nach dem Trocknen mischt man den Rest der Kartoffelstärke, den Talk, das Magnesiumstearat und das hochdisperse Siliciumdioxid zu und presst das Gemisch zu Tabletten von je 145,0 mg Gewicht und 50,0 mg Wirkstoffgehalt, die gewünschtenfalls mit Teilkerben zur feineren Anpassung der Dosierung versehen sein können.

Beispiel 93:

Lacktabletten, enthaltend je 100 mg Wirkstoff, z.B. (S)-N-(1-Carboxy-2-methyl-prop-1-yl)-N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin, können wie folgt hergestellt werden:

Zusammensetzung (für 1000 Tabletten):

Wirkstoff	100,00 g
Lactose	100,00 g
Maisstärke	70,00 g
Talk	8,50 g
Calciumstearat	1,50 g
Hydroxypropylmethylcellulose	2,36 g
Schellack	0,64 g
Wasser	q.s.
Dichlormethan	q.s.

Der Wirkstoff, die Lactose und 40 g der Maisstärke werden gemischt und mit einem Kleister, hergestellt aus 15 g Maisstärke und Wasser (unter Erwärmen), befeuchtet und granuliert. Das Granulat wird getrocknet, der Rest der Maisstärke, der Talk und das Calciumstearat werden zugegeben und mit dem Granulat vermischt. Das Gemisch wird zu Tabletten (Gewicht: 280 mg) verpresst und diese mit einer Lösung der Hydroxypropylmethylcellulose und des Schellacks in Dichlormethan lackiert (Endgewicht der Lacktablette: 283 mg).

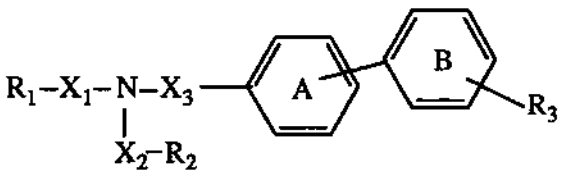
Beispiel 94:

In analoger Weise wie in den Beispielen 92 und 93 beschrieben können auch Tabletten und Lacktabletten, enthaltend eine andere Verbindung der Formel I oder ein pharmazeutisch verwendbares Salz einer Verbindung der Formel I, z.B. gemäss einem der Beispiele 1 bis 91, hergestellt werden.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE

1. Eine Verbindung der Formel



(I),

worin R_1 gegebenenfalls durch Halogen oder Hydroxy substituiertes Niederalkyl, Niederalkenyl oder Niederalkinyl oder C_3-C_7-Cycloalkyl- oder C_3-C_7-Cycloalkenyl oder Phenylniederalkyl, Phenylniederalkenyl oder Phenylniederalkinyl bedeutet; X_1 für CO, SO_2 oder -O-C(=O)- steht, wobei das Kohlenstoffatom der Carbonylgruppe an das in der Formel I eingezeichnete Stickstoffatom gebunden ist; X_2 gegebenenfalls durch Hydroxy, Carboxy, Amino, Guanidino, C_3-C_7-Cycloalkyl, C_3-C_7-Cycloalkenyl, Phenyl oder einen entsprechenden 5- oder 6-gliedrigen und monocyclischen aromatischen Rest, der bis zu vier gleiche oder verschiedene Heteroatome aufweist, substituiertes C_1-C_{10}-Alkylen, C_2-C_{10}-Alkyliden oder C_3-C_7-Cycloalkylen bedeutet, wobei ein Kohlenstoffatom von C_1-C_{10}-Alkylen bzw. C_2-C_{10}-Alkyliden zusätzlich durch C_2-C_6-Alkylen überbrückt sein kann, und wobei C_3-C_7-Cycloalkyl oder C_3-C_7-Cycloalkenyl gegebenenfalls ein- oder mehrfach substituiert sind durch Carboxy, Carboxy, welches durch einen Alkohol verestert ist, der sich von Niederalkyl, Phenylniederalkyl, Niederalkenyl, Niederalkinyl, Niederalkoxyniederalkyl, Niederalkoxyniederalkenyl oder Niederalkoxyniederalkinyl ableitet, Carbamoyl, Carbamoyl, in welchem die Aminogruppe durch Niederalkyl, Niederalkenyl, Niederalkinyl, Phenylniederalkyl, Phenylniederalkenyl oder Phenylniederalkinyl mono- oder unabhängig voneinander disubstituiert oder durch C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden disubstituiert ist, wobei C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden gegebenenfalls durch -O- unterbrochen oder an zwei benachbarten C-Atomen mit einem Benzolring kondensiert sind, Formyl, Diniederalkoxymethyl oder Oxyniederalkylenoxymethylen; R_2 Carboxy, Carboxy, welches durch einen Alkohol verestert ist, der sich von Niederalkyl, Phenylniederalkyl, Niederalkenyl, Niederalkinyl, Niederalkoxyniederalkyl, Niederalkoxyniederalkenyl oder Niederalkoxyniederalkinyl ableitet, Carbamoyl, Carbamoyl, in welchem die Aminogruppe durch Niederalkyl, Niederalkenyl, Niederalkinyl, Phenylniederalkyl, Phenylniederalkenyl oder Phenylniederalkinyl mono- oder unabhängig voneinander disubstituiert oder durch C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden disubstituiert ist, wobei C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden gegebenenfalls durch -O- unterbrochen oder an zwei benachbarten C-Atomen mit einem Benzolring kondensiert sind, Amino, Amino, welches durch Niederalkyl, Niederalkenyl, Niederalkinyl, Phenylniederalkyl, Phenylniederalkenyl oder Phenylniederalkinyl mono- oder unabhängig voneinander disubstituiert oder durch C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden disubstituiert ist, wobei C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden gegebenenfalls durch -O- unterbrochen oder an zwei benachbarten C-Atomen mit einem Benzolring kondensiert sind, Niederalkanoyl-, Phenylniederalkanoyl-, Benzoyl-, Niederalkansulfonyl-, Benzolsulfonyl-amino, Formyl, Diniederalkoxymethyl, Oxyniederalkylenoxymethylen, 1H-Tetrazol-5-yl, Pyridyl, Hydroxy, Niederalkoxy, Niederalkenyloxy, Phenylniederalkoxy, Phenoxy, $S(O)_m$-R, wobei m für 0, 1 oder 2 steht und R Wasserstoff, Niederalkyl, Niederalkenyl oder Niederalkinyl bedeutet, Niederalkanoyl, Sulfamoyl, Sulfamoyl, in welchem die Aminogruppe durch Niederalkyl, Niederalkenyl, Niederalkinyl, Phenylniederalkyl, Phenylniederalkenyl oder Phenylniederalkinyl mono- oder unabhängig voneinander disubstituiert oder durch C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden disubstituiert ist, wobei C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden gegebenenfalls durch -O- unterbrochen oder an zwei benachbarten C-Atomen mit einem Benzolring kondensiert sind, oder PO_nH_2 bedeutet, wobei n für 2 oder 3 steht; X_3 C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden bedeutet; R_3 Carboxy, 5-Tetrazolyl, SO_3H, PO_2H_2, PO_3H_2 oder Halogenniederalkylsulfamoyl ist; und wobei (hetero-)aromatische Reste einschliesslich der Ringe A und B unabhängig voneinander gegebenenfalls substituiert sind durch Substituenten ausgewählt aus der Gruppe bestehend aus: Halogen, Hydroxy, Niederalkoxy, Niederalkenyloxy, Phenylniederalkoxy, Phenoxy, $S(O)_m$-R und gegebenenfalls durch Halogen oder Hydroxy substituiertes Niederalkyl, Niederalkenyl oder Niederalkinyl, wobei Niederalkyl, Niederalkenyl oder Niederalkinyl gegebenenfalls durch -O- unterbrochen sind, sowie, im Falle von (hetero-)aromatischen Resten, gegebenenfalls zusätzlich substituiert sind

durch Carboxy, Carboxy, welches durch einen Alkohol verestert ist, der sich von Niederalkyl, Phenylniederalkyl, Niederalkenyl, Niederalkinyl, Niederalkoxyniederalkyl, Niederalkoxyniederalkenyl oder Niederalkoxyniederalkinyl ableitet, durch Carbamoyl, Carbamoyl, in welchem die Aminogruppe durch Niederalkyl, Niederalkenyl, Niederalkinyl, Phenylniederalkyl, Phenylniederalkenyl oder Phenylniederalkinyl mono- oder unabhängig voneinander disubstituiert oder durch C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden disubstituiert ist, wobei C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden gegebenenfalls durch -O- unterbrochen oder an zwei benachbarten C-Atomen mit einem Benzolring kondensiert sind, durch Formyl, Diniederalkoxymethyl oder Oxyniederalkylenoxymethylen; wobei mit "nieder" bezeichnete Reste und Gruppen bis und mit 7 Kohlenstoffatome enthalten; in freier Form oder in Salzform.

2. Eine Verbindung gemäss Anspruch 1 der Formel I, worin R_1 gegebenenfalls durch Halogen oder Hydroxy substituiertes Niederalkyl, Niederalkenyl oder Niederalkinyl oder C_3-C_7-Cycloalkyl oder C_3-C_7-Cycloalkenyl oder Phenylniederalkyl, Phenylniederalkenyl oder Phenylniederalkinyl bedeutet; X_1 für CO oder SO_2 steht; X_2 einen gegebenenfalls durch Hydroxy, C_3-C_7-Cycloalkyl oder C_3-C_7-Cycloalkenyl oder Phenyl oder einen entsprechenden 5- oder 6-gliedrigen und monocyclischen aromatischen Rest, der bis zu vier gleiche oder verschiedene Heteroatome aufweist, substituiertes C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden oder C_3-C_7-Cycloalkylen bedeutet, wobei ein Kohlenstoffatom von C_1-C_{10}-Alkylen bzw. C_2-C_{10}-Alkyliden zusätzlich durch C_2-C_6-Alkylen überbrückt sein kann, und wobei C_3-C_7-Cycloalkylen gegebenenfalls ein- oder mehrfach substituiert sind durch Carboxy, Carboxy, welches durch einen Alkohol verestert ist, der sich von Niederalkyl, Phenylniederalkyl, Niederalkenyl, Niederalkinyl, Niederalkoxyniederalkyl, Niederalkoxyniederalkenyl oder Niederalkoxyniederalkinyl ableitet, Carbamoyl, Carbamoyl, in welchem die Aminogruppe durch Niederalkyl, Niederalkenyl, Niederalkinyl, Phenylniederalkyl, Phenylniederalkenyl oder Phenylniederalkinyl mono- oder unabhängig voneinander disubstituiert oder durch C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden disubstituiert ist, wobei C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden gegebenenfalls durch -O- unterbrochen sind, Formyl, Diniederalkoxymethyl oder Oxyniederalkylenoxymethylen; R_2 Carboxy, Carboxy, welches durch einen Alkohol verestert ist, der sich von Niederalkyl, Phenylniederalkyl, Niederalkenyl, Niederalkinyl, Niederalkoxyniederalkyl, Niederalkoxyniederalkenyl oder Niederalkoxyniederalkinyl ableitet, Carbamoyl, Carbamoyl, in welchem die Aminogruppe durch Niederalkyl, Niederalkenyl, Niederalkinyl, Phenylniederalkyl, Phenylniederalkenyl oder Phenylniederalkinyl mono- oder unabhängig voneinander disubstituiert oder durch C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden disubstituiert ist, wobei C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden gegebenenfalls durch -O- unterbrochen sind, Amino, Amino, welches durch Niederalkyl, Niederalkenyl, Niederalkinyl, Phenylniederalkyl, Phenylniederalkenyl oder Phenylniederalkinyl mono- oder unabhängig voneinander disubstituiert oder durch C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden disubstituiert ist, wobei C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden gegebenenfalls durch -O- unterbrochen sind, Niederalkanoyl-, Phenylniederalkanoyl-, Benzoyl-, Niederalkansulfonyl-, Benzolsulfonyl-amino, Formyl, Diniederalkoxymethyl, Oxyniederalkylenoxymethylen, Hydroxy, Niederalkoxy, Niederalkenyloxy, Phenylniederalkoxy, Phenoxy, $S(O)_m$-R, wobei m für 0, 1 oder 2 steht und R Wasserstoff, Niederalkyl, Niederalkenyl oder Niederalkinyl bedeutet, Niederalkanoyl, Sulfamoyl, Sulfamoyl, in welchem die Aminogruppe durch Niederalkyl, Niederalkenyl, Niederalkinyl, Phenylniederalkyl, Phenylniederalkenyl oder Phenylniederalkinyl mono- oder unabhängig voneinander disubstituiert oder durch C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden disubstituiert ist, wobei C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden gegebenenfalls durch -O-unterbrochen sind, oder PO_nH_2 bedeutet, wobei n für 2 oder 3 steht; X_3 C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden bedeutet; R_3 Carboxy, 5-Tetrazolyl, SO_3H, PO_2H_2, PO_3H_2 oder Halogenniederalkylsulfamoyl ist; wobei (hetero-)aromatische Reste einschliesslich der Ringe A und B unabhängig voneinander gegebenenfalls substituiert sind durch Substituenten ausgewählt aus der Gruppe bestehend aus: Halogen, Hydroxy, Niederalkoxy, Niederalkenyloxy, Phenylniederalkoxy, Phenoxy, $S(O)_m$-R und gegebenenfalls durch Halogen oder Hydroxy substituiertes Niederalkyl, Niederalkenyl oder Niederalkinyl, wobei Niederalkyl, Niederalkenyl oder Niederalkinyl gegebenenfalls durch -O- unterbrochen sind, sowie, im Falle von (hetero-)aromatischen Resten, gegebenenfalls zusätzlich substituiert sind durch Carboxy, Carboxy, welches durch einen Alkohol verestert ist, der sich von Niederalkyl, Phenylniederalkyl, Niederalkenyl, Niederalkinyl, Niederalkoxyniederalkyl, Niederalkoxyniederalkenyl oder Niederalkoxyniederalkinyl ableitet, durch Carbamoyl, Carbamoyl, in welchem die Aminogruppe durch Niederalkyl, Niederalkenyl, Niederalkinyl, Phenylniederalkyl, Phenylniederalkenyl oder Phenylniederalkinyl mono- oder unabhängig voneinander disubstituiert oder durch C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden disubstituiert ist, wobei C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden gegebenenfalls durch -O- unterbrochen sind, durch Formyl, Diniederalkoxymethyl oder Oxyniederalkylenoxymethylen; in freier Form oder in Salzform.

3. Eine Verbindung gemäss Anspruch 1 der Formel I, worin R_1 gegebenenfalls durch Halogen oder Hydroxy substituiertes Niederalkyl, Niederalkenyl oder Niederalkinyl oder C_3-C_7-Cycloalkyl oder C_3-C_7-Cycloalkenyl oder Phenylniederalkyl, Phenylniederalkenyl oder Phenylniederalkinyl bedeutet; X_1 für CO oder SO_2 steht; X_2 gegebenenfalls durch Hydroxy, C_3-C_7-Cycloalkyl oder C_3-C_7-Cycloalkenyl oder Phenyl oder einen entsprechenden 5- oder 6-gliedrigen und monocyclischen aromatischen Rest, der bis zu vier gleiche oder verschiedene Heteroatome aufweist, substituiertes C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden bedeutet; R_2 Carboxy, Carboxy, welches durch einen Alkohol verestert ist, der sich von Niederalkyl, Phenylniederalkyl, Niederalkenyl, Niederalkinyl, Niederalkoxyniederalkyl, Nie-

deralkoxyniederalkenyl oder Niederalkoxyniederalkinyl ableitet, Carbamoyl, Carbamoyl, in welchem die Aminogruppe durch Niederalkyl, Niederalkenyl, Niederalkinyl, Phenylniederalkyl, Phenylniederalkenyl oder Phenylniederalkinyl mono- oder unabhängig voneinander disubstituiert oder durch C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden disubstituiert ist, wobei C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden gegebenenfalls durch -O- unterbrochen sind, Amino, Amino, welches durch Niederalkyl, Niederalkenyl, Niederalkinyl, Phenylniederalkyl, Phenylniederalkenyl oder Phenylniederalkinyl mono- oder unabhängig voneinander disubstituiert oder durch C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden disubstituiert ist, wobei C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden gegebenenfalls durch -O- unterbrochen sind, Niederalkanoyl-, Phenylniederalkanoyl-, Benzoyl-, Niederalkansulfonyl-, Benzolsulfonyl-amino, Formyl, Diniederalkoxymethyl, Oxyniederalkylenoxymethylen, Hydroxy, Niederalkoxy, Niederalkenyloxy, Phenylniederalkoxy oder Phenoxy, $S(O)_m$-R, wobei m für 0, 1 oder 2 steht und R Wasserstoff, Niederalkyl, Niederalkenyl oder Niederalkinyl bedeutet, Niederalkanoyl, Sulfamoyl, Sulfamoyl, in welchem die Aminogruppe durch Niederalkyl, Niederalkenyl, Niederalkinyl, Phenylniederalkyl, Phenylniederalkenyl oder Phenylniederalkinyl mono- oder unabhängig voneinander disubstituiert oder durch C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden disubstituiert ist, wobei C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden gegebenenfalls durch -O- unterbrochen sind, oder PO_nH_2 bedeutet, wobei n für 2 oder 3 steht; X_3 -CH_2- bedeutet; R_3 Carboxy, 5-Tetrazolyl, SO_3H, PO_2H_2, PO_3H_2 oder Halogenniederalkylsulfamoyl ist; und wobei (hetero-)aromatische Reste einschliesslich der Ringe A und B unabhängig voneinander gegebenenfalls substituiert sind durch Substituenten ausgewählt aus der Gruppe bestehend aus: Halogen, Hydroxy, Niederalkoxy, Niederalkenyloxy, Phenylniederalkoxy, Phenoxy, $S(O)_m$-R und gegebenenfalls durch Halogen oder Hydroxy substituiertes Niederalkyl, Niederalkenyl oder Niederalkinyl, wobei Niederalkyl, Niederalkenyl oder Niederalkinyl gegebenenfalls durch -O- unterbrochen sind, sowie, im Falle von (hetero-)aromatischen Resten, gegebenenfalls zusätzlich substituiert sind durch Carboxy, Carboxy, welches durch einen Alkohol verestert ist, der sich von Niederalkyl, Phenylniederalkyl, Niederalkenyl, Niederalkinyl, Niederalkoxyniederalkyl, Niederalkoxyniederalkenyl oder Niederalkoxyniederalkinyl ableitet, durch Carbamoyl, Carbamoyl, in welchem die Aminogruppe durch Niederalkyl, Niederalkenyl, Niederalkinyl, Phenylniederalkyl, Phenylniederalkenyl oder Phenylniederalkinyl mono- oder unabhängig voneinander disubstituiert oder durch C_1-C_{10}-Alkylen oder C_1-C_{10}-Alkyliden disubstituiert ist, wobei C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden gegebenenfalls durch -O- unterbrochen sind, durch Formyl, Diniederalkoxymethyl oder Oxyniederalkylenoxymethylen; in freier Form oder in Salzform.

4. Eine Verbindung gemäss Anspruch 1 der Formel I, worin R_1 Niederalkyl, Niederalkenyl, Niederalkinyl, Halogenniederalkyl, -niederalkenyl, -niederalkinyl, Hydroxyniederalkyl, -niederalkenyl, -niederalkinyl, C_3-C_7-Cycloalkyl, C_3-C_7-Cycloalkenyl, Phenylniederalkyl, Phenylniederalkenyl oder Phenylniederalkinyl bedeutet; X_1 für CO oder SO_2 steht; X_2 C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden bedeutet, die gegebenenfalls durch Hydroxy, einen C_3-C_7-Cycloalkyl-, C_3-C_7-Cycloalkenyl-, einen Phenylrest oder einen 5- oder 6-gliedrigen, monocyclischen heteroaromatischen Rest mit bis zu vier gleichen oder verschiedenen Heteroatomen substituiert sind, wobei die cyclischen Reste ihrerseits gegebenenfalls substituiert sind durch Carboxy, welches gegebenenfalls verestert ist mit einem Alkohol, der sich von Niederalkyl, Phenylniederalkyl, Niederalkenyl, Niederalkinyl, Niederalkoxyniederalkyl, -niederalkenyl oder -niederalkinyl ableitet, Carbamoyl, in dem die Aminogruppe gegebenenfalls durch Niederalkyl, Niederalkenyl, Niederalkinyl, Phenylniederalkyl, Phenylniederalkenyl, Phenylniederalkinyl mono- oder unabhängig voneinander disubstituiert oder durch Niederalkylen- oder Niederalkylenoxyniederalkylen disubstituiert ist, Formyl, Diniederalkoxymethyl, Oxyniederalkylenoxymethylen; R_2 Carboxy, welches gegebenenfalls verestert ist mit einem Alkohol, der sich von Niederalkyl, Phenylniederalkyl, Niederalkenyl, Niederalkinyl, Niederalkoxyniederalkyl, -niederalkenyl oder -niederalkinyl ableitet, Carbamoyl, in dem die Aminogruppe gegebenenfalls durch Niederalkyl, Niederalkenyl, Niederalkinyl, Phenylniederalkyl, Phenylniederalkenyl, Phenylniederalkinyl mono- oder unabhängig voneinander disubstituiert oder durch Niederalkylen- oder Niederalkylenoxyniederalkylen disubstituiert ist, Amino, in dem die Aminogruppe gegebenenfalls durch Niederalkyl, Niederalkenyl, Niederalkinyl, Phenylniederalkyl, Phenylniederalkenyl, Phenylniederalkinyl mono- oder unabhängig voneinander disubstituiert oder durch Niederalkylen- oder Niederalkylenoxyniederalkylen disubstituiert ist, Niederalkanoyl-, Phenylniederalkanoyl-, Benzoyl-, Niederalkansulfonyl-, Benzolsulfonyl-amino, Formyl, Diniederalkoxymethyl, Oxyniederalkylenoxymethylen, Hydroxy, Niederalkoxy, Niederalkenyloxy, Phenylniederalkoxy, Phenoxy, $S(O)_m$-R, wobei m für 0, 1 oder 2 und R für Wasserstoff, Niederalkyl, Niederalkenyl oder Niederalkinyl steht, Niederalkanoyl, Sulfamoyl, in dem die Aminogruppe gegebenenfalls durch Niederalkyl, Niederalkenyl, Niederalkinyl, Phenylniederalkyl, Phenylniederalkenyl, Phenylniederalkinyl mono- oder unabhängig voneinander disubstituiert oder durch Niederalkylen- oder Niederalkylenoxyniederalkylen disubstituiert ist, oder PO_nH_2 bedeutet, wobei n für 2 oder 3 steht; X_3 -CH_2- bedeutet; und R_3 Carboxy, 5-Tetrazolyl, SO_3H, PO_2H_2, PO_3H_2 oder Halogenniederalkylsulfamoyl bedeutet; wobei (hetero-)aromatische Reste einschliesslich der Ringe A und B unabhängig voneinander jeweils gegebenenfalls substituiert sind durch einen oder mehrere Substituenten ausgewählt aus Halogen, Hydroxy, Niederalkoxy, Niederalkenyloxy, jeweils gegebenenfalls durch Halogen oder Hydroxy substituiertes Niederalkyl, Niederalkenyl, Niederalkinyl, Niederalkoxyniederalkyl, -niederalkenyl, -niederalkinyl, Niederalkenyloxyniederalkyl, -niederalkenyl und -niederalkinyl, in freier Form oder in Salzform.

5. Eine Verbindung gemäss Anspruch 1 der Formel I, worin X_2 C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden bedeutet, die gegebenenfalls durch Hydroxy, einen C_3-C_7-Cycloalkyl-, C_3-C_7-Cycloalkenyl-, einen Phenylrest oder einen 5- oder 6-gliedrigen, monocyclischen heteroaromatischen Rest mit bis zu vier gleichen oder verschiedenen Heteroatomen substituiert sind, wobei ein C-Atom von C_1-C_{10}-Alkylen bzw. C_2-C_{10}-Alkyliden durch C_2-C_6-Alkylen überbrückt sein kann und wobei die cyclischen Reste ihrerseits gegebenenfalls substituiert sind durch Carboxy, welches gegebenenfalls verestert ist mit einem Alkohol, der sich von Niederalkyl, Phenylniederalkyl, Niederalkenyl, Niederalkinyl, Niederalkoxyniederalkyl, -niederalkenyl oder -niederalkinyl ableitet, Carbamoyl, in dem die Aminogruppe gegebenenfalls durch Niederalkyl, Niederalkenyl, Niederalkinyl, Phenylniederalkyl, Phenylniederalkenyl, Phenylniederalkinyl mono- oder unabhängig voneinander disubstituiert oder durch Niederalkylen- oder Niederalkylenoxyniederalkylen disubstituiert ist, Formyl, Diniederalkoxymethyl oder durch Oxyniederalkylenoxymethylen, oder X_2 C_3-C_7-Cycloalkylen bedeutet; X_3 Niederalkylen oder Niederalkyliden bedeutet; die Variablen X_1, R_1, R_2, und R_3 die in Anspruch 4 angegebenen Bedeutungen haben; und die (hetero)-aromatischen Ringe einschliesslich der Ringe A und B wie in Anspruch 4 angegeben substituiert sein können, in freier Form oder in Salzform.

6. Eine Verbindung gemäss Anspruch 1 der Formel I, worin R_1 Niederalkyl, Niederalkenyl, Halogenniederalkyl, -niederalkenyl, Hydroxyniederalkyl, 3- bis 7-gliedriges Cycloalkyl oder Phenylniederalkyl bedeutet; X_1 für CO, SO_2 oder -O-C(=O)-, wobei das Kohlenstoffatom der Carbonylgruppe an das in der Formel I eingezeichnete Stickstoffatom gebunden ist, steht; X_2 C_1-C_{10}-Alkylen oder C_1-C_7-Alkyliden, die gegebenenfalls substituiert sind durch Hydroxy, Carboxy, Amino, Guanidino, einen 3- bis 7-gliedrigen Cycloalkyl-, 3- bis 7-gliedrigen Cycloalkenyl-, Phenyl-, Pyrrolyl-, Pyrazolyl-, Imidazolyl-, Triazolyl-, Tetrazolyl-, Furyl-, Thienyl- oder Pyridylrest, welche ihrerseits gegebenenfalls zusätzlich durch Carboxy, Niederalkoxycarbonyl, Phenylniederalkoxycarbonyl, Carbamoyl, in dem die Aminogruppe gegebenenfalls durch Niederalkyl oder Phenylniederalkyl mono- oder unabhängig voneinander disubstituiert ist, Formyl, Diniederalkoxymethyl oder Oxyniederalkylenoxymethylen substituiert sein können; R_2 Carboxy, Niederalkoxy-, Phenylniederalkoxy-, Niederalkenyloxy-, Niederalkoxyniederalkoxy-carbonyl, Carbamoyl, in dem die Aminogruppe gegebenenfalls durch Niederalkyl, Phenylniederalkyl mono- oder unabhängig voneinander disubstituiert oder durch Niederalkylen, das gegebenenfalls an zwei benachbarten Kohlenstoffatomen mit einem Benzolring kondensiert ist, oder Niederalkylenoxyniederalkylen disubstituiert ist, Amino, in dem die Aminogruppe gegebenenfalls durch Niederalkyl, Phenylniederalkyl mono- oder unabhängig voneinander disubstituiert oder durch Niederalkylen- oder Niederalkylenoxyniederalkylen disubstituiert ist, Niederalkanoyl-, Phenylniederalkanoyl-, Benzoyl-, Niederalkansulfonyl-, Benzolsulfonyl-amino, Formyl, Diniederalkoxymethyl, Oxyniederalkylenoxymethylen, Hydroxy, Niederalkoxy, Phenylniederalkoxy, Phenoxy, $S(O)_m$-R, wobei m für 0, 1 oder 2 und R für Niederalkyl steht, Niederalkanoyl, Sulfamoyl, in dem die Aminogruppe gegebenenfalls durch Niederalkyl, Phenylniederalkyl mono- oder unabhängig voneinander disubstituiert ist, oder PO_nH_2 bedeutet, wobei n für 2 oder 3 steht; X_3 Methylen ist; R_3 Carboxy, 5-Tetrazolyl, SO_3H, PO_2H_2, PO_3H_2 oder Halogenniederalkylsulfamoyl bedeutet; und (hetero-)aromatische Reste einschliesslich der Ringe A und B jeweils gegebenenfalls zusätzlich substituiert sind durch einen oder mehrere Substituenten ausgewählt aus Halogen, Hydroxy, Niederalkoxy, jeweils gegebenenfalls durch Halogen oder Hydroxy substituiertes Niederalkyl bzw. Niederalkoxyniederalkyl, in freier Form oder in Salzform.

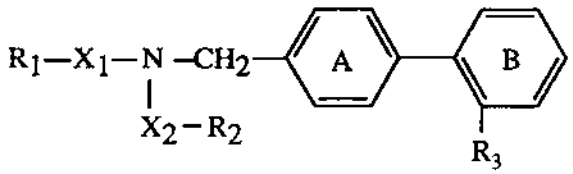
7. Eine Verbindung gemäss Anspruch 1 der Formel I, worin R_1 Niederalkyl, Niederalkenyl, Halogenniederalkyl, -niederalkenyl, Hydroxyniederalkyl, 3- bis 7-gliedriges Cycloalkyl oder Phenylniederalkyl bedeutet; X_1 für CO oder SO_2 steht; X_2 C_1-C_{10}-Alkylen oder C_1-C_7-Alkyliden, die gegebenenfalls substituiert sind durch Hydroxy, einen 3- bis 7-gliedrigen Cycloalkyl-, 3- bis 7-gliedrigen Cycloalkenyl-, Phenyl-, Pyrrolyl-, Pyrazolyl-, Imidazolyl-, Triazolyl-, Tetrazolyl-, Furyl-, Thienyl- oder Pyridylrest, welche ihrerseits gegebenenfalls zusätzlich durch Carboxy, Niederalkoxycarbonyl, Phenylniederalkoxycarbonyl, Carbamoyl, in dem die Aminogruppe gegebenenfalls durch Niederalkyl oder Phenylniederalkyl mono- oder unabhängig voneinander disubstituiert ist, Formyl, Diniederalkoxymethyl oder Oxyniederalkylenoxymethylen substituiert sein können; R_2 Carboxy, Niederalkoxy-, Phenylniederalkoxy-, Niederalkenyloxy-, Niederalkoxyniederalkoxy-carbonyl, Carbamoyl, in dem die Aminogruppe gegebenenfalls durch Niederalkyl, Phenylniederalkyl mono- oder unabhängig voneinander disubstituiert oder durch Niederalkylen- oder Niederalkylenoxyniederalkylen disubstituiert ist, Amino, in dem die Aminogruppe gegebenenfalls durch Niederalkyl, Phenylniederalkyl mono- oder unabhängig voneinander disubstituiert oder durch Niederalkylen- oder Niederalkylenoxyniederalkylen disubstituiert ist, Niederalkanoyl-, Phenylniederalkanoyl-, Benzoyl-, Niederalkansulfonyl-, Benzolsulfonyl-amino, Formyl, Diniederalkoxymethyl, Oxyniederalkylenoxymethylen, Hydroxy, Niederalkoxy, Phenylniederalkoxy, Phenoxy, $S(O)_m$-R, wobei m für 0, 1 oder 2 und R für Niederalkyl steht, Niederalkanoyl, Sulfamoyl, in dem die Aminogruppe gegebenenfalls durch Niederalkyl, Phenylniederalkyl mono- oder unabhängig voneinander disubstituiert ist, oder PO_nH_2 bedeutet, wobei n für 2 oder 3 steht; X_3 Methylen ist; R_3 Carboxy, 5-Tetrazolyl, SO_3H, PO_2H_2, PO_3H_2 oder Halogenniederalkylsulfamoyl bedeutet; und (hetero-)aromatische Reste einschliesslich der Ringe A und B jeweils gegebenenfalls zusätzlich substituiert sind durch einen oder mehrere Substituenten ausgewählt aus Halogen, Hydroxy, Niederalkoxy, jeweils gegebenenfalls durch Halogen oder Hydroxy substituiertes Niederalkyl bzw. Niederalkoxyniederalkyl, in freier Form oder in Salzform.

8. Eine Verbindung gemäss Anspruch 1 der Formel I, worin X_2 C_1-C_{10}-Alkylen oder C_1-C_7-Alkyliden, die gegebenenfalls substituiert sind durch Hydroxy, einen 3- bis 7-gliedrigen Cycloalkyl-, 3- bis 7-gliedrigen Cycloalkenyl-, Phenyl-, Pyrrolyl-, Pyrazolyl-, Imidazolyl-, Triazolyl-, Tetrazolyl-, Furyl-, Thienyl- oder Pyridylrest, welche ihrerseits gegebenenfalls zusätzlich durch Carboxy, Niederalkoxycarbonyl, Phenylniederalkoxycarbonyl, Carbamoyl, in dem die Aminogruppe gegebenenfalls durch Niederalkyl oder Phenylniederalkyl mono- oder unabhängig voneinander disubstituiert ist, Formyl, Diniederalkoxymethyl oder durch Oxyniederalkylenoxymethylen substituiert sein können, wobei ein C-Atom von C_1-C_{10}-Alkylen bzw. C_1-C_7-Alkyliden durch C_2-C_6-Alkylen überbrückt sein kann, oder X_2 C_3-C_7-Cycloalkylen bedeutet; X_3 Niederalkylen oder Niederalkyliden bedeutet; die Variablen X_1, R_1, R_2, R_3 die in Anspruch 7 angegebenen Bedeutungen haben; und die (hetero-)aromatischen Ringe einschliesslich der Ringe A und B wie in Anspruch 7 angegeben substituiert sein können, in freier Form oder in Salzform.

9. Eine Verbindung gemäss Anspruch 1 der Formel I, worin die Variablen R_1, X_1, R_3 die jeweils in einem der Ansprüche 1-7 angegebenen Bedeutungen haben; X_2 gegebenenfalls durch Hydroxy, 3- bis 7-gliedriges Cycloalkyl, Phenyl oder Imidazolyl substituiertes Niederalkylen oder Niederalkyliden bedeutet und R_2 Carboxy, Niederalkoxy-, Phenylniederalkoxy-, Niederalkoxyniederalkoxy-carbonyl, Carbamoyl, welches gegebenenfalls durch Niederalkyl, Phenylniederalkyl mono- oder unabhängig voneinander disubstituiert ist, Amino, Niederalkanoyl-, Phenylniederalkanoyl-, Niederalkansulfonylamino, Hydroxy, Niederalkoxy, Phenylniederalkoxy oder Phenoxy bedeutet; X_3 -CH_2- bedeutet; wobei (hetero-)aromatische Reste einschliesslich der Ringe A und B jeweils gegebenenfalls durch einen oder mehrere Substituenten ausgewählt aus Halogen, Trifluormethyl, Hydroxy, Niederalkoxy, Niederalkyl, Hydroxyniederalkyl oder Niederalkoxyniederalkyl substituiert sind, in freier Form oder in Salzform.

10. Eine Verbindung gemäss Anspruch 1 der Formel I, worin X_2 gegebenenfalls durch Hydroxy, 3- bis 7-gliedriges Cycloalkyl, 7-gliedriges Cycloalkenyl, Phenyl oder Imidazolyl substituiertes Niederalkylen oder Niederalkyliden bedeutet, wobei ein C-Atom von Niederalkylen bzw. Niederalkyliden durch C_2-C_6-Alkylen überbrückt sein kann, oder X_2 C_3-C_7-Cycloalkylen bedeutet; die Variablen X_1, X_3, R_1, R_2 und R_3 die in Anspruch 7 bis 9 angegebenen Bedeutungen haben; und die Ringe A und B wie in Anspruch 9 angegeben substituiert sein können, in freier Form oder in Salzform.

11. Eine Verbindung gemäss Anspruch 1 der Formel

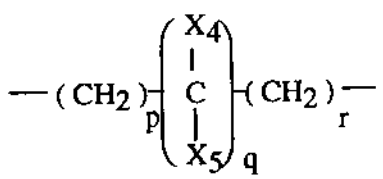


(Ia),

worin die Variablen R_1, X_1, X_2, R_2 und R_3 die jeweils in einem der Ansprüche 1-10 angegebenen Bedeutungen haben und die Ringe A und B wie in Anspruch 10 angegeben substituiert sein können, in freier Form oder in Salzform.

12. Eine Verbindung gemäss Anspruch 1 der Formel Ia, worin X_2 gegebenenfalls durch Hydroxy oder 3- bis 7-gliedriges Cycloalkyl substituiertes Niederalkylen oder Niederalkyliden bedeutet, wobei ein C-Atom von Niederalkylen bzw. Niederalkyliden durch C_2-C_6-Alkylen, überbrückt sein kann, oder worin X_2 C_3-C_7-Cycloalkylen bedeutet; die Variablen R_1, X_1, R_2 und R_3 die jeweils in einem der Ansprüche 1-10 angegebenen Bedeutungen haben; und die Ringe A und B wie in Anspruch 10 angegeben substituiert sein können, in freier Form oder in Salzform.

13. Eine Verbindung gemäss Anspruch 1 der Formel Ia, worin X_2 für die Gruppe der Formel



(Ib)

steht, in der p für 0 oder 1, q für 1 und r für 0 oder 1 stehen oder in der p für 1 bis 8 und q sowie r jeweils für 0 stehen; X_4 gegebenenfalls durch Hydroxy, 3- bis 7-gliedriges Cycloalkyl, Phenyl oder Imidazolyl substituiertes Nie-

deralkyl oder Phenyl bedeutet; und X_5 Wasserstoff oder Niederalkyl bedeutet; R_2 Carboxy, Niederalkoxycarbonyl, Phenylniederalkoxycarbonyl, Niederalkoxyniederalkoxycarbonyl, Hydroxy, Niederalkoxy, Phenylniederalkoxy, Phenoxy, Amino, Niederalkanoylamino, Phenylniederalkanoylamino oder Niederalkansulfonylamino bedeutet; und die Variablen R_1, X_1 und R_3 die jeweils in einem der Ansprüche 1-7 angegebenen Bedeutungen haben; wobei (hetero-)aromatische Reste einschliesslich der Ringe A und B jeweils gegebenenfalls durch Halogen, Trifluormethyl, Hydroxy, Niederalkoxy, Niederalkyl oder Hydroxyniederalkyl substituiert sind, in freier Form oder in Salzform.

14. Eine Verbindung gemäss Anspruch 1 der Formel Ia, worin X_2 für die Gruppe der Formel Ib steht, in der p für 0 oder 1, q für 1 und r für 0 oder 1 stehen oder in der p für 1 bis 8 und q sowie r jeweils für 0 stehen; X_4 gegebenenfalls durch Hydroxy, 3- bis 7-gliedriges Cycloalkyl, Phenyl oder Imidazolyl substituiertes Niederalkyl oder Phenyl bedeutet; und X_5 Wasserstoff oder Niederalkyl bedeutet; oder X_4 und X_5 gemeinsam für C_2-C_6-Alkylen, wie C_4-C_5-Alkylen, stehen; oder X_2 C_3-C_7-Cycloalkylen, wie C_5-C_6-Cycloalkylen, bedeutet; R_2 Carboxy, Niederalkoxycarbonyl, Phenylniederalkoxycarbonyl, Niederalkoxyniederalkoxycarbonyl, Hydroxy, Niederalkoxy, Phenylniederalkoxy, Phenoxy, Amino, Niederalkanoylamino, Phenylniederalkanoylamino oder Niederalkansulfonylamino bedeutet; und die Variablen R_1, X_1 und R_3 die jeweils in einem der Ansprüche 1-7 angegebenen Bedeutungen haben; wobei (hetero-)aromatische Reste einschliesslich der Ringe A und B jeweils gegebenenfalls durch Halogen, Trifluormethyl, Hydroxy, Niederalkoxy, Niederalkyl oder Hydroxyniederalkyl substituiert sind, in freier Form oder in Salzform.

15. Eine Verbindung gemäss Anspruch 1 der Formel Ia, worin R_1 Niederalkyl, wie C_3-C_5-Alkyl, oder Niederalkenyl, wie C_3-C_5-Alkenyl, bedeutet; X_1 für CO oder ferner SO_2 steht; X_2 für die Gruppe der Formel Ib steht, in der p und r für 0 oder 1 und q für 1 stehen; X_4 gegebenenfalls durch Hydroxy, 3- bis 7-gliedriges Cycloalkyl, wie Cyclohexyl, durch gegebenenfalls durch Halogen oder Hydroxy substituiertes Phenyl oder Imidazolyl, wie 4-Imidazolyl, substituiertes Niederalkyl, wie C_1-C_4-Alkyl, oder Phenyl bedeutet; und X_5 Wasserstoff oder Niederalkyl, wie C_1-C_4-Alkyl, bedeutet; oder X_4 und X_5 gemeinsam C_2-C_6-Alkylen, wie C_4-C_5-Alkylen, bedeuten; oder X_2 C_3-C_7-Cycloalkylen, wie C_5-C_6-Cycloalkylen, bedeutet; R_2 Carboxy, Niederalkoxycarbonyl, wie C_2-C_5-Alkoxycarbonyl, Phenylniederalkoxycarbonyl, wie Phenyl-C_1-C_4-alkoxycarbonyl, Niederalkoxyniederalkoxycarbonyl, wie C_1-C_4-Alkoxy-C_2-C_5-alkoxycarbonyl, Hydroxy oder Niederalkoxy, wie C_1-C_4-Alkoxy, bedeutet; und R_3 Carboxy oder 5-Tetrazolyl bedeutet; wobei (hetero-)aromatische Reste einschliesslich der Ringe A und B jeweils gegebenenfalls durch Halogen, Trifluormethyl, Hydroxy, Niederalkoxy, Niederalkyl oder Hydroxyniederalkyl substituiert sind, in freier Form oder in Salzform.

16. Eine Verbindung gemäss Anspruch 1 der Formel Ia, worin R_1 Niederalkyl, wie C_3-C_5-Alkyl, oder Niederalkenyl, wie C_3-C_5-Alkenyl, bedeutet; X_1 für CO oder ferner SO_2 steht; X_2 für die Gruppe der Formel Ib steht, in der p und r für 0 oder 1 und q für 1 stehen; X_4 gegebenenfalls durch Hydroxy, 3- bis 7-gliedriges Cycloalkyl, durch gegebenenfalls durch Halogen oder Hydroxy substituiertes Phenyl oder Imidazolyl, wie 4-Imidazolyl, substituiertes Niederalkyl, wie C_1-C_4-Alkyl, oder Phenyl bedeutet; und X_5 Wasserstoff oder Niederalkyl, wie C_1-C_4-Alkyl, bedeutet; R_2 Carboxy, Niederalkoxycarbonyl, wie C_2-C_5-Alkoxycarbonyl, Phenylniederalkoxycarbonyl, wie Phenyl-C_1-C_4-alkoxycarbonyl, Niederalkoxyniederalkoxycarbonyl, wie C_1-C_4-Alkoxy-C_2-C_5-alkoxycarbonyl, Hydroxy oder Niederalkoxy, wie C_1-C_4-Alkoxy, bedeutet; und R_3 Carboxy oder 5-Tetrazolyl bedeutet; wobei (hetero-)aromatische Reste einschliesslich der Ringe A und B jeweils gegebenenfalls durch Halogen, Trifluormethyl, Hydroxy, Niederalkoxy, Niederalkyl oder Hydroxyniederalkyl substituiert sind, in freier Form oder in Salzform.

17. Eine Verbindung gemäss Anspruch 1 der Formel Ia, worin R_1 Niederalkyl, wie C_3-C_5-Alkyl, oder ferner Niederalkenyl, wie C_3-C_5-Alkenyl, bedeutet; X_1 für CO oder ferner SO_2 steht; X_2 für die Gruppe der Formel Ib steht, in der p für eine ganze Zahl von 1 bis 8 und q sowie r für 0 stehen; R_2 Hydroxy, Niederalkoxy, wie C_1-C_4-Alkoxy, Phenylniederalkoxy, wie Phenyl-C_1-C_4-alkoxy, Phenoxy, Niederalkanoylamino, wie C_1-C_4-Alkanoylamino, Phenylniederalkanoylamino, wie Phenyl-C_1-C_4-alkanoylamino, Niederalkansulfonylamino, wie C_1-C_4-Alkansulfonylamino, bedeutet; und R_3 Carboxy oder in erster Linie 5-Tetrazolyl bedeutet; wobei (hetero-)aromatische Reste einschliesslich der Ringe A und B jeweils gegebenenfalls durch Halogen, Trifluormethyl, Hydroxy, Niederalkoxy, Niederalkyl oder Hydroxyniederalkyl substituiert sind, in freier Form oder in Salzform.

18. Eine Verbindung gemäss Anspruch 1 der Formel Ia, worin R_1 C_3-C_5-Alkyl oder in zweiter Linie C_3-C_5-Alkenyl, bedeutet; X_1 für CO, ferner SO_2 steht; X_2 für die Gruppe der Formel Ib steht, in der p und r unabhängig voneinander für 0 oder 1 und q für 1 stehen; X_4 C_1-C_4-Alkyl, Hydroxy-C_1-C_4-alkyl, C_3-C_7-Cycloalkyl-C_1-C_4-alkyl, Phenyl-C_1-C_4-alkyl oder Imidazolyl-C_1-C_4-alkyl bedeutet; und X_5 Wasserstoff oder C_1-C_4-Alkyl bedeutet; oder X_4 und X_5 gemeinsam für Tetramethylen, ferner Pentamethylen stehen; R_2 Carboxy oder C_2-C_5-Alkoxycarbonyl, ferner Phenyl-C_1-C_4-alkoxycarbonyl bedeutet; und R_3 Carboxy oder 5-Tetrazolyl bedeutet, in freier Form oder in Salzform.

19. Eine Verbindung gemäss Anspruch 1 der Formel Ia, worin R_1 C_3-C_5-Alkyl oder in zweiter Linie C_3-C_5-Alkenyl bedeutet; X_1 für CO, ferner SO_2 steht; X_2 für die Gruppe der Formel Ib steht, in der p und r jeweils für 0 oder 1 und q für

1 stehen; X_4 C_1-C_4-Alkyl, Hydroxy-C_1-C_4-alkyl, C_3-C_7-Cycloalkyl-C_1-C_4-alkyl, Phenyl-C_1-C_4-alkyl oder Imidazolyl-C_1-C_4-alkyl bedeutet; und X_5 Wasserstoff bedeutet; R_2 Carboxy oder C_2-C_5-Alkoxycarbonyl, ferner Phenyl-C_1-C_4-alkoxycarbonyl bedeutet; und R_3 Carboxy oder 5-Tetrazolyl bedeutet, in freier Form oder in Salzform.

20. Eine Verbindung gemäss Anspruch 1 der Formel Ia, worin R_1 C_3-C_5-Alkyl bedeutet; X_1 für CO steht; X_2 für die Gruppe der Formel Ib steht, in der q und r für 0 und p für 1 bis 3 stehen oder in der p und q für 1 und r für 0 stehen; X_4 C_1-C_4-Alkyl bedeutet; X_5 Wasserstoff oder C_1-C_4-Alkyl bedeutet; R_2 Carboxy oder C_2-C_5-Alkoxycarbonyl bedeutet; und R_3 Carboxy oder 5-Tetrazolyl bedeutet, in freier Form oder in Salzform.

21. Eine Verbindung gemäss einem der Ansprüche 1-20, worin R_3 5-Tetrazolyl bedeutet, in freier Form oder in Salzform.

22. Eine Verbindung gemäss Anspruch 1 der Formel Ia, worin R_1 C_3-C_5-Alkyl bedeutet; X_1 für CO steht; X_2 für die Gruppe der Formel Ib steht, in der p für 0 oder 1, r für 0 and q für 1 stehen; X_4 C_1-C_4-Alkyl bedeutet; und X_5 Wasserstoff oder C_1-C_4-Alkyl bedeutet; oder X_4 und X_5 gemeinsam für Tetramethylen oder Pentamethylen stehen; R_2 Carboxy, oder C_2-C_5-Alkoxycarbonyl bedeutet; und R_3 5-Tetrazolyl bedeutet, in freier Form oder in Salzform.

23. Eine Verbindung gemäss Anspruch 1 der Formel Ia, worin R_1 C_3-C_5-Alkyl bedeutet; X_1 für CO steht; X_2 für die Gruppe der Formel Ib steht, in der p für 0 oder 1, r für 0 und q für 1 stehen; X_4 und X_5 gemeinsam für Tetramethylen, ferner Pentamethylen stehen; R_2 Carboxy oder C_2-C_5-Alkoxycarbonyl bedeutet; und R_3 5-Tetrazolyl bedeutet, in freier Form oder in Salzform.

24. Eine Verbindung gemäss Anspruch 1 der Formel Ia, worin R_1 C_3-C_5-Alkyl bedeutet; X_1 für CO steht; X_2 für die Gruppe der Formel Ib steht, in der p und r für 0 oder 1 und q für 1 stehen; X_4 C_1-C_4-Alkyl bedeutet; und X_5 Wasserstoff bedeutet; R_2 Carboxy oder C_2-C_5-Alkoxycarbonyl bedeutet; und R_3 5-Tetrazolyl bedeutet, in freier Form oder in Salzform.

25. Eine Verbindung der Formel Ia gemäss einem der Ansprüche 13-24, worin X_2 für die Gruppe der Formel Ib steht, q 1 bedeutet und X_4 und X_5 unterschiedliche Bedeutungen haben, in freier Form oder in Salzform, in welcher das betreffende, die Variablen X_4 und X_5 aufweisende, asymmetrische C-Atom die S-Konfiguration hat.

26. (S)-N-(1-Carboxy-2-methyl-prop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin, in freier Form oder in Salzform gemäss Anspruch 1.

27. N-(2-Carboxy-2,2-tetramethylen-ethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin, in freier Form oder in Salzform gemäss Anspruch 1.

28. N-(2-Carboxy-2-ethyl-but-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin, in freier Form oder in Salzform gemäss Anspruch 1.

29. (S)-N-(1-Carboxy-2-methyl-prop-1-yl)-N-ethoxycarbonyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin, in freier Form oder in Salzform gemäss Anspruch 1.

30. N-(1-carboxycyclohexyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin, in freier Form oder in Salzform gemäss Anspruch 1.

31. Eine Verbindung gemäss Anspruch 1 ausgewählt aus der Gruppe bestehend aus:
(S)-N-(1-Carboxyethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-(2-Hydroxyethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-(2-Ethoxycarbonyl-2,2-tetramethylen-ethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-(2-Ethoxycarbonyl-2-ethyl-but-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-(2-Ethoxycarbonyl-2-methyl-prop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
(S)-N-(1-Hydroxymethyl-2-methyl-prop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-(2-Ethoxycarbonyl-2,2-pentamethylen-ethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
(S)-N-(1-Carboxy-2-methyl-prop-1-yl)-N-propyloxycarbonyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-(2-carboxy-2-methyl-propyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-(2-carboxy-2,2-pentamethylen-ethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
(S)-N-(1-aminocarbonyl-2-methyl-prop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin und
(S)-N-(1-carboxy-2-methyl-prop-1-yl)-N-(5-oxopent-1-en-5-yl)-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
jeweils in freier Form oder in Salzform.

32. Eine Verbindung gemäss Anspruch 1 ausgewählt aus der Gruppe bestehend aus:
N-Carboxymethyl-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
(S)-N-(1-Methoxycarbonylethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-[1-Carboxy-2-(4-fluorphenyl)-ethyl]-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-[2-(4-Fluorphenyl)-1-methoxycarbonyl-ethyl]-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-[2-(4-Fluorphenyl)-1-hydroxymethyl-ethyl]-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-(2'-Carboxybiphenyl-4-ylmethyl)-N-[1-carboxy-2-(4-fluorphenyl)-ethyl]-N-pentanoyl-amin,
N-(2'-Carboxybiphenyl-4-ylmethyl)-N-[2-(4-fluorphenyl)-1-methoxycarbonyl-ethyl]-N-pentanoyl-amin,
(S)-N-(2'-Carboxybiphenyl-4-ylmethyl)-N-(1-hydroxymethyl-2-phenyl-ethyl)-N-pentanoyl-amin,
(S)-N-(2'-Carboxybiphenyl-4-ylmethyl)-N-(1-hydroxymethyl-2-imidazol-4-yl-ethyl)-N-pentanoyl-amin,
(R)-N-(1-Carboxyethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
(1S),(2S)-N-(1-Carboxy-2-methyl-but-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
(1S),(2S)-N-(1-Methoxycarbonyl-2-methyl-but-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
(S)-N-(1-Carboxybut-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
(S)-N-(1-Methoxycarbonylbut-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
(S)-N-(1-Carboxyethyl)-N-hexanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
(S)-N-Butanoyl-N-(1-carboxyethyl)-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
(S)-N-(1-Carboxyprop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
(S)-N-(1-Carboxy-2-cyclohexyl-ethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
(S)-N-(2-Cyclohexyl-1-methoxycarbonyl-ethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
(R)-N-(1-Carboxy-2-methyl-prop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-(2-Methoxyethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-(2-Benzyloxyethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-(3-Methoxyprop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-(3-Benzyloxyprop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-(3-Hydroxyprop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-(1-Methoxycarbonyl-1-methyl-ethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-(2-Carboxyethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-(2-Carboxyprop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-(1-Carboxy-1-methyl-ethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-(5-Hydroxypent-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-(1-Carboxyprop-2-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-(2-Ethoxycarbonyl-3-methyl-but-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-(2-Carboxy-3-methyl-but-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-(3-Phenoxyprop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-[2-(4-Hydroxyphenyl)ethyl]-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-[3-(4-Hydroxyphenyl)prop-1-yl]-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-(8-Hydroxyoct-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-(2-Methansulfonylaminoethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-(3-Acetylaminoprop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-(2-Methoxy-2-oxo-1-phenyl-ethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-(4-Hydroxybut-2-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-(2-Hydroxy-1-phenyl-ethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-[3-(4-Hydroxybenzylcarbonylamino)prop-1-yl]-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-(3-Ethoxycarbonylcyclohexyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-(3-Carboxycyclohexyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
cis-N-(4-Carboxycyclohexyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
cis-N-(2-Ethoxycarbonylcyclohexyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
cis-N-(2-Carboxycyclohexyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-{2-[2-(4-Hydroxyphenyl)ethylaminocarbonyl]-2,2-tetramethylen-ethyl}-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
(S)-N-{1-[2-(4-Hydroxyphenyl)ethylaminocarbonyl]-2-methyl-prop-1-yl}-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
(S)-N-(1-Carboxy-2,2-dimethyl-prop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
(S)-N-(1-Methoxycarbonyl-2-methyl-prop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-(4-Phenoxybut-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-(2-Hydroxy-1-phenyl-2-oxo-ethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
(S)-N-(1-Benzyloxycarbonyl-2-methyl-prop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-Butanoyl-N-(1-carboxy-1-methyl-ethyl)-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,

N-(4-Hydroxybut-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
(S)-N-(1-Benzyloxycarbonyl-2-methyl-prop-1-yl)-N-[3-bromo-2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-N-pentanoyl-amin,
(S)-N-[3-Brom-2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-N-(1-carboxy-2-methyl-prop-1-yl)-N-pentanoyl-amin,
N-(2-Acetylaminoethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-[2-(n-Butoxycarbonyl)-2,2-tetramethylen-ethyl]-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-(2-Benzylaminocarbonyl-2,2-tetramethylen-ethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
(S)-N-Butyloxycarbonyl-N-(1-Carboxy-2-methyl-prop-1-yl)-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
(S)-N-(1-Carboxy-2-methyl-prop-1-yl)-N-methoxycarbonyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-(2-Diethylaminocarbonyl-2,2-tetramethylen-ethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-(2-Methyl-2-morpholin-4-ylcarbonyl-propyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-(1-Carboxycyclopentyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-(1-Carboxy-1-ethyl-prop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
(S)-N-(5-Amino-1-carboxy-pent-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-Butansulfonyl-N-(2-ethoxycarbonyl-2,2-pentamethylen-ethyl)-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-Butansulfonyl-N-(2-carboxy-2,2-pentamethylen-ethyl)-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-Butansulfonyl-N-(2-ethoxycarbonyl-2-methyl-prop-1-yl)-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-Butansulfonyl-N-(2-carboxy-2-methyl-prop-1-yl)-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
(S)-N-Butansulfonyl-N-(1-tert.-butoxycarbonylethyl)-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
(S)-N-Butansulfonyl-N-(1-carboxyethyl)-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
(S)-N-Butansulfonyl-N-(1-carboxy-2-methyl-prop-1-yl)-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
(S)-N-(2-Methyl-1-methylaminocarbonyl-prop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
(S)-N-(1-Dimethylaminocarbonyl-2-methyl-prop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
(S)-N-(2-Methyl-1-morpholin-4-ylcarbonyl-prop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
(S)-N-(2'-Carboxybiphenyl-4-ylmethyl)-N-(1-carboxy-2-methyl-prop-1-yl)-N-pentanoyl-amin,
(S)-N-(1,2-Dicarboxyethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
(S)-N-(1-Carboxy-3-phenyl-prop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
(S)-N-(2-Cyclohexyl-1-hydroxymethyl-ethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
(R)-N-(1-Methoxycarbonyl-2-methyl-prop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
(S)-N-(2-Hydroxy-1-methoxycarbonyl-ethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-Pentanoyl-N-(1H-tetrazol-5-ylmethyl)-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-Pentanoyl-N-pyrid-3-ylmethyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
(S)-N-(1-Carboxy-4-guanidino-but-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-(2-Hydroxy-1-methoxycarbonyl-prop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-(1-Benzyloxycarbonyl-1-methyl-ethyl)-N-butanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
(S)-N-(1-Carboxy-3-methyl-but-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-(1-Carboxy-2-hydroxy-ethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
(S)-N-(1-Carboxy-2-hydroxy-ethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
(S)-N-[2-Methyl-1-(2-phenylethylaminocarbonyl)-prop-1-yl]-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
(S)-N-(2-Benzyloxy-1-hydroxymethyl-ethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
(S)-N-(1-Carboxy-2-methyl-prop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-3-ylmethyl]-amin,
(S)-N-(1-Carboxy-2-methyl-prop-1-yl)-N-pentanoyl-N-[3'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
(S)-N-[2-Methyl-1-(1,2,3,4-tetrahydrochinol-1-ylcarbonyl)-prop-1-yl]-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
(S)-N-(2-Methyl-1-piperidin-1-ylcarbonyl-prop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
(S)-N-[2-Methyl-1-(1,2,3,4-tetrahydroisochinol-2-ylcarbonyl)-prop-1-yl]-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-(2-Hydroxymethyl-2-methyl-prop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-Ethoxycarbonyl-N-(2-ethoxycarbonyl-2-methyl-prop-1-yl)-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin und
N-(2-Carboxy-2-methyl-prop-1-yl)-N-ethoxycarbonyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin, jeweils in freier Form oder in Salzform.

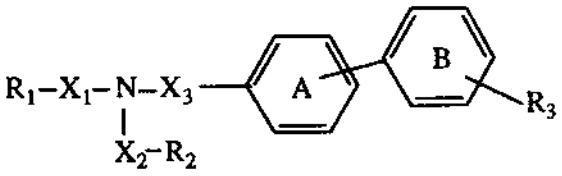
33. Eine Verbindung gemäss einem der Ansprüche 1 bis 32, in freier Form oder in Form eines pharmazeutisch verwendbaren Salzes, zur Anwendung in einem Verfahren zur therapeutischen Behandlung des menschlichen oder tierischen Körpers.

34. Eine Verbindung gemäss einem der Ansprüche 1 bis 33, in freier Form oder in Form eines pharmazeutisch verwendbaren Salzes, zur Anwendung als Antihypertensivum.

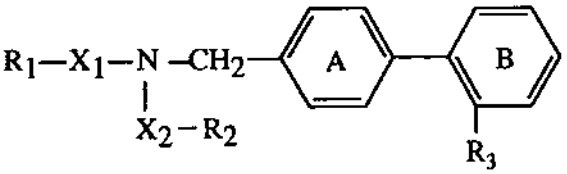
35. Ein pharmazeutisches Präparat, als Wirkstoff enthaltend eine Verbindung gemäss einem der Ansprüche 1 bis 34, in freier Form oder in Form eines pharmazeutisch verwendbaren Salzes, gegebenenfalls neben üblichen pharmazeutischen Hilfsstoffen.

36. Ein antihypertensiv wirksames pharmazeutisches Präparat gemäss Anspruch 35, dadurch gekennzeichnet, dass man einen antihypertensiv wirksamen Wirkstoff wählt.

37. Verfahren zur Herstellung einer Verbindung der Formel



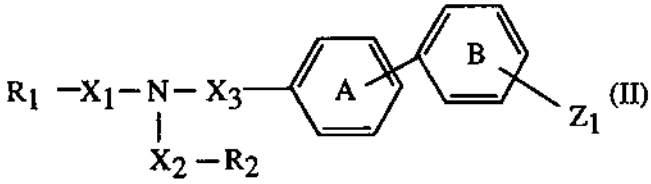
(I) oder



(Ia),

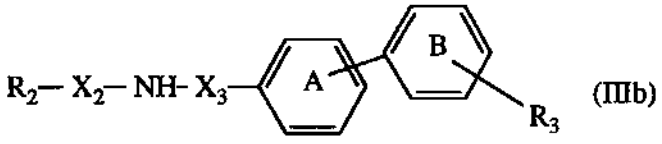
worin R_1, R_2, R_3, X_1, X_2 und X_3 sowie die Substituenten der Ringe A und B die jeweils in einem der Ansprüche 1-25 angegebenen Bedeutungen haben; in freier Form oder in Salzform, dadurch gekennzeichnet, dass man

a) in einer Verbindung der Formel



(II)

oder einem Salz davon, worin Z_1 einen in R_3 überführbaren Rest bedeutet, Z_1 in R_3 überführt oder
b) eine Verbindung der Formel R_1-X_1OH (IIIa), ein reaktionsfähiges Derivat davon oder ein Salz davon mit einer Verbindung der Formel



(IIIb)

oder einem Salz davon umsetzt und jeweils, wenn erwünscht, eine verfahrensgemäss oder auf andere Weise erhältliche Verbindung I in freier Form oder in Salzform in eine andere Verbindung I überführt, ein verfahrensgemäss erhältliches Gemisch von Isomeren auftrennt und das gewünschte Isomere isoliert und/oder eine ver-

fahrensgemäss erhältliche freie Verbindung I in ein Salz oder ein verfahrensgemäss erhältliches Salz einer Verbindung I in die freie Verbindung I oder in ein anderes Salz überführt.

38. Verfahren zur Herstellung eines pharmazeutischen Präparats gemäss Anspruch 35 oder 36, dadurch gekennzeichnet, dass man den Wirkstoff, gegebenenfalls unter Beimischung von üblichen pharmazeutischen Hilfsstoffen, zu einem pharmazeutischen Präparat verarbeitet.

39. Verfahren gemäss Anspruch 38 zur Herstellung eines antihypertensiv wirksamen pharmazeutischen Präparats gemäss Anspruch 34, dadurch gekennzeichnet, dass man einen antihypertensiv wirksamen Wirkstoff wählt.

40. Verwendung einer Verbindung gemäss einem der Ansprüche 1 bis 34, in freier Form oder in Form eines pharmazeutisch verwendbaren Salzes, zur Herstellung eines pharmazeutischen Präparats.

41. Verwendung einer Verbindung gemäss einem der Ansprüche 1 bis 34, in freier Form oder in Form eines pharmazeutisch verwendbaren Salzes, zur Herstellung eines pharmazeutischen Präparats auf nicht-chemischem Wege.

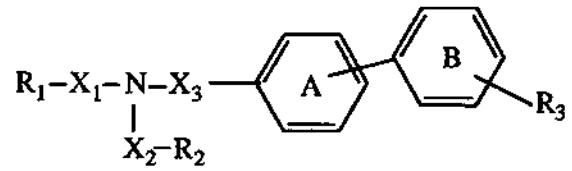
42. Verwendung einer Verbindung gemäss einem der Ansprüche 1-34, in freier Form oder in Form eines pharmazeutisch verwendbaren Salzes, zur Herstellung eines Antihypertensivums.

43. Verwendung einer Verbindung gemäss einem der Ansprüche 1-34, in freier Form oder in Form eines pharmazeutisch verwendbaren Salzes, zur Herstellung eines pharmazeutischen Präparats zur therapeutischen oder prophylaktischen Behandlung von Herzinsuffizienz.

44. Verwendung einer Verbindung gemäss einem der Ansprüche 1-34, in freier Form oder in Form eines pharmazeutisch verwendbaren Salzes, zur Herstellung eines pharmazeutischen Präparats zur therapeutischen oder prophylaktischen Behandlung von Erkrankungen, die durch Angiotensin-II-Aktivität verursacht werden.

Patentansprüche für folgende Vertragsstaaten : ES, GR

1. Verfahren zur Herstellung einer Verbindung der Formel

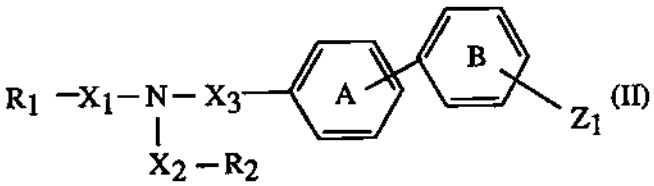


(I),

worin R_1 gegebenenfalls durch Halogen oder Hydroxy substituiertes Niederalkyl, Niederalkenyl oder Niederalkinyl oder C_3-C_7-Cycloalkyl- oder C_3-C_7-Cycloalkenyl oder Phenylniederalkyl, Phenylniederalkenyl oder Phenylniederalkinyl bedeutet; X_1 für CO, SO_2 oder -O-C(=O)- steht, wobei das Kohlenstoffatom der Carbonylgruppe an das in der Formel I eingezeichnete Stickstoffatom gebunden ist; X_2 gegebenenfalls durch Hydroxy, Carboxy, Amino, Guanidino, C_3-C_7-Cycloalkyl, C_3-C_7-Cycloalkenyl, Phenyl oder einen entsprechenden 5- oder 6-gliedrigen und monocyclischen aromatischen Rest, der bis zu vier gleiche oder verschiedene Heteroatome aufweist, substituiertes C_1-C_{10}-Alkylen, C_2-C_{10}-Alkyliden oder C_3-C_7-Cycloalkylen bedeutet, wobei ein Kohlenstoffatom von C_1-C_{10}-Alkylen bzw. C_2-C_{10}-Alkyliden zusätzlich durch C_2-C_6-Alkylen überbrückt sein kann, und wobei C_3-C_7-Cycloalkyl oder C_3-C_7-Cycloalkenyl gegebenenfalls ein- oder mehrfach substituiert sind durch Carboxy, Carboxy, welches durch einen Alkohol verestert ist, der sich von Niederalkyl, Phenylniederalkyl, Niederalkenyl, Niederalkinyl, Niederalkoxyniederalkyl, Niederalkoxyniederalkenyl oder Niederalkoxyniederalkinyl ableitet, Carbamoyl, Carbamoyl, in welchem die Aminogruppe durch Niederalkyl, Niederalkenyl, Niederalkinyl, Phenylniederalkyl, Phenylniederalkenyl oder Phenylniederalkinyl mono- oder unabhängig voneinander disubstituiert oder durch C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden disubstituiert ist, wobei C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden gegebenenfalls durch -O- unterbrochen oder an zwei benachbarten C-Atomen mit einem Benzolring kondensiert sind, Formyl, Diniederalkoxymethyl oder Oxyniederalkylenoxymethylen; R_2 Carboxy, Carboxy, welches durch einen Alkohol verestert ist, der sich von Niederalkyl, Phenylniederalkyl, Niederalkenyl, Niederalkinyl, Niederalkoxyniederalkyl, Niederalkoxyniederalkenyl oder Niederalkoxyniederalkinyl ableitet, Carbamoyl, Carbamoyl, in welchem die Aminogruppe durch Niederalkyl, Niederalkenyl, Niederalkinyl, Phenylniederalkyl, Phenylniederalkenyl oder Phenylniederalkinyl mono- oder unabhängig voneinander disubstituiert oder durch C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden disubstituiert ist, wobei C_1-C_{10}-Alkylen

oder C_2-C_{10}-Alkyliden gegebenenfalls durch -O- unterbrochen oder an zwei benachbarten C-Atomen mit einem Benzolring kondensiert sind, Amino, Amino, welches durch Niederalkyl, Niederalkenyl, Niederalkinyl, Phenylniederalkyl, Phenylniederalkenyl oder Phenylniederalkinyl mono- oder unabhängig voneinander disubstituiert oder durch C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden disubstituiert ist, wobei C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden gegebenenfalls durch -O- unterbrochen oder an zwei benachbarten C-Atomen mit einem Benzolring kondensiert sind, Niederalkanoyl-, Phenylniederalkanoyl-, Benzoyl-, Niederalkansulfonyl-, Benzolsulfonyl-amino, Formyl, Diniederalkoxymethyl, Oxyniederalkylenoxymethylen, 1H-Tetrazol-5-yl, Pyridyl, Hydroxy, Niederalkoxy, Niederalkenyloxy, Phenylniederalkoxy, Phenoxy, $S(O)_m$-R, wobei m für 0, 1 oder 2 steht und R Wasserstoff, Niederalkyl, Niederalkenyl oder Niederalkinyl bedeutet, Niederalkanoyl, Sulfamoyl, Sulfamoyl, in welchem die Aminogruppe durch Niederalkyl, Niederalkenyl, Niederalkinyl, Phenylniederalkyl, Phenylniederalkenyl oder Phenylniederalkinyl mono- oder unabhängig voneinander disubstituiert oder durch C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden disubstituiert ist, wobei C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden gegebenenfalls durch -O- unterbrochen oder an zwei benachbarten C-Atomen mit einem Benzolring kondensiert sind, oder PO_nH_2 bedeutet, wobei n für 2 oder 3 steht; X_3 C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden bedeutet; R_3 Carboxy, 5-Tetrazolyl, SO_3H, PO_2H_2, PO_3H_2 oder Halogenniederalkylsulfamoyl ist; und wobei (hetero-)aromatische Reste einschliesslich der Ringe A und B unabhängig voneinander gegebenenfalls substituiert sind durch Substituenten ausgewählt aus der Gruppe bestehend aus: Halogen, Hydroxy, Niederalkoxy, Niederalkenyloxy, Phenylniederalkoxy, Phenoxy, $S(O)_m$-R und gegebenenfalls durch Halogen oder Hydroxy substituiertes Niederalkyl, Niederalkenyl oder Niederalkinyl, wobei Niederalkyl, Niederalkenyl oder Niederalkinyl gegebenenfalls durch -O- unterbrochen sind, sowie, im Falle von (hetero-)aromatischen Resten, gegebenenfalls zusätzlich substituiert sind durch Carboxy, Carboxy, welches durch einen Alkohol verestert ist, der sich von Niederalkyl, Phenylniederalkyl, Niederalkenyl, Niederalkinyl, Niederalkoxyniederalkyl, Niederalkoxyniederalkenyl oder Niederalkoxyniederalkinyl ableitet, durch Carbamoyl, Carbamoyl, in welchem die Aminogruppe durch Niederalkyl, Niederalkenyl, Niederalkinyl, Phenylniederalkyl, Phenylniederalkenyl oder Phenylniederalkinyl mono- oder unabhängig voneinander disubstituiert oder durch C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden disubstituiert ist, wobei C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden gegebenenfalls durch -O- unterbrochen oder an zwei benachbarten C-Atomen mit einem Benzolring kondensiert sind, durch Formyl, Diniederalkoxymethyl oder Oxyniederalkylenoxymethylen; wobei mit "nieder" bezeichnete Reste und Gruppen bis und mit 7 Kohlenstoffatome enthalten; in freier Form oder in Salzform; dadurch gekennzeichnet, dass man

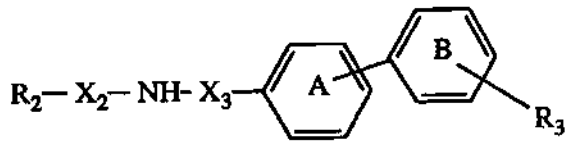
a) in einer Verbindung der Formel



(II)

oder einem Salz davon, worin Z_1 einen in R_3 überführbaren Rest bedeutet, Z_1 in R_3 überführt oder

b) eine Verbindung der Formel R_1-X_1OH (IIIa), ein reaktionsfähiges Derivat davon oder ein Salz davon mit einer Verbindung der Formel



(IIIb)

oder einem Salz davon umsetzt und jeweils, wenn erwünscht, eine verfahrensgemäss oder auf andere Weise erhältliche Verbindung I in freier Form oder in Salzform in eine andere Verbindung I überführt, ein verfahrensgemäss erhaltliches Gemisch von Isomeren auftrennt und das gewünschte Isomere isoliert und/oder eine verfahrensgemäss erhältliche freie Verbindung I in ein Salz oder ein verfahrensgemäss erhältliches Salz einer Verbindung I in die freie Verbindung I oder in ein anderes Salz überführt.

2. Verfahren gemäss Anspruch 1 zur Herstellung einer Verbindung der Formel I, worin R_2 von Carboxy verschieden ist und R_3 5-Tetrazolyl bedeutet, dadurch gekennzeichnet, dass man

(i) von einer Verbindung der Formel (II) ausgeht, worin Z_1 Cyano bedeutet, und diese mit HN_3 oder einem Alkalimetallsalz davon, mit einem Triniederalkylzinnazid oder Triphenylzinnazid umsetzt; oder

(ii) von einer Verbindung der Formel (II) ausgeht, worin Z_1 durch Triphenylmethyl, gegebenenfalls durch Nitro substituiertes Benzyl, Niederalkoxymethyl, Niederalkylthiomethyl, Triniederalkylsilyl, 2-Cyanoethyl, Niederalkoxyniederalkoxymethyl, Benzyloxymethyl oder Phenacyl geschütztes 5-Tetrazolyl bedeutet, und die Schutzgruppe abspaltet und,

wenn erwünscht, eine verfahrensgemäss erhältliche Verbindung der Formel I, worin R_2 von Carboxy verschieden ist und R_3 5-Tetrazolyl bedeutet, in eine Verbindung der Formel I überführt, worin R_2 Carboxy ist.

3. Verfahren gemäss Anspruch 1 oder 2 zur Herstellung einer Verbindung der Formel I, worin worin R_1 gegebenenfalls durch Halogen oder Hydroxy substituiertes Niederalkyl, Niederalkenyl oder Niederalkinyl oder C_3-C_7-Cycloalkyl oder C_3-C_7-Cycloalkenyl oder Phenylniederalkyl, Phenylniederalkenyl oder Phenylniederalkinyl bedeutet; X_1 für CO oder SO_2 steht; X_2 einen gegebenenfalls durch Hydroxy, C_3-C_7-Cycloalkyl oder C_3-C_7-Cycloalkenyl oder Phenyl oder einen entsprechenden 5- oder 6-gliedrigen und monocyclischen aromatischen Rest, der bis zu vier gleiche oder verschiedene Heteroatome aufweist, substituiertes C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden oder C_3-C_7-Cycloalkylen bedeutet, wobei ein Kohlenstoffatom von C_1-C_{10}-Alkylen bzw. C_2-C_{10}-Alkyliden zusätzlich durch C_2-C_6-Alkylen überbrückt sein kann, und wobei C_3-C_7-Cycloalkylen gegebenenfalls ein- oder mehrfach substituiert sind durch Carboxy, Carboxy, welches durch einen Alkohol verestert ist, der sich von Niederalkyl, Phenylniederalkyl, Niederalkenyl, Niederalkinyl, Niederalkoxyniederalkyl, Niederalkoxyniederalkenyl oder Niederalkoxyniederalkinyl ableitet, Carbamoyl, Carbamoyl, in welchem die Aminogruppe durch Niederalkyl, Niederalkenyl, Niederalkinyl, Phenylniederalkyl, Phenylniederalkenyl oder Phenylniederalkinyl mono- oder unabhängig voneinander disubstituiert oder durch C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden disubstituiert ist, wobei C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden gegebenenfalls durch -O- unterbrochen sind, Formyl, Diniederalkoxymethyl oder Oxyniederalkylenoxymethylen; R_2 Carboxy, Carboxy, welches durch einen Alkohol verestert ist, der sich von Niederalkyl, Phenylniederalkyl, Niederalkenyl, Niederalkinyl, Niederalkoxyniederalkyl, Niederalkoxyniederalkenyl oder Niederalkoxyniederalkinyl ableitet, Carbamoyl, Carbamoyl, in welchem die Aminogruppe durch Niederalkyl, Niederalkenyl, Niederalkinyl, Phenylniederalkyl, Phenylniederalkenyl oder Phenylniederalkinyl mono- oder unabhängig voneinander disubstituiert oder durch C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden disubstituiert ist, wobei C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden gegebenenfalls durch -O- unterbrochen sind, Amino, Amino, welches durch Niederalkyl, Niederalkenyl, Niederalkinyl, Phenylniederalkyl, Phenylniederalkenyl oder Phenylniederalkinyl mono- oder unabhängig voneinander disubstituiert oder durch C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden disubstituiert ist, wobei C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden gegebenenfalls durch -O- unterbrochen sind, Niederalkanoyl-, Phenylniederalkanoyl-, Benzoyl-, Niederalkansulfonyl-, Benzolsulfonyl-amino, Formyl, Diniederalkoxymethyl, Oxynieder-alkylenoxymethylen, Hydroxy, Niederalkoxy, Niederalkenyloxy, Phenylniederalkoxy, Phenoxy, $S(O)_m$-R, wobei m für 0, 1 oder 2 steht und R Wasserstoff, Niederalkyl, Niederalkenyl oder Niederalkinyl bedeutet, Niederalkanoyl, Sulfamoyl, Sulfamoyl, in welchem die Aminogruppe durch Niederalkyl, Niederalkenyl, Niederalkinyl, Phenylniederalkyl, Phenylniederalkenyl oder Phenylniederalkinyl mono- oder unabhängig voneinander disubstituiert oder durch C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden disubstituiert ist, wobei C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden gegebenenfalls durch -O- unterbrochen sind, oder PO_nH_2 bedeutet, wobei n für 2 oder 3 steht; X_3 C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden bedeutet; R_3 Carboxy, 5-Tetrazolyl, SO_3H, PO_2H_2, PO_3H_2 oder Halogenniederalkylsulfamoyl ist; wobei (hetero-)aromatische Reste einschliesslich der Ringe A und B unabhängig voneinander gegebenenfalls substituiert sind durch Substituenten ausgewählt aus der Gruppe bestehend aus: Halogen, Hydroxy, Niederalkoxy, Niederalkenyloxy, Phenylniederalkoxy, Phenoxy, $S(O)_m$-R und gegebenenfalls durch Halogen oder Hydroxy substituiertes Niederalkyl, Niederalkenyl oder Niederalkinyl, wobei Niederalkyl, Niederalkenyl oder Niederalkinyl gegebenenfalls durch -O- unterbrochen sind, sowie, im Falle von (hetero-)aromatischen Resten, gegebenenfalls zusätzlich substituiert sind durch Carboxy, Carboxy, welches durch einen Alkohol verestert ist, der sich von Niederalkyl, Phenylniederalkyl, Niederalkenyl, Niederalkinyl, Niederalkoxyniederalkyl, Niederalkoxyniederalkenyl oder Niederalkoxyniederalkinyl ableitet, durch Carbamoyl, Carbamoyl, in welchem die Aminogruppe durch Niederalkyl, Niederalkenyl, Niederalkinyl, Phenylniederalkyl, Phenylniederalkenyl oder Phenylniederalkinyl mono- oder unabhängig voneinander disubstituiert oder durch C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden disubstituiert ist, wobei C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden gegebenenfalls durch -O- unterbrochen sind, durch Formyl, Diniederalkoxymethyl oder Oxyniederalkylenoxymethylen; in freier Form oder in Salzform.

4. Verfahren gemäss Anspruch 1 oder 2 zur Herstellung einer Verbindung der Formel I, worin gegebenenfalls durch Halogen oder Hydroxy substituiertes Niederalkyl, Niederalkenyl oder Niederalkinyl oder C_3-C_7-Cycloalkyl oder C_3-C_7-Cycloalkenyl oder Phenylniederalkyl, Phenylniederalkenyl oder Phenylniederalkinyl bedeutet; X_1 für CO oder SO_2 steht; X_2 gegebenenfalls durch Hydroxy, C_3-C_7-Cycloalkyl oder C_3-C_7-Cycloalkenyl oder Phenyl oder einen entsprechenden 5- oder 6-gliedrigen und monocyclischen aromatischen Rest, der bis zu vier gleiche oder verschiedene Heteroatome aufweist, substituiertes C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden bedeutet; R_2 Carboxy, Carboxy,

welches durch einen Alkohol verestert ist, der sich von Niederalkyl, Phenylniederalkyl, Niederalkenyl, Niederalkinyl, Niederalkoxyniederalkyl, Niederalkoxyniederalkenyl oder Niederalkoxyniederalkinyl ableitet, Carbamoyl, Carbamoyl, in welchem die Aminogruppe durch Niederalkyl, Niederalkenyl, Niederalkinyl, Phenylniederalkyl, Phenylniederalkenyl oder Phenylniederalkinyl mono- oder unabhängig voneinander disubstituiert oder durch C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden disubstituiert ist, wobei C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden gegebenenfalls durch -O- unterbrochen sind, Amino, Amino, welches durch Niederalkyl, Niederalkenyl, Niederalkinyl, Phenylniederalkyl, Phenylniederalkenyl oder Phenylniederalkinyl mono- oder unabhängig voneinander disubstituiert oder durch C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden disubstituiert ist, wobei C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden gegebenenfalls durch -O- unterbrochen sind, Niederalkanoyl-, Phenylniederalkanoyl-, Benzoyl-, Niederalkansulfonyl-, Benzolsulfonyl-amino, Formyl, Diniederalkoxymethyl, Oxyniederalkylenoxymethylen, Hydroxy, Niederalkoxy, Niederalkenyloxy, Phenylniederalkoxy oder Phenoxy, $S(O)_m$-R, wobei m für 0, 1 oder 2 steht und R Wasserstoff, Niederalkyl, Niederalkenyl oder Niederalkinyl bedeutet, Niederalkanoyl, Sulfamoyl, Sulfamoyl, in welchem die Aminogruppe durch Niederalkyl, Niederalkenyl, Niederalkinyl, Phenylniederalkyl, Phenylniederalkenyl oder Phenylniederalkinyl mono- oder unabhängig voneinander disubstituiert oder durch C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden disubstituiert ist, wobei C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden gegebenenfalls durch -O- unterbrochen sind, oder PO_nH_2 bedeutet, wobei n für 2 oder 3 steht; X_3 -CH_2- bedeutet; R_3 Carboxy, 5-Tetrazolyl, SO_3H, PO_2H_2, PO_3H_2 oder Halogenniederalkylsulfamoyl ist; und wobei (hetero-)aromatische Reste einschliesslich der Ringe A und B unabhängig voneinander gegebenenfalls substituiert sind durch Substituenten ausgewählt aus der Gruppe bestehend aus: Halogen, Hydroxy, Niederalkoxy, Niederalkenyloxy, Phenylniederalkoxy, Phenoxy, $S(O)_m$-R und gegebenenfalls durch Halogen oder Hydroxy substituiertes Niederalkyl, Niederalkenyl oder Niederalkinyl, wobei Niederalkyl, Niederalkenyl oder Niederalkinyl gegebenenfalls durch -O- unterbrochen sind, sowie, im Falle von (hetero-)aromatischen Resten, gegebenenfalls zusätzlich substituiert sind durch Carboxy, Carboxy, welches durch einen Alkohol verestert ist, der sich von Niederalkyl, Phenylniederalkyl, Niederalkenyl, Niederalkinyl, Niederalkoxyniederalkyl, Niederalkoxyniederalkenyl oder Niederalkoxyniederalkinyl ableitet, durch Carbamoyl, Carbamoyl, in welchem die Aminogruppe durch Niederalkyl, Niederalkenyl, Niederalkinyl, Phenylniederalkyl, Phenylniederalkenyl oder Phenylniederalkinyl mono- oder unabhängig voneinander disubstituiert oder durch C_1-C_{10}-Alkylen oder C_1-C_{10}-Alkyliden disubstituiert ist, wobei C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden gegebenenfalls durch -O- unterbrochen sind, durch Formyl, Diniederalkoxymethyl oder Oxyniederalkylenoxymethylen; in freier Form oder in Salzform.

5. Verfahren gemäss Anspruch 1 oder 2 zur Herstellung einer Verbindung der Formel I, worin R_1 R_1 Niederalkyl, Niederalkenyl, Niederalkinyl, Halogenniederalkyl, -niederalkenyl, -niederalkinyl, Hydroxyniederalkyl, -niederalkenyl, -niederalkinyl, C_3-C_7-Cycloalkyl, C_3-C_7-Cycloalkenyl, Phenylniederalkyl, Phenylniederalkenyl oder Phenylniederalkinyl bedeutet; X_1 für CO oder SO_2 steht; X_2 C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden bedeutet, die gegebenenfalls durch Hydroxy, einen C_3-C_7-Cycloalkyl-, C_3-C_7-Cycloalkenyl-, einen Phenylrest oder einen 5- oder 6-gliedrigen, monocyclischen heteroaromatischen Rest mit bis zu vier gleichen oder verschiedenen Heteroatomen substituiert sind, wobei die cyclischen Reste ihrerseits gegebenenfalls substituiert sind durch Carboxy, welches gegebenenfalls verestert ist mit einem Alkohol, der sich von Niederalkyl, Phenylniederalkyl, Niederalkenyl, Niederalkinyl, Niederalkoxyniederalkyl, -niederalkenyl oder -niederalkinyl ableitet, Carbamoyl, in dem die Aminogruppe gegebenenfalls durch Niederalkyl, Niederalkenyl, Niederalkinyl, Phenylniederalkyl, Phenylniederalkenyl, Phenylniederalkinyl mono- oder unabhängig voneinander disubstituiert oder durch Niederalkylen- oder Niederalkylenoxyniederalkylen disubstituiert ist, Formyl, Diniederalkoxymethyl, Oxyniederalkylenoxymethylen; R_2 Carboxy, welches gegebenenfalls verestert ist mit einem Alkohol, der sich von Niederalkyl, Phenylniederalkyl, Niederalkenyl, Niederalkinyl, Niederalkoxyniederalkyl, -niederalkenyl oder -niederalkinyl ableitet, Carbamoyl, in dem die Aminogruppe gegebenenfalls durch Niederalkyl, Niederalkenyl, Niederalkinyl, Phenylniederalkyl, Phenylniederalkenyl, Phenylniederalkinyl mono- oder unabhängig voneinander disubstituiert oder durch Niederalkylen- oder Niederalkylenoxyniederalkylen disubstituiert ist, Amino, in dem die Aminogruppe gegebenenfalls durch Niederalkyl, Niederalkenyl, Niederalkinyl, Phenylniederalkyl, Phenylniederalkenyl, Phenylniederalkinyl mono- oder unabhängig voneinander disubstituiert oder durch Niederalkylen- oder Niederalkylenoxyniederalkylen disubstituiert ist, Niederalkanoyl-, Phenylniederalkanoyl-, Benzoyl-, Niederalkansulfonyl-, Benzolsulfonyl-amino, Formyl, Diniederalkoxymethyl, Oxyniederalkylenoxymethylen, Hydroxy, Niederalkoxy, Niederalkenyloxy, Phenylniederalkoxy, Phenoxy, $S(O)_m$-R, wobei m für 0, 1 oder 2 und R für Wasserstoff, Niederalkyl, Niederalkenyl oder Niederalkinyl steht, Niederalkanoyl, Sulfamoyl, in dem die Aminogruppe gegebenenfalls durch Niederalkyl, Niederalkenyl, Niederalkinyl, Phenylniederalkyl, Phenylniederalkenyl, Phenylniederalkinyl mono- oder unabhängig voneinander disubstituiert oder durch Niederalkylen- oder Niederalkylenoxyniederalkylen disubstituiert ist, oder PO_nH_2 bedeutet, wobei n für 2 oder 3 steht; X_3 -CH_2- bedeutet; und R_3 Carboxy, 5-Tetrazolyl, SO_3H, PO_2H_2, PO_3H_2 oder Halogenniederalkylsulfamoyl bedeutet; wobei (hetero-)aromatische Reste einschliesslich der Ringe A und B unabhängig voneinander jeweils gegebenenfalls substituiert sind durch einen oder mehrere Substituenten ausgewählt aus Halogen, Hydroxy, Niederalkoxy, Niederalkenyloxy, jeweils gegebenenfalls durch Halogen oder Hydroxy substituiertes Niederalkyl, Niederalkenyl,

Niederalkinyl, Niederalkoxyniederalkyl, -niederalkenyl, -niederalkinyl, Niederalkenyloxyniederalkyl, -niederalkenyl und -niederalkinyl, in freier Form oder in Salzform.

6. Verfahren gemäss Anspruch 1 oder 2 zur Herstellung einer Verbindung der Formel I, worin X_2 C_1-C_{10}-Alkylen oder C_2-C_{10}-Alkyliden bedeutet, die gegebenenfalls durch Hydroxy, einen C_3-C_7-Cycloalkyl-, C_3-C_7-Cycloalkenyl-, einen Phenylrest oder einen 5- oder 6-gliedrigen, monocyclischen heteroaromatischen Rest mit bis zu vier gleichen oder verschiedenen Heteroatomen substituiert sind, wobei ein C-Atom von C_1-C_{10}-Alkylen bzw. C_2-C_{10}-Alkyliden durch C_2-C_8-Alkylen überbrückt sein kann und wobei die cyclischen Reste ihrerseits gegebenenfalls substituiert sind durch Carboxy, welches gegebenenfalls verestert ist mit einem Alkohol, der sich von Niederalkyl, Phenylniederalkyl, Niederalkenyl, Niederalkinyl, Niederalkoxyniederalkyl, -niederalkenyl oder -niederalkinyl ableitet, Carbamoyl, in dem die Aminogruppe gegebenenfalls durch Niederalkyl, Niederalkenyl, Niederalkinyl, Phenylniederalkyl, Phenylniederalkenyl, Phenylniederalkinyl mono- oder unabhängig voneinander disubstituiert oder durch Niederalkylen- oder Niederalkylenoxyniederalkylen disubstituiert ist, Formyl, Diniederalkoxymethyl oder durch Oxyniederalkylenoxymethylen, oder X_2 C_3-C_7-Cycloalkylen bedeutet; X_3 Niederalkylen oder Niederalkyliden bedeutet; die Variablen X_1, R_1, R_2, und R_3 die in Anspruch 5 angegebenen Bedeutungen haben; und die (hetero-)aromatischen Ringe einschliesslich der Ringe A und B wie in Anspruch 5 angegeben substituiert sein können, in freier Form oder in Salzform.

7. Verfahren gemäss Anspruch 1 oder 2 zur Herstellung einer Verbindung der Formel I, worin R_1 Niederalkyl, Niederalkenyl, Halogenniederalkyl, -niederalkenyl, Hydroxyniederalkyl, 3- bis 7-gliedriges Cycloalkyl oder Phenylniederalkyl bedeutet; X_1 für CO, SO_2 oder
-O-C(=O)-, wobei das Kohlenstoffatom der Carbonylgruppe an das in der Formel I eingezeichnete Stickstoffatom gebunden ist, steht; X_2 C_1-C_{10}-Alkylen oder C_1-C_7-Alkyliden, die gegebenenfalls substituiert sind durch Hydroxy, Carboxy, Amino, Guanidino, einen 3- bis 7-gliedrigen Cycloalkyl-, 3- bis 7-gliedrigen Cycloalkenyl-, Phenyl-, Pyrrolyl-, Pyrazolyl-, Imidazolyl-, Triazolyl-, Tetrazolyl-, Furyl-, Thienyl- oder Pyridylrest, welche ihrerseits gegebenenfalls zusätzlich durch Carboxy, Niederalkoxycarbonyl, Phenylniederalkoxycarbonyl, Carbamoyl, in dem die Aminogruppe gegebenenfalls durch Niederalkyl oder Phenylniederalkyl mono- oder unabhängig voneinander disubstituiert ist, Formyl, Diniederalkoxymethyl oder Oxyniederalkylenoxymethylen substituiert sein können; R_2 Carboxy, Niederalkoxy-, Phenylniederalkoxy-, Niederalkenyloxy-, Niederalkoxyniederalkoxy-carbonyl, Carbamoyl, in dem die Aminogruppe gegebenenfalls durch Niederalkyl, Phenylniederalkyl mono- oder unabhängig voneinander disubstituiert oder durch Niederalkylen, das gegebenenfalls an zwei benachbarten Kohlenstoffatomen mit einem Benzolring kondensiert ist, oder Niederalkylenoxyniederalkylen disubstituiert ist, Amino, in dem die Aminogruppe gegebenenfalls durch Niederalkyl, Phenylniederalkyl mono- oder unabhängig voneinander disubstituiert oder durch Niederalkylen- oder Niederalkylenoxyniederalkylen disubstituiert ist, Niederalkanoyl-, Phenylniederalkanoyl-, Benzoyl-, Niederalkansulfonyl-, Benzolsulfonyl-amino, Formyl, Diniederalkoxymethyl, Oxyniederalkylenoxymethylen, Hydroxy, Niederalkoxy, Phenylniederalkoxy, Phenoxy, $S(O)_m$-R, wobei m für 0, 1 oder 2 und R für Niederalkyl steht, Niederalkanoyl, Sulfamoyl, in dem die Aminogruppe gegebenenfalls durch Niederalkyl, Phenylniederalkyl mono- oder unabhängig voneinander disubstituiert ist, oder PO_nH_2 bedeutet, wobei n für 2 oder 3 steht; X_3 Methylen ist; R_3 Carboxy, 5-Tetrazolyl, SO_3H, PO_2H_2, PO_3H_2 oder Halogenniederalkylsulfamoyl bedeutet; und (hetero-)aromatische Reste einschliesslich der Ringe A und B jeweils gegebenenfalls zusätzlich substituiert sind durch einen oder mehrere Substituenten ausgewählt aus Halogen, Hydroxy, Niederalkoxy, jeweils gegebenenfalls durch Halogen oder Hydroxy substituiertes Niederalkyl bzw. Niederalkoxyniederalkyl, in freier Form oder in Salzform.

8. Verfahren gemäss Anspruch 1 oder 2 zur Herstellung einer Verbindung der Formel I, worin R_1 Niederalkyl, Niederalkenyl, Halogenniederalkyl, -niederalkenyl, Hydroxyniederalkyl, 3- bis 7-gliedriges Cycloalkyl oder Phenylniederalkyl bedeutet; X_1 für CO oder SO_2 steht; X_2 C_1-C_{10}-Alkylen oder C_1-C_7-Alkyliden, die gegebenenfalls substituiert sind durch Hydroxy, einen 3- bis 7-gliedrigen Cycloalkyl-, 3- bis 7-gliedrigen Cycloalkenyl-, Phenyl-, Pyrrolyl-, Pyrazolyl-, Imidazolyl-, Triazolyl-, Tetrazolyl-, Furyl-, Thienyl- oder Pyridylrest, welche ihrerseits gegebenenfalls zusätzlich durch Carboxy, Niederalkoxycarbonyl, Phenylniederalkoxycarbonyl, Carbamoyl, in dem die Aminogruppe gegebenenfalls durch Niederalkyl oder Phenylniederalkyl mono- oder unabhängig voneinander disubstituiert ist, Formyl, Diniederalkoxymethyl oder Oxyniederalkylenoxymethylen substituiert sein können; R_2 Carboxy, Niederalkoxy-, Phenylniederalkoxy-, Niederalkenyloxy-, Niederalkoxyniederalkoxy-carbonyl, Carbamoyl, in dem die Aminogruppe gegebenenfalls durch Niederalkyl, Phenylniederalkyl mono- oder unabhängig voneinander disubstituiert oder durch Niederalkylen- oder Niederalkylenoxyniederalkylen disubstituiert ist, Amino, in dem die Aminogruppe gegebenenfalls durch Niederalkyl, Phenylniederalkyl mono- oder unabhängig voneinander disubstituiert oder durch Niederalkylen- oder Niederalkylenoxyniederalkylen disubstituiert ist, Niederalkanoyl-, Phenylniederalkanoyl-, Benzoyl-, Niederalkansulfonyl-, Benzolsulfonyl-amino, Formyl, Diniederalkoxymethyl, Oxyniederalkylenoxymethylen, Hydroxy, Niederalkoxy, Phenylniederalkoxy, Phenoxy, $S(O)_m$-R, wobei m für 0, 1 oder 2 und R für Niederalkyl steht, Niederalkanoyl, Sulfamoyl, in dem die Aminogruppe gegebenenfalls durch Niederalkyl, Phenylniederalkyl mono-

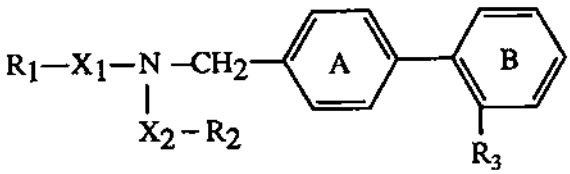
oder unabhängig voneinander disubstituiert ist, oder PO_nH_2 bedeutet, wobei n für 2 oder 3 steht; X_3 Methylen ist; R_3 Carboxy, 5-Tetrazolyl, SO_3H, PO_2H_2, PO_3H_2 oder Halogenniederalkylsulfamoyl bedeutet; und (hetero-)aromatische Reste einschliesslich der Ringe A und B jeweils gegebenenfalls zusätzlich substituiert sind durch einen oder mehrere Substituenten ausgewählt aus Halogen, Hydroxy, Niederalkoxy, jeweils gegebenenfalls durch Halogen oder Hydroxy substituiertes Niederalkyl bzw. Niederalkoxyniederalkyl, in freier Form oder in Salzform.

9. Verfahren gemäss Anspruch 1 oder 2 zur Herstellung einer Verbindung der Formel I, worin X_2 C_1-C_{10}-Alkylen oder C_1-C_7-Alkyliden, die gegebenenfalls substituiert sind durch Hydroxy, einen 3- bis 7-gliedrigen Cycloalkyl-, 3- bis 7-gliedrigen Cycloalkenyl-, Phenyl-, Pyrrolyl-, Pyrazolyl-, Imidazolyl-, Triazolyl-, Tetrazolyl-, Furyl-, Thienyl- oder Pyridylrest, welche ihrerseits gegebenenfalls zusätzlich durch Carboxy, Niederalkoxycarbonyl, Phenylniederalkoxycarbonyl, Carbamoyl, in dem die Aminogruppe gegebenenfalls durch Niederalkyl oder Phenylniederalkyl mono- oder unabhängig voneinander disubstituiert ist, Formyl, Diniederalkoxymethyl oder durch Oxyniederalkylenoxymethylen substituiert sein können, wobei ein C-Atom von C_1-C_{10}-Alkylen bzw. C_1-C_7-Alkyliden durch C_2-C_6-Alkylen überbrückt sein kann, oder X_2 C_3-C_7-Cycloalkylen bedeutet; X_3 Niederalkylen oder Niederalkyliden bedeutet; die Variablen X_1, R_1, R_2, R_3 die in Anspruch 8 angegebenen Bedeutungen haben; und die (hetero-)aromatischen Ringe einschliesslich der Ringe A und B wie in Anspruch 8 angegeben substituiert sein können, in freier Form oder in Salzform.

10. Verfahren gemäss Anspruch 1 oder 2 zur Herstellung einer Verbindung der Formel I, worin die Variablen R_1, X_1, R_3 die jeweils in einem der Ansprüche 1-8 angegebenen Bedeutungen haben; X_2 gegebenenfalls durch Hydroxy, 3- bis 7-gliedriges Cycloalkyl, Phenyl oder Imidazolyl substituiertes Niederalkylen oder Niederalkyliden bedeutet und R_2 Carboxy, Niederalkoxy-, Phenylniederalkoxy-, Niederalkoxyniederalkoxy-carbonyl, Carbamoyl, welches gegebenenfalls durch Niederalkyl, Phenylniederalkyl mono- oder unabhängig voneinander disubstituiert ist, Amino, Niederalkanoyl-, Phenylniederalkanoyl-, Niederalkansulfonylamino, Hydroxy, Niederalkoxy, Phenylniederalkoxy oder Phenoxy bedeutet; X_3 $-CH_2-$ bedeutet; wobei (hetero-)aromatische Reste einschliesslich der Ringe A und B jeweils gegebenenfalls durch einen oder mehrere Substituenten ausgewählt aus Halogen, Trifluormethyl, Hydroxy, Niederalkoxy, Niederalkyl, Hydroxyniederalkyl oder Niederalkoxyniederalkyl substituiert sind, in freier Form oder in Salzform.

11. Verfahren gemäss Anspruch 1 oder 2 zur Herstellung einer Verbindung der Formel I, worin X_2 gegebenenfalls durch Hydroxy, 3- bis 7-gliedriges Cycloalkyl, 7-gliedriges Cycloalkenyl, Phenyl oder Imidazolyl substituiertes Niederalkylen oder Niederalkyliden bedeutet, wobei ein C-Atom von Niederalkylen bzw. Niederalkyliden durch C_2-C_6-Alkylen überbrückt sein kann, oder X_2 C_3-C_7-Cycloalkylen bedeutet; die Variablen X_1, X_3, R_1, R_2 und R_3 die in Anspruch 8 bis 10 angegebenen Bedeutungen haben; und die Ringe A und B wie in Anspruch 10 angegeben substituiert sein können, in freier Form oder in Salzform.

12. Verfahren gemäss Anspruch 1 oder 2 zur Herstellung einer Verbindung der Formel

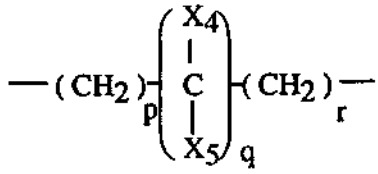


(Ia),

worin die Variablen R_1, X_1, X_2, R_2 und R_3 die jeweils in einem der Ansprüche 1 oder 3-11 angegebenen Bedeutungen haben und die Ringe A und B wie in Anspruch 11 angegeben substituiert sein können, in freier Form oder in Salzform.

13. Verfahren gemäss Anspruch 1 oder 2 zur Herstellung einer Verbindung der Formel Ia, worin X_2 gegebenenfalls durch Hydroxy oder 3- bis 7-gliedriges Cycloalkyl substituiertes Niederalkylen oder Niederalkyliden bedeutet, wobei ein C-Atom von Niederalkylen bzw. Niederalkyliden durch C_2-C_6-Alkylen, überbrückt sein kann, oder worin X_2 C_3-C_7-Cycloalkylen bedeutet; die Variablen R_1, X_1, R_2 und R_3 die jeweils in einem der Ansprüche 1 oder 3-11 angegebenen Bedeutungen haben; und die Ringe A und B wie in Anspruch 11 angegeben substituiert sein können, in freier Form oder in Salzform.

14. Verfahren gemäss Anspruch 1 oder 2 zur Herstellung einer Verbindung der Formel Ia, worin X_2 für die Gruppe der Formel



(Ib)

steht, in der p für 0 oder 1, q für 1 und r für 0 oder 1 stehen oder in der p für 1 bis 8 und q sowie r jeweils für 0 stehen; X_4 gegebenenfalls durch Hydroxy, 3- bis 7-gliedriges Cycloalkyl, Phenyl oder Imidazolyl substituiertes Niederalkyl oder Phenyl bedeutet; und X_5 Wasserstoff oder Niederalkyl bedeutet; R_2 Carboxy, Niederalkoxycarbonyl, Phenylniederalkoxycarbonyl, Niederalkoxyniederalkoxycarbonyl, Hydroxy, Niederalkoxy, Phenylniederalkoxy, Phenoxy, Amino, Niederalkanoylamino, Phenylniederalkanoylamino oder Niederalkansulfonylamino bedeutet; und die Variablen R_1, X_1 und R_3 die jeweils in einem der Ansprüche 1 oder 3-8 angegebenen Bedeutungen haben; wobei (hetero-)aromatische Reste einschliesslich der Ringe A und B jeweils gegebenenfalls durch Halogen, Trifluormethyl, Hydroxy, Niederalkoxy, Niederalkyl oder Hydroxyniederalkyl substituiert sind, in freier Form oder in Salzform.

15. Verfahren gemäss Anspruch 1 oder 2 zur Herstellung einer Verbindung der Formel Ia, worin X_2 für die Gruppe der Formel Ib steht, in der p für 0 oder 1, q für 1 und r für 0 oder 1 stehen oder in der p für 1 bis 8 und q sowie r jeweils für 0 stehen; X_4 gegebenenfalls durch Hydroxy, 3- bis 7-gliedriges Cycloalkyl, Phenyl oder Imidazolyl substituiertes Niederalkyl oder Phenyl bedeutet; und X_5 Wasserstoff oder Niederalkyl bedeutet; oder X_4 und X_5 gemeinsam für C_2-C_8-Alkylen, wie C_4-C_5-Alkylen, stehen; oder X_2 C_3-C_7-Cycloalkylen, wie C_5-C_6-Cycloalkylen, bedeutet; R_2 Carboxy, Niederalkoxycarbonyl, Phenylniederalkoxycarbonyl, Niederalkoxyniederalkoxycarbonyl, Hydroxy, Niederalkoxy, Phenylniederalkoxy, Phenoxy, Amino, Niederalkanoylamino, Phenylniederalkanoylamino oder Niederalkansulfonylamino bedeutet; und die Variablen R_1, X_1 und R_3 die jeweils in einem der Ansprüche 1 oder 3-8 angegebenen Bedeutungen haben; wobei (hetero-)aromatische Reste einschliesslich der Ringe A und B jeweils gegebenenfalls durch Halogen, Trifluormethyl, Hydroxy, Niederalkoxy, Niederalkyl oder Hydroxyniederalkyl substituiert sind, in freier Form oder in Salzform.

16. Verfahren gemäss Anspruch 1 oder 2 zur Herstellung einer Verbindung der Formel Ia, worin R_1 Niederalkyl, wie C_3-C_5-Alkyl, oder Niederalkenyl, wie C_3-C_5-Alkenyl, bedeutet; X_1 für CO oder ferner SO_2 steht; X_2 für die Gruppe der Formel Ib steht, in der p und r für 0 oder 1 und q für 1 stehen; X_4 gegebenenfalls durch Hydroxy, 3- bis 7-gliedriges Cycloalkyl, wie Cyclohexyl, durch gegebenenfalls durch Halogen oder Hydroxy substituiertes Phenyl oder Imidazolyl, wie 4-Imidazolyl, substituiertes Niederalkyl, wie C_1-C_4-Alkyl, oder Phenyl bedeutet; und X_5 Wasserstoff oder Niederalkyl, wie C_1-C_4-Alkyl, bedeutet; oder X_4 und X_5 gemeinsam C_2-C_6-Alkylen, wie C_4-C_5-Alkylen, bedeuten; oder X_2 C_3-C_7-Cycloalkylen, wie C_5-C_6-Cycloalkylen, bedeutet; R_2 Carboxy, Niederalkoxycarbonyl, wie C_2-C_5-Alkoxycarbonyl, Phenylniederalkoxycarbonyl, wie Phenyl-C_1-C_4-alkoxycarbonyl, Niederalkoxyniederalkoxycarbonyl, wie C_1-C_4-Alkoxy-C_2-C_5-alkoxycarbonyl, Hydroxy oder Niederalkoxy, wie C_1-C_4-Alkoxy, bedeutet; und R_3 Carboxy oder 5-Tetrazolyl bedeutet; wobei (hetero-)aromatische Reste einschliesslich der Ringe A und B jeweils gegebenenfalls durch Halogen, Trifluormethyl, Hydroxy, Niederalkoxy, Niederalkyl oder Hydroxyniederalkyl substituiert sind, in freier Form oder in Salzform.

17. Verfahren gemäss Anspruch 1 oder 2 zur Herstellung einer Verbindung der Formel Ia, worin R_1 Niederalkyl, wie C_3-C_5-Alkyl, oder Niederalkenyl, wie C_3-C_5-Alkenyl, bedeutet; X_1 für CO oder ferner SO_2 steht; X_2 für die Gruppe der Formel Ib steht, in der p und r für 0 oder 1 und q für 1 stehen; X_4 gegebenenfalls durch Hydroxy, 3- bis 7-gliedriges Cycloalkyl, durch gegebenenfalls durch Halogen oder Hydroxy substituiertes Phenyl oder Imidazolyl, wie 4-Imidazolyl, substituiertes Niederalkyl, wie C_1-C_4-Alkyl, oder Phenyl bedeutet; und X_5 Wasserstoff oder Niederalkyl, wie C_1-C_4-Alkyl, bedeutet; R_2 Carboxy, Niederalkoxycarbonyl, wie C_2-C_5-Alkoxycarbonyl, Phenylniederalkoxycarbonyl, wie Phenyl-C_1-C_4-alkoxycarbonyl, Niederalkoxyniederalkoxycarbonyl, wie C_1-C_4-Alkoxy-C_2-C_5-alkoxycarbonyl, Hydroxy oder Niederalkoxy, wie C_1-C_4-Alkoxy, bedeutet; und R_3 Carboxy oder 5-Tetrazolyl bedeutet; wobei (hetero-)aromatische Reste einschliesslich der Ringe A und B jeweils gegebenenfalls durch Halogen, Trifluormethyl, Hydroxy, Niederalkoxy, Niederalkyl oder Hydroxyniederalkyl substituiert sind, in freier Form oder in Salzform.

18. Verfahren gemäss Anspruch 1 oder 2 zur Herstellung einer Verbindung der Formel Ia, worin R_1 Niederalkyl, wie C_3-C_5-Alkyl, oder ferner Niederalkenyl, wie C_3-C_5-Alkenyl, bedeutet; X_1 für CO oder ferner SO_2 steht; X_2 für die Gruppe der Formel Ib steht, in der p für eine ganze Zahl von 1 bis 8 und q sowie r für 0 stehen; R_2 Hydroxy, Nie-

deralkoxy, wie C_1-C_4-Alkoxy, Phenylniederalkoxy, wie Phenyl-C_1-C_4-alkoxy, Phenoxy, Niederalkanoylamino, wie C_1-C_4-Alkanoylamino, Phenylniederalkanoylamino, wie Phenyl-C_1-C_4-alkanoylamino, Niederalkansulfonylamino, wie C_1-C_4-Alkansulfonylamino, bedeutet; und R_3 Carboxy oder in erster Linie 5-Tetrazolyl bedeutet; wobei (hetero-)aromatische Reste einschliesslich der Ringe A und B jeweils gegebenenfalls durch Halogen, Trifluormethyl, Hydroxy, Niederalkoxy, Niederalkyl oder Hydroxyniederalkyl substituiert sind, in freier Form oder in Salzform.

19. Verfahren gemäss Anspruch 1 oder 2 zur Herstellung einer Verbindung der Formel Ia, worin R_1 C_3-C_5-Alkyl oder in zweiter Linie C_3-C_5-Alkenyl, bedeutet; X_1 für CO, ferner SO_2 steht; X_2 für die Gruppe der Formel Ib steht, in der p und r unabhängig voneinander für 0 oder 1 und q für 1 stehen; X_4 C_1-C_4-Alkyl, Hydroxy-C_1-C_4-alkyl, C_3-C_7-Cycloalkyl-C_1-C_4-alkyl, Phenyl-C_1-C_4-alkyl oder Imidazolyl-C_1-C_4-alkyl bedeutet; und X_5 Wasserstoff oder C_1-C_4-Alkyl bedeutet; oder X_4 und X_5 gemeinsam für Tetramethylen, ferner Pentamethylen stehen; R_2 Carboxy oder C_2-C_5-Alkoxycarbonyl, ferner Phenyl-C_1-C_4-alkoxycarbonyl bedeutet; und R_3 Carboxy oder 5-Tetrazolyl bedeutet, in freier Form oder in Salzform.

20. Verfahren gemäss Anspruch 1 oder 2 zur Herstellung einer Verbindung der Formel Ia, worin R_1 C_3-C_5-Alkyl oder in zweiter Linie C_3-C_5-Alkenyl bedeutet; X_1 für CO, ferner SO_2 steht; X_2 für die Gruppe der Formel Ib steht, in der p und r jeweils für 0 oder 1 und q für 1 stehen; X_4 C_1-C_4-Alkyl, Hydroxy-C_1-C_4-alkyl, C_3-C_7-Cycloalkyl-C_1-C_4-alkyl, Phenyl-C_1-C_4-alkyl oder Imidazolyl-C_1-C_4-alkyl bedeutet; und X_5 Wasserstoff bedeutet; R_2 Carboxy oder C_2-C_5-Alkoxycarbonyl, ferner Phenyl-C_1-C_4-alkoxycarbonyl bedeutet; und R_3 Carboxy oder 5-Tetrazolyl bedeutet, in freier Form oder in Salzform.

21. Verfahren gemäss Anspruch 1 oder 2 zur Herstellung einer Verbindung der Formel Ia, worin R_1 C_3-C_5-Alkyl bedeutet; X_1 für CO steht; X_2 für die Gruppe der Formel Ib steht, in der q und r für 0 und p für 1 bis 3 stehen oder in der p und q für 1 und r für 0 stehen; X_4 C_1-C_4-Alkyl bedeutet; X_5 Wasserstoff oder C_1-C_4-Alkyl bedeutet; R_2 Carboxy oder C_2-C_5-Alkoxycarbonyl bedeutet; und R_3 Carboxy oder 5-Tetrazolyl bedeutet, in freier Form oder in Salzform.

22. Verfahren gemäss Anspruch 1 oder 2 zur Herstellung einer Verbindung der Formel Ia, worin R_3 5-Tetrazolyl bedeutet, in freier Form oder in Salzform.

23. Verfahren gemäss Anspruch 1 oder 2 zur Herstellung einer Verbindung der Formel Ia, worin R_1 C_3-C_5-Alkyl bedeutet; X_1 für CO steht; X_2 für die Gruppe der Formel Ib steht, in der p für 0 oder 1, r für 0 und q für 1 stehen; X_4 C_1-C_4-Alkyl bedeutet; und X_5 Wasserstoff oder C_1-C_4-Alkyl bedeutet; oder X_4 und X_5 gemeinsam für Tetramethylen oder Pentamethylen stehen; R_2 Carboxy, oder C_2-C_5-Alkoxycarbonyl bedeutet; und R_3 5-Tetrazolyl bedeutet, in freier Form oder in Salzform.

24. Verfahren gemäss Anspruch 1 oder 2 zur Herstellung einer Verbindung der Formel Ia, worin $_1$ C_3-C_5-Alkyl bedeutet; X_1 für CO steht; X_2 für die Gruppe der Formel Ib steht, in der p für 0 oder 1, r für 0 und q für 1 stehen; X_4 und X_5 gemeinsam für Tetramethylen, ferner Pentamethylen stehen; R_2 Carboxy oder C_2-C_5-Alkoxycarbonyl bedeutet; und R_3 5-Tetrazolyl bedeutet, in freier Form oder in Salzform.

25. Verfahren gemäss Anspruch 1 oder 2 zur Herstellung einer Verbindung der Formel Ia, worin R_1 C_3-C_5-Alkyl bedeutet; X_1 für CO steht; X_2 für die Gruppe der Formel Ib steht, in der p und r für 0 oder 1 und q für 1 stehen; X_4 C_1-C_4-Alkyl bedeutet; und X_5 Wasserstoff bedeutet; R_2 Carboxy oder C_2-C_5-Alkoxycarbonyl bedeutet; und R_3 5-Tetrazolyl bedeutet, in freier Form oder in Salzform.

26. Verfahren gemäss Anspruch 1 oder 2 zur Herstellung einer Verbindung der Formel Ia gemäss einem der Ansprüche 14-25, worin X_2 für die Gruppe der Formel Ib steht, q 1 bedeutet und X_4 und X_5 unterschiedliche Bedeutungen haben, in freier Form oder in Salzform, in welcher das betreffende, die Variablen X_4 und X_5 aufweisende, asymmetrische C-Atom die S-Konfiguration hat.

27. Verfahren gemäss Anspruch 1 oder 2 zur Herstellung von (S)-N-(1-Carboxy-2-methyl-prop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin, in freier Form oder in Salzform gemäss Anspruch 1.

28. Verfahren gemäss Anspruch 1 oder 2 zur Herstellung von N-(2-Carboxy-2,2-tetramethylen-ethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin, in freier Form oder in Salzform gemäss Anspruch 1.

29. Verfahren gemäss Anspruch 1 oder 2 zur Herstellung von N-(2-Carboxy-2-ethyl-but-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin, in freier Form oder in Salzform gemäss Anspruch 1.

30. Verfahren gemäss Anspruch 1 oder 2 zur Herstellung von S)-N-(1-Carboxy-2-methyl-prop-1-yl)-N-ethoxycarbonyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin, in freier Form oder in Salzform gemäss Anspruch 1.

31. Verfahren gemäss Anspruch 1 oder 2 zur Herstellung von N-(1-carboxycyclohexyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin, in freier Form oder in Salzform gemäss Anspruch 1.

32. Verfahren gemäss Anspruch 1 oder 2 zur Herstellung einer Verbindung gemäss Anspruch 1 ausgewählt aus der Gruppe bestehend aus:
(S)-N-(1-Carboxyethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-(2-Hydroxyethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-(2-Ethoxycarbonyl-2,2-tetramethylen-ethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-(2-Ethoxycarbonyl-2-ethyl-but-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-(2-Ethoxycarbonyl-2-methyl-prop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)
biphenyl-4-ylmethyl]-amin,
(S)-N-(1-Hydroxymethyl-2-methyl-prop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-(2-Ethoxycarbonyl-2,2-pentamethylen-ethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
(S)-N-(1-Carboxy-2-methyl-prop-1-yl)-N-propyloxycarbonyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-(2-carboxy-2-methyl-propyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-(2-carboxy-2,2-pentamethylen-ethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
(S)-N-(1-aminocarbonyl-2-methyl-prop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin und
(S)-N-(1-carboxy-2-methyl-prop-1-yl)-N-(5-oxopent-1-en-5-yl)-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
jeweils in freier Form oder in Salzform.

33. Verfahren gemäss Anspruch 1 oder 2 zur Herstellung einer Verbindung gemäss Anspruch 1 ausgewählt aus der Gruppe bestehend aus:
N-Carboxymethyl-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
(S)-N-(1-Methoxycarbonylethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-[1-Carboxy-2-(4-fluorphenyl)-ethyl]-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-[2-(4-Fluorphenyl)-1-methoxycarbonyl-ethyl]-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-[2-(4-Fluorphenyl)-1-hydroxymethyl-ethyl]-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-(2'-Carboxybiphenyl-4-ylmethyl)-N-[1-carboxy-2-(4-fluorphenyl)-ethyl]-N-pentanoyl-amin,
N-(2'-Carboxybiphenyl-4-ylmethyl)-N-[2-(4-fluorphenyl)-1-methoxycarbonyl-ethyl]-N-pentanoyl-amin,
(S)-N-(2'-Carboxybiphenyl-4-ylmethyl)-N-(1-hydroxymethyl-2-phenyl-ethyl)-N-pentanoyl-amin,
(S)-N-(2'-Carboxybiphenyl-4-ylmethyl)-N-(1-hydroxymethyl-2-imidazol-4-yl-ethyl)-N-pentanoyl-amin,
(R)-N-(1-Carboxyethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
(1S),(2S)-N-(1-Carboxy-2-methyl-but-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
(1S),(2S)-N-(1-Methoxycarbonyl-2-methyl-but-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
(S)-N-(1-Carboxybut-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
(S)-N-(1-Methoxycarbonylbut-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
(S)-N-(1-Carboxyethyl)-N-hexanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
(S)-N-Butanoyl-N-(1-carboxyethyl)-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
(S)-N-(1-Carboxyprop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
(S)-N-(1-Carboxy-2-cyclohexyl-ethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
(S)-N-(2-Cyclohexyl-1-methoxycarbonyl-ethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
(R)-N-(1-Carboxy-2-methyl-prop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-(2-Methoxyethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-(2-Benzyloxyethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-(3-Methoxyprop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-(3-Benzyloxyprop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-(3-Hydroxyprop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-(1-Methoxycarbonyl-1-methyl-ethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-(2-Carboxyethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-(2-Carboxyprop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-(1-Carboxy-1-methyl-ethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-(5-Hydroxypent-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-(1-Carboxyprop-2-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-(2-Ethoxycarbonyl-3-methyl-but-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-(2-Carboxy-3-methyl-but-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-(3-Phenoxyprop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,

N-[2-(4-Hydroxyphenyl)ethyl]-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-[3-(4-Hydroxyphenyl)prop-1-yl]-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-(8-Hydroxyoct-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-(2-Methansulfonylaminoethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-(3-Acetylaminoprop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-(2-Methoxy-2-oxo-1-phenyl-ethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-(4-Hydroxybut-2-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-(2-Hydroxy-1-phenyl-ethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-[3-(4-Hydroxybenzylcarbonylamino)prop-1-yl]-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-(3-Ethoxycarbonylcyclohexyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-(3-Carboxycyclohexyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
cis-N-(4-Carboxycyclohexyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
cis-N-(2-Ethoxycarbonylcyclohexyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
cis-N-(2-Carboxycyclohexyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-{2-[2-(4-Hydroxyphenyl)ethylaminocarbonyl]-2,2-tetramethylen-ethyl}-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
(S)-N-{1-[2-(4-Hydroxyphenyl)ethylaminocarbonyl]-2-methyl-prop-1-yl}-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
(S)-N-(1-Carboxy-2,2-dimethyl-prop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
(S)-N-(1-Methoxycarbonyl-2-methyl-prop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-(4-Phenoxybut-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-(2-Hydroxy-1-phenyl-2-oxo-ethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
(S)-N-(1-Benzyloxycarbonyl-2-methyl-prop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-Butanoyl-N-(1-carboxy-1-methyl-ethyl)-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-(4-Hydroxybut-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
(S)-N-(1-Benzyloxycarbonyl-2-methyl-prop-1-yl)-N-[3-bromo-2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-N-pentanoyl-amin,
(S)-N-[3-Brom-2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-N-(1-carboxy-2-methyl-prop-1-yl)-N-pentanoyl-amin,
N-(2-Acetylaminoethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-[2-(n-Butoxycarbonyl)-2,2-tetramethylen-ethyl]-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-(2-Benzylaminocarbonyl-2,2-tetramethylen-ethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
(S)-N-Butyloxycarbonyl-N-(1-Carboxy-2-methyl-prop-1-yl)-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
(S)-N-(1-Carboxy-2-methyl-prop-1-yl)-N-methoxycarbonyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-(2-Diethylaminocarbonyl-2,2-tetramethylen-ethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-(2-Methyl-2-morpholin-4-ylcarbonyl-propyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-(1-Carboxycyclopentyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-(1-Carboxy-1-ethyl-prop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
(S)-N-(5-Amino-1-carboxy-pent-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-Butansulfonyl-N-(2-ethoxycarbonyl-2,2-pentamethylen-ethyl)-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-Butansulfonyl-N-(2-carboxy-2,2-pentamethylen-ethyl)-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-Butansulfonyl-N-(2-ethoxycarbonyl-2-methyl-prop-1-yl)-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-Butansulfonyl-N-(2-carboxy-2-methyl-prop-1-yl)-N-[2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-amin,
(S)-N-Butansulfonyl-N-(1-tert.-butoxycarbonylethyl)-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
(S)-N-Butansulfonyl-N-(1-carboxyethyl)-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
(S)-N-Butansulfonyl-N-(1-carboxy-2-methyl-prop-1-yl)-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
(S)-N-(2-Methyl-1-methylaminocarbonyl-prop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
(S)-N-(1-Dimethylaminocarbonyl-2-methyl-prop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
(S)-N-(2-Methyl-1-morpholin-4-ylcarbonyl-prop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
(S)-N-(2'-Carboxybiphenyl-4-ylmethyl)-N-(1-carboxy-2-methyl-prop-1-yl)-N-pentanoyl-amin,
(S)-N-(1,2-Dicarboxyethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
(S)-N-(1-Carboxy-3-phenyl-prop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
(S)-N-(2-Cyclohexyl-1-hydroxymethyl-ethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
(R)-N-(1-Methoxycarbonyl-2-methyl-prop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
(S)-N-(2-Hydroxy-1-methoxycarbonyl-ethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-Pentanoyl-N-(1H-tetrazol-5-ylmethyl)-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,

N-Pentanoyl-N-pyrid-3-ylmethyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
(S)-N-(1-Carboxy-4-guanidino-but-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-(2-Hydroxy-1-methoxycarbonyl-prop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-(1-Benzyloxycarbonyl-1-methyl-ethyl)-N-butanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
(S)-N-(1-Carboxy-3-methyl-but-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-(1-Carboxy-2-hydroxy-ethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl- 4-ylmethyl]-amin, (S)-N-(1-Carboxy-2-hydroxy-ethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
(S)-N-[2-Methyl-1-(2-phenylethylaminocarbonyl)-prop-1-yl]-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
(S)-N-(2-Benzyloxy-1-hydroxymethyl-ethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
(S)-N-(1-Carboxy-2-methyl-prop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-3-ylmethyl]-amin,
(S)-N-(1-Carboxy-2-methyl-prop-1-yl)-N-pentanoyl-N-[3'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
(S)-N-[2-Methyl-1-(1,2,3,4-tetrahydrochinol-1-ylcarbonyl)-prop-1-yl]-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
(S)-N-(2-Methyl-1-piperidin-1-ylcarbonyl-prop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
(S)-N-[2-Methyl-1-(1,2,3,4-tetrahydroisochinol-2-ylcarbonyl)-prop-1-yl]-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-(2-Hydroxymethyl-2-methyl-prop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin,
N-Ethoxycarbonyl-N-(2-ethoxycarbonyl-2-methyl-prop-1-yl)-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin und
N-(2-Carboxy-2-methyl-prop-1-yl)-N-ethoxycarbonyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amin, jeweils in freier Form oder in Salzform.

34. Verfahren zur Herstellung eines pharmazeutischen Präparats als Wirkstoff enthaltend eine Verbindung gemäss einem der Ansprüche 1 oder 3 bis 33, in freier Form oder in Form eines pharmazeutisch verwendbaren Salzes, gegebenenfalls neben üblichen pharmazeutischen Hilfsstoffen, dadurch gekennzeichnet, dass man den Wirkstoff, gegebenenfalls unter Beimischung von üblichen pharmazeutischen Hilfsstoffen, zu einem pharmazeutischen Präparat verarbeitet.

35. Verwendung einer Verbindung gemäss einem der Ansprüche 1 oder 3-33, in freier Form oder in Form eines pharmazeutisch verwendbaren Salzes, zur Herstellung eines Antihypertensivums.

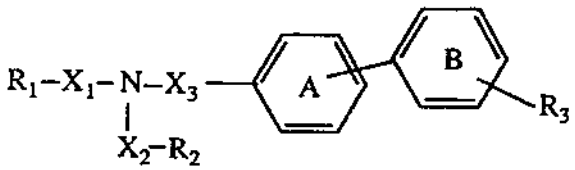
36. Verwendung einer Verbindung gemäss einem der Ansprüche 1 oder 3-33, in freier Form oder in Form eines pharmazeutisch verwendbaren Salzes, zur Herstellung eines pharmazeutischen Präparats zur therapeutischen oder prophylaktischen Behandlung von Herzinsuffizienz.

37. Verwendung einer Verbindung gemäss einem der Ansprüche 1 oder 3-33, in freier Form oder in Form eines pharmazeutisch verwendbaren Salzes, zur Herstellung eines pharmazeutischen Präparats zur therapeutischen oder prophylaktischen Behandlung von Erkrankungen, die durch Angiotensin-II-Aktivität verursacht werden.

Claims

Claims for the following Contracting States : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE

1. A compound of the formula



(I),

in which R_1 is lower alkyl, lower alkenyl or lower alkynyl or C_3-C_7cycloalkyl or C_3-C_7cycloalkenyl or phenyl-lower alkyl, phenyl-lower alkenyl or phenyl-lower alkynyl, each of which is unsubstituted or substituted by halogen or hydroxyl; X_1 is CO, SO_2 or -O-C(=O)-, the carbon atom of the carbonyl group being bonded to the nitrogen atom drawn in in the formula 1; X_2 is C_1-C_{10}alkylene, C_2-C_{10}alkylidene or C_3-C_7cycloalkylene which is unsubstituted or substituted by hydroxyl, carboxyl, amino, guanidino, C_3-C_7cycloalkyl, C_3-C_7cycloalkenyl, phenyl or a corresponding

5- or 6-membered and monocyclic aromatic radical which has up to four identical or different heteroatoms, it being possible for a carbon atom of C_1-C_{10}alkylene or C_2-C_{10}alkylidene additionally to be bridged by C_2-C_8alkylene, and C_3-C_7cycloalkyl or C_3-C_7cycloalkenyl being unsubstituted, monosubstituted or polysubstituted by carboxyl, carboxyl which is esterified by an alcohol which is derived from lower alkyl, phenyl-lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy-lower alkyl, lower alkoxy-lower alkenyl or lower alkoxy-lower alkynyl, carbamoyl, carbamoyl in which the amino group is monosubstituted or independently of one another disubstituted by lower alkyl, lower alkenyl, lower alkynyl, phenyl-lower alkyl, phenyl-lower alkenyl or phenyl-lower alkynyl or is disubstituted by C_1-C_{10}alkylene or C_2-C_{10}alkylidene, C_1-C_{10}alkylene or C_2-C_{10}alkylidene being uninterrupted or interrupted by -O- or being fused at two adjacent C atoms to a benzene ring, formyl, di-lower alkoxymethyl or oxy-lower alkylenoxymethylene; R_2 is carboxyl, carboxyl which is esterified by an alcohol which is derived from lower alkyl, phenyl-lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy-lower alkyl, lower alkoxy-lower alkenyl or lower alkoxy-lower alkynyl, carbamoyl, carbamoyl in which the amino group is monosubstituted or independently of one another disubstituted by lower alkyl, lower alkenyl, lower alkynyl, phenyl-lower alkyl, phenyl-lower alkenyl or phenyl-lower alkynyl or is disubstituted by C_1-C_{10}alkylene or C_2-C_{10}alkylidene, C_1-C_{10}alkylene or C_2-C_{10}alkylidene being uninterrupted or interrupted by -O- or being fused at two adjacent C atoms to a benzene ring, amino, amino which is monosubstituted or independently of one another disubstituted by lower alkyl, lower alkenyl, lower alkynyl, phenyl-lower alkyl, phenyl-lower alkenyl or phenyl-lower alkynyl or is disubstituted by C_1-C_{10}alkylene or C_2-C_{10}alkylidene, C_1-C_{10}alkylene or C_2-C_{10}alkylidene being uninterrupted or interrupted by -O- or fused at two adjacent C atoms to a benzene ring, lower alkanoyl-, phenyl-lower alkanoyl-, benzoyl-, lower alkanesulfonyl- or benzenesulfonyl-amino, formyl, di-lower alkoxymethyl, oxy-lower alkylenoxymethylene, 1H-tetrazol-5-yl, pyridyl, hydroxyl, lower alkoxy, lower alkenyloxy, phenyl-lower alkoxy phenoxy, $S(O)_m$-R, m being 0, 1 or 2 and R being hydrogen, lower alkyl, lower alkenyl or lower alkynyl, lower alkanoyl, sulfamoyl, sulfamoyl in which the amino group is monosubstituted or independently of one another disubstituted by lower alkyl, lower alkenyl, lower alkynyl, phenyl-lower alkyl, phenyl-lower alkenyl or phenyl-lower alkynyl or is disubstituted by C_1-C_{10}alkylene or C_2-C_{10}alkylidene, C_1-C_{10}alkylene or C_2-C_{10}alkylidene being uninterrupted or interrupted by -O- or being fused at two adjacent C atoms to a benzene ring, or is PO_nH_2, n being 2 or 3; X_3 is C_1-C_{10}alkylene or C_2-C_{10}alkylidene; R_3 is carboxyl, 5-tetrazolyl, SO_3H, PO_2H_2, PO_3H_2 or halo-lower alkylsulfamoyl; and (hetero)aromatic radicals including the rings A and B independently of one another being unsubstituted or substituted by substituents selected from the group consisting of: halogen hydroxyl lower alkoxy, lower alkenyloxy, phenyl-lower alkoxy, phenoxy, $S(O)_m$-R and lower alkyl, lower alkenyl or lower alkynyl, each of which is unsubstituted or substituted by halogen or hydroxyl, lower alkyl, lower alkenyl or lower alkynyl being uninterrupted or interrupted by -O-, and, in the case of (hetero)aromatic radicals, additionally being unsubstituted or substituted by carboxyl, carboxyl which is esterified by an alcohol which is derived from lower alkyl, phenyl-lower alkyl, lower alkenyl lower alkynyl, lower alkoxy-lower alkyl, lower alkoxy-lower alkenyl or lower alkoxy-lower alkynyl, by carbamoyl, carbamoyl in which the amino group is monosubstituted or independently of one another disubstituted by lower alkyl, lower alkenyl, lower alkynyl, phenyl-lower alkyl, phenyl-lower alkenyl or phenyl-lower alkynyl or is disubstituted by C_1-C_{10}alkylene or C_2-C_{10}alkylidene, C_1-C_{10}alkylene or C_2-C_{10}alkylidene being uninterrupted or interrupted by -O- or being fused at two adjacent C atoms to a benzene ring, by formyl, di-lower alkoxymethyl or oxy-lower alkylenoxymethylene; radicals and groups designated by "lower" containing up to and including 7 carbon atoms; in free form or in salt form.

2. A compound according to claim 1 of the formula I, in which R_1 is lower alkyl, lower alkenyl or lower alkynyl or C_3-C_7cycloalkyl or C_3-C_7cycloalkenyl or phenyl-lower alkyl, phenyl-lower alkenyl or phenyl-lower alkynyl, each of which is unsubstituted or substituted by halogen or hydroxyl; X_1 is CO or SO_2; X_2 is C_1-C_{10}alkylene or C_2-C_{10}alkylidene or C_3-C_7cycloalkylene which is unsubstituted or substituted by hydroxyl, C_3-C_7cycloalkyl or C_3-C_7cycloalkenyl or phenyl or a corresponding 5- or 6-membered and monocyclic aromatic radical which has up to 4 identical or different heteroatoms, it being possible for a carbon atom of C_1-C_{10}alkylene or C_2-C_{10}alkylidene additionally to be bridged by C_2-C_6alkylene, and C_3-C_7cycloalkylene being unsubstituted, monosubstituted or polysubstituted by carboxyl, carboxyl which is esterified by an alcohol which is derived from lower alkyl, phenyl-lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy-lower alkyl lower alkoxy-lower alkenyl or lower alkoxy-lower alkynyl, carbamoyl, carbamoyl in which the amino group is monosubstituted or independently of one another disubstituted by lower alkyl, lower alkenyl, lower alkynyl, phenyl-lower alkyl, phenyl-lower alkenyl or phenyl-lower alkynyl or is disubstituted by C_1-C_{10}alkylene or C_2-C_{10}alkylidene, C_1-C_{10}alkylene or C_2-C_{10}alkylidene being uninterrupted or interrupted by -O-, formyl, di-lower alkoxymethyl or oxy-lower alkylenoxymethylene; R_2 is carboxyl, carboxyl which is esterified by an alcohol which is derived from lower alkyl, phenyl-lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy-lower alkyl, lower alkoxy-lower alkenyl or lower alkoxy-lower alkynyl, carbamoyl, carbamoyl in which the amino group is monosubstituted or independently of one another disubstituted by lower alkyl, lower alkenyl, lower alkynyl, phenyl-lower alkyl, phenyl-lower alkenyl or phenyl-lower alkynyl or is disubstituted by C_1-C_{10}alkylene or C_2-C_{10}alkylidene, C_1-C_{10}alkylene or C_2-C_{10}alkylidene being uninterrupted or interrupted by -O-, amino, amino which is monosubstituted or independently of one another disubstituted by lower alkyl, lower alkenyl, lower alkynyl, phenyl-lower alkyl, phenyl-lower alkenyl or

phenyl-lower alkynyl or is disubstituted by C_1-C_{10}alkylene or C_2-C_{10}alkylidene, C_1-C_{10}alkylene or C_2-C_{10}alkylidene being uninterrupted or interrupted by -O-, lower alkanoyl- phenyl-lower alkanoyl-, benzoyl- lower alkanesulfonyl- or benzenesulfonyl-amino formyl, di-lower alkoxymethyl, oxy-lower alkylenoxymethylene, hydroxyl, lower alkoxy, lower alkenyloxy, phenyl-lower alkoxy, phenoxy, $S(O)_m$-R, m being 0, 1 or 2 and R being hydrogen, lower alkyl, lower alkenyl or lower alkynyl, lower alkanoyl, sulfamoyl, sulfamoyl in which the amino group is monosubstituted or independently of one another disubstituted by lower alkyl, lower alkenyl, lower alkynyl, phenyl-lower alkyl, phenyl-lower alkenyl or phenyl-lower alkynyl or is disubstituted by C_1-C_{10}alkylene or C_2-C_{10}alkylidene, C_1-C_{10}alkylene or C_2-C_{10}alkylidene being uninterrupted or interrupted by -O-, or is PO_nH_2, n being 2 or 3; X_3 is C_1-C_{10}alkylene or C_2-C_{10}alkylidene; R_3 is carboxyl, 5-tetrazolyl, SO_3H, PO_2H_2, PO_3H_2 or halo-lower alkylsulfamoyl; (hetero)aromatic radicals including the rings A and B independently of one another being unsubstituted or substituted by substituents selected from the group consisting of: halogen, hydroxyl, lower alkoxy, lower alkenyloxy, phenyl-lower alkoxy, phenoxy, $S(O)_m$-R and lower alkyl, lower alkenyl or lower alkynyl, each of which is unsubstituted or substituted by halogen or hydroxyl, lower alkyl, lower alkenyl or lower alkynyl being uninterrupted or interrupted by -O-, and, in the case of (hetero)aromatic radicals, additionally unsubstituted or substituted by carboxyl, carboxyl which is esterified by an alcohol which is derived from lower alkyl, phenyl-lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy-lower alkyl, lower alkoxy-lower alkenyl or lower alkoxy-lower alkynyl, by carbamoyl, carbamoyl in which the amino group is monosubstituted or independently of one another disubstituted by lower alkyl, lower alkenyl, lower alkynyl, phenyl-lower alkyl, phenyl-lower alkenyl or phenyl-lower alkynyl or is disubstituted by C_1-C_{10}alkylene or C_2-C_{10}alkylidene, C_1-C_{10}alkylene or C_2-C_{10}alkylidene being uninterrupted or interrupted by -O-, by formyl, di-lower alkoxymethyl or oxy-lower alkylenoxymethylene; in free form or in salt form.

3. A compound according to claim 1 of the formula I, in which R_1 is lower alkyl, lower alkenyl or lower alkynyl or C_3-C_7cycloalkyl or C_3-C_7cycloalkenyl or phenyl-lower alkyl, phenyl-lower alkenyl or phenyl-lower alkynyl, each of which is unsubstituted or substituted by halogen or hydroxyl; X_1 is CO or SO_2; X_2 is C_1-C_{10}alkylene or C_2-C_{10}alkylidene which is unsubstituted or substituted by hydroxyl, C_3-C_7cycloalkyl or C_3-C_7cycloalkenyl or phenyl or a corresponding 5- or 6-membered and monocyclic aromatic radical which has up to 4 identical or different heteroatoms; R_2 is carboxyl, carboxyl which is esterified by an alcohol which is derived from lower alkyl, phenyl-lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy-lower alkyl, lower alkoxy-lower alkenyl or lower alkoxy-lower alkynyl, carbamoyl, carbamoyl in which the amino group is monosubstituted or independently of one another disubstituted by lower alkyl, lower alkenyl, lower alkynyl, phenyl-lower alkyl phenyl-lower alkenyl or phenyl-lower alkynyl or is disubstituted by C_1-C_{10}alkylene or C_2-C_{10}alkylidene C_1-C_{10}alkylene or C_2-C_{10}alkylidene being uninterrupted or interrupted by -O-, amino, amino which is monosubstituted or independently of one another disubstituted by lower alkyl, lower alkenyl, lower alkynyl, phenyl-lower alkyl, phenyl-lower alkenyl or phenyl-lower alkynyl or is disubstituted by C_1-C_{10}alkylene or C_2-C_{10}alkylidene, C_1-C_{10}alkylene or C_2-C_{10}alkylidene being uninterrupted or interrupted by -O-, lower alkanoyl-, phenyl-lower alkanoyl-, benzoyl- lower alkanesulfonyl- or benzenesulfonyl-amino, formyl, di-lower alkoxymethyl, oxy-lower alkylenoxymethylene, hydroxyl, lower alkoxy, lower alkenyloxy, phenyl-lower alkoxy or phenoxy, $S(O)_m$-R, m being 0, 1 or 2 and R being hydrogen, lower alkyl, lower alkenyl or lower alkynyl, lower alkanoyl, sulfamoyl, sulfamoyl in which the amino group is monosubstituted or independently of one another disubstituted by lower alkyl, lower alkenyl, lower alkynyl, phenyl-lower alkyl, phenyl-lower alkenyl or phenyl-lower alkynyl or is disubstituted by C_1-C_{10}alkylene or C_2-C_{10}alkylidene, C_1-C_{10}alkylene or C_2-C_{10}alkylidene being uninterrupted or interrupted by -O-, or is PO_nH_2, n being 2 or 3; X_3 is $-CH_2-$; R_3 is carboxyl, 5-tetrazolyl, SO_3H, PO_2H_2, PO_3H_2 or halo-lower alkylsulfamoyl; and (hetero)aromatic radicals including the rings A and B independently of one another being unsubstituted or substituted by substituents selected from the group consisting of: halogen, hydroxyl, lower alkoxy, lower alkenyloxy, phenyl-lower alkoxy, phenoxy, $S(O)_m$-R and lower alkyl, lower alkenyl or lower alkynyl, each of which is unsubstituted or substituted by halogen or hydroxyl, lower alkyl, lower alkenyl or lower alkynyl being uninterrupted or interrupted by -O-, and, in the case of (hetero)aromatic radicals, additionally unsubstituted or substituted by carboxyl, carboxyl which is esterified by an alcohol which is derived from lower alkyl, phenyl-lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy-lower alkyl, lower alkoxy-lower alkenyl or lower alkoxy-lower alkynyl, by carbamoyl, carbamoyl in which the amino group is monosubstituted or independently of one another disubstituted by lower alkyl, lower alkenyl, lower alkynyl, phenyl-lower alkyl, phenyl-lower alkenyl or phenyl-lower alkynyl or is disubstituted by C_1-C_{10}alkylene or C_1-C_{10}alkylidene, C_1-C_{10}alkylene or C_2-C_{10}alkylidene being uninterrupted or interrupted by -O-, by formyl, di-lower alkoxymethyl or oxy-lower alkylenoxymethylene; in free form or in salt form.

4. A compound according to claim 1 of the formula I, in which R_1 is lower alkyl, lower alkenyl, lower alkynyl, halo-lower alkyl, -lower alkenyl or -lower alkynyl, hydroxy-lower alkyl, -lower alkenyl or -lower alkynyl, C_3-C_7cycloalkyl, C_3-C_7cycloalkenyl, phenyl-lower alkyl, phenyl-lower alkenyl or phenyl-lower alkynyl; X_1 is CO or SO_2; X_2 is C_1-C_{10}alkylene or C_2-C_{10}alkylidene, each of which is unsubstituted or substituted by hydroxyl, a C_3-C_7cycloalkyl, C_3-C_7cycloalkenyl or a phenyl radical or a 5- or 6-membered, monocyclic heteroaromatic radical having up to four identical or different heteroatoms, the cyclic radicals for their part being unsubstituted or substituted by carboxyl

which can be esterified with an alcohol which is derived from lower alkyl, phenyl-lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy-lower alkyl, -lower alkenyl or -lower alkynyl, carbamoyl in which the amino group is unsubstituted, monosubstituted or independently of one another disubstituted by lower alkyl, lower alkenyl, lower alkynyl, phenyl-lower alkyl, phenyl-lower alkenyl or phenyl-lower alkynyl or is disubstituted by lower alkylene or lower alkylenoxy-lower alkylene, formyl, di-lower alkoxymethyl or oxy-lower alkylenoxymethylene; R_2 is carboxyl which can be esterified with an alcohol which is derived from lower alkyl, phenyl-lower alkyl, lower alkenyl, lower alkynyl, or lower alkoxy-lower alkyl, -lower alkenyl or -lower alkynyl, carbamoyl in which the amino group is unsubstituted, monosubstituted or independently of one another disubstituted by lower alkyl, lower alkenyl, lower alkynyl, phenyl-lower alkyl, phenyl-lower alkenyl or phenyl-lower alkynyl or is disubstituted by lower alkylene- or lower alkylenoxy-lower alkylene, amino in which the amino group is unsubstituted, monosubstituted or independently of one another disubstituted by lower alkyl, lower alkenyl, lower alkynyl, phenyl-lower alkyl, phenyl-lower alkenyl or phenyl-lower alkynyl or is disubstituted by lower alkylene- or lower-alkylenoxy-lower alkylene, lower alkanoyl-, phenyl-lower alkanoyl-, benzoyl-, lower alkanesulfonyl- or benzenesulfonyl-amino, formyl, di-lower alkoxymethyl, oxy-lower alkylenoxymethylene, hydroxyl, lower alkoxy, lower alkenyloxy, phenyl-lower alkoxy, phenoxy, $S(O)_m$-R, m being 0, 1 or 2 and R being hydrogen, lower alkyl, lower alkenyl or lower alkynyl, lower alkanoyl, sulfamoyl in which the amino group is unsubstituted, monosubstituted or independently of one another disubstituted by lower alkyl, lower alkenyl, lower alkynyl, phenyl-lower alkyl, phenyl-lower alkenyl or phenyl-lower alkynyl or is disubstituted by lower alkylene- or lower alkylenoxy-lower alkylene, or is PO_nH_2, n being 2 or 3; X_3 is $-CH_2-$; and R_3 is carboxyl, 5-tetrazolyl, SO_3H, PO_2H_2, PO_3H_2 or halo-lower alkylsulfamoyl; (hetero)aromatic radicals including the rings A and B independently of one another each being unsubstituted or substituted by one or more substituents selected from halogen, hydroxyl, lower alkoxy, lower alkenyloxy, or lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy-lower alkyl, -lower alkenyl or -lower alkynyl, lower alkenyloxy-lower alkyl, -lower alkenyl and -lower alkynyl, each of which is unsubstituted or substituted by halogen or hydroxyl, in free form or in salt form.

5. A compound according to claim 1 of the formula I, in which X_2 is C_1-C_{10}alkylene or C_2-C_{10}alkylidene, each of which is unsubstituted or substituted by hydroxyl, a C_3-C_7cycloalkyl, C_3-C_7cycloalkenyl or a phenyl radical or a 5- or 6-membered, monocyclic heteroaromatic radical having up to four identical or different heteroatoms, it being possible for a C atom of C_1-C_{10}alkylene or C_2-C_{10}alkylidene to be bridged by C_2-C_6alkylene and the cyclic radicals for their part being unsubstituted or substituted by carboxyl which can be esterified with an alcohol which is derived from lower alkyl, phenyl-lower alkyl, lower alkenyl, lower alkynyl, or lower alkoxy-lower alkyl, -lower alkenyl or -lower alkynyl, carbamoyl in which the amino group is unsubstituted, monosubstituted or independently of one another disubstituted by lower alkyl, lower alkenyl, lower alkynyl, phenyl-lower alkyl, phenyl-lower alkenyl or phenyl-lower alkynyl or is disubstituted by lower alkylene- or lower alkylenoxy-lower alkylene, formyl, di-lower alkoxymethyl or by oxy-lower alkylenoxymethylene, or X_2 is C_3-C_7cycloalkylene; X_3 is lower alkylene or lower alkylidene; the variables X_1, R_1, R_2 and R_3 are as defined in claim 4; and the (hetero)aromatic rings including the rings A and B can be substituted as indicated in claim 4, in free form or in salt form.

6. A compound according to claim 1 of the formula I, in which R_1 is lower alkyl, lower alkenyl, halo-lower alkyl or -lower alkenyl, hydroxy-lower alkyl, 3- to 7-membered cycloalkyl or phenyl-lower alkyl; X_1 is CO, SO_2 or -O-C(=O)-, the carbon atom of the carbonyl group being bonded to the nitrogen atom drawn in in the formula I; X_2 is C_1-C_{10}alkylene or C_1-C_7alkylidene, each of which is unsubstituted or substituted by hydroxyl, carboxyl, amino, guanidino, a 3- to 7-membered cycloalkyl, 3- to 7-membered cycloalkenyl, phenyl, pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, furyl, thienyl or pyridyl radical can which for its part additionally be unsubstituted or substituted by carboxyl, lower alkoxycarbonyl, phenyl-lower alkoxycarbonyl, carbamoyl in which the amino group is unsubstituted, monosubstituted or independently of one another disubstituted by lower alkyl or phenyl-lower alkyl, formyl, di-lower alkoxymethyl or oxy-lower alkylenoxymethylene; R_2 is carboxyl, lower alkoxy-, phenyl-lower alkoxy-, lower alkenyloxy- or lower alkoxy-lower alkoxy-carbonyl, carbamoyl in which the amino group is unsubstituted, monosubstituted or independently of one another disubstituted by lower alkyl or phenyl-lower alkyl or is disubstituted by lower alkylene which can be fused at two adjacent carbon atoms to a benzene ring, or lower alkylenoxy-lower alkylene, amino in which the amino group is unsubstituted, monosubstituted or independently of one another disubstituted by lower alkyl or phenyl-lower alkyl or is disubstituted by lower alkylene- or lower alkylenoxy-lower alkylene, lower alkanoyl-, phenyl-lower alkanoyl-, benzoyl-, lower alkanesulfonyl- or benzenesulfonyl-amino, formyl, di-lower alkoxymethyl, oxy-lower alkylenoxymethylene, hydroxyl, lower alkoxy, phenyl-lower alkoxy, phenoxy, $S(O)_m$-R, m being 0, 1 or 2 and R being lower alkyl, lower alkanoyl, sulfamoyl in which the amino group is unsubstituted, monosubstituted or independently of one another disubstituted by lower alkyl or phenyl-lower alkyl, or is PO_nH_2, n being 2 or 3; X_3 is methylene; R_3 is carboxyl, 5-tetrazolyl, SO_3H, PO_2H_2, PO_3H_2 or halo-lower alkylsulfamoyl; and (hetero)aromatic radicals including the rings A and B are each additionally unsubstituted or substituted by one or more substituents selected from halogen, hydroxyl, lower alkoxy, or lower alkyl or lower alkoxy-lower alkyl, each of which is unsubstituted or substituted by halogen or hydroxyl, in free form or in salt form.

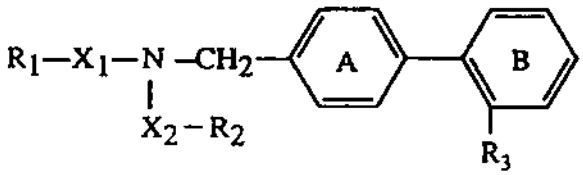
7. A compound according to claim 1 of the formula I, in which R_1 is lower alkyl, lower alkenyl, halo-lower alkyl or -lower alkenyl, hydroxy-lower alkyl, 3- to 7-membered cycloalkyl or phenyl-lower alkyl; X_1 is CO or SO_2; X_2 is C_1-C_{10}alkylene or C_1-C_7alkylidene, each of which is unsubstituted or substituted by hydroxyl, a 3- to 7-membered cycloalkyl, 3- to 7-membered cycloalkenyl, phenyl, pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, furyl, thienyl or pyridyl radical which for its part can additionally be unsubstituted or substituted by carboxyl, lower alkoxycarbonyl, phenyl-lower alkoxycarbonyl, carbamoyl in which the amino group is unsubstituted, monosubstituted or independently of one another disubstituted by lower alkyl or phenyl-lower alkyl formyl, di-lower alkoxymethyl or oxy-lower alkylenoxymethylene; R_2 is carboxyl, lower alkoxy-, phenyl-lower alkoxy-, lower alkenyloxy- or lower alkoxy-lower alkoxy-carbonyl, carbamoyl in which the amino group is unsubstituted, monosubstituted or independently of one another disubstituted by lower alkyl or phenyl-lower alkyl or is disubstituted by lower alkylene- or lower alkylenoxy-lower alkylene, amino in which the amino group is unsubstituted, monosubstituted or independently of one another disubstituted by lower alkyl or phenyl-lower alkyl or is disubstituted by lower alkylene- or lower alkylenoxy-lower alkylene, lower alkanoyl, phenyl-lower alkanoyl-, benzoyl-, lower alkanesulfonyl- or benzenesulfonyl-amino, formyl, di-lower alkoxymethyl, oxy-lower alkylenoxymethylene, hydroxyl, lower alkoxy, phenyl-lower alkoxy, phenoxy, $S(O)_m$-R, m being 0, 1 or 2 and R being lower alkyl, lower alkanoyl, sulfamoyl in which the amino group is unsubstituted, monosubstituted or independently of one another disubstituted by lower alkyl or phenyl-lower alkyl, or is PO_nH_2, n being 2 or 3; X_3 is methylene; R_3 is carboxyl, 5-tetrazolyl, SO_3H, PO_2H_2, PO_3H_2 or halo-lower alkylsulfamoyl; and (hetero)aromatic radicals including the rings A and B are in each case additionally unsubstituted or substituted by one or more substituents selected from halogen, hydroxyl, lower alkoxy, or lower alkyl or lower alkoxy-lower alkyl, each of which is unsubstituted or substituted by halogen or hydroxyl, in free form or in salt form.

8. A compound according to claim 1 of the formula I, in which X_2 is C_1-C_{10}alkylene or C_1-C_7alkylidene, each of which is unsubstituted or substituted by hydroxyl, a 3- to 7-membered cycloalkyl, 3- to 7-membered cycloalkenyl, phenyl, pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, furyl, thienyl or pyridyl radical which for its part can additionally be substituted by carboxyl, lower alkoxycarbonyl, phenyl-lower alkoxycarbonyl, carbamoyl in which the amino group is unsubstituted, monosubstituted or independently of one another disubstituted by lower alkyl or phenyl-lower alkyl, formyl, di-lower alkoxymethyl or by oxy-lower alkylenoxymethylene, it being possible for a C atom of C_1-C_{10}alkylene or C_1-C_7alkylidene to be bridged by C_2-C_6alkylene, or X_2 is C_3-C_7cycloalkylene; X_3 is lower alkylene or lower alkylidene; the variables X_1, R_1, R_2 and R_3 are as defined in claim 7; and the (hetero)aromatic rings including the rings A and B can be substituted as indicated in claim 7, in free form or in salt form.

9. A compound according to claim 1 of the formula I, in which the variables R_1, X_1 and R_3 are as detined in each case in any one of claims 1-7; X_2 is lower alkylene or lower alkylidene, each of which is unsubstituted or substituted by hydroxyl, 3- to 7-membered cycloalkyl, phenyl or imidazolyl and R_2 is carboxyl, lower alkoxy-, phenyl-lower alkoxy- or lower alkoxy-lower alkoxy-carbonyl, carbamoyl which is unsubstituted, monosubstituted or independently of one another disubstituted by lower alkyl or phenyl-lower alkyl, amino, lower alkanoyl-, phenyl-lower alkanoyl- or lower alkanesulfonylamino, hydroxyl, lower alkoxy, phenyl-lower alkoxy or phenoxy; X_3 is -CH_2-; (hetero)aromatic radicals including the rings A and B each being unsubstituted or substituted by one or more substituents selected from halogen, trifluoromethyl, hydroxyl, lower alkoxy, lower alkyl, hydroxy-lower alkyl or lower alkoxy-lower alkyl, in free form or in salt form.

10. A compound according to claim 1 of the formula I, in which X_2 is lower alkylene or lower alkylidene which is unsubstituted or substituted by hydroxyl, 3- to 7-membered cycloalkyl, 7-membered cycloalkenyl, phenyl or imidazolyl, where a C atom of lower alkylene or lower alkylidene can be bridged by C_2-C_6alkylene, or X_2 is C_3-C_7cycloalkylene; the variables X_1, X_3, R_1, R_2 and R_3 are as defined in claims 7 to 9; and the rings A and B can be substituted as indicated in claim 9, in free form or in salt form.

11. A compound according to claim 1 of the formula

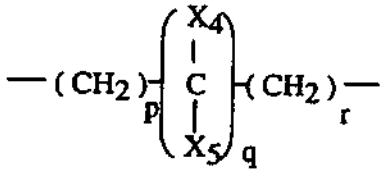


(Ia),

in which the variables R_1, X_1, X_2, R_2 and R_3 are as defined in each case in any one of claims 1-10 and the rings A and B can be substituted as indicated in claim 10, in free form or in salt form.

12. A compound according to claim 1 of the formula Ia, in which X_2 is lower alkylene or lower alkylidene, which is unsubstituted or substituted by hydroxyl or 3- to 7-membered cycloalkyl, it being possible for a C atom of lower alkylene or lower alkylidene to be bridged by C_2-C_6alkylene, or in which X_2 is C_3-C_7cycloalkylene; the variables R_1,X_1, R_2 and R_3 are as defined in each case in any one of claims 1-10; and the rings A and B can be substituted as indicated in claim 10, in free form or in salt form.

13. A compound according to claim 1 of the formula Ia, in which X_2 is the group of the formula



(Ib)

in which p is 0 or 1, q is 1 and r is 0 or 1 or in which p is 1 to 8 and q and r are in each case 0; X_4 is lower alkyl or phenyl which is unsubstituted or substituted by hydroxyl, 3- to 7-membered cycloalkyl, phenyl or imidazolyl; and X_5 is hydrogen or lower alkyl; R_2 is carboxyl, lower alkoxycarbonyl, phenyl-lower alkoxycarbonyl, lower alkoxy-lower alkoxycarbonyl, hydroxyl, lower alkoxy, phenyl-lower alkoxy, phenoxy, amino, lower alkanoylamino, phenyl-lower alkanoylamino or lower alkanesulfonylamino; and the variables R_1, X_1 and R_3 are as defined in each case in any one of claims 1-7; (hetero)aromatic radicals including the rings A and B each being unsubstituted or substituted by halogen, trifluoromethyl, hydroxyl, lower alkoxy, lower alkyl or hydroxy-lower alkyl, in free form or in salt form.

14. A compound according to claim 1 of the formula Ia, in which X_2 is the group of the formula Ib in which p is 0 or 1, q is 1 and r is 0 or 1 or in which p is 1 to 8 and q and r are each 0; X_4 is lower alkyl or phenyl, which is unsubstituted or substituted by hydroxyl, 3- to 7-membered cycloalkyl, phenyl or imidazolyl; and X_5 is hydrogen or lower alkyl; or X_4 and X_5 together are C_2-C_6alkylene, such as C_4-C_5alkylene; or X_2 is C_3-C_7cycloalkylene, such as C_5-C_6cycloalkylene; R_2 is carboxyl, lower alkoxycarbonyl, phenyl-lower alkoxycarbonyl, lower alkoxy-lower alkoxycarbonyl, hydroxyl, lower alkoxy, phenyl-lower alkoxy, phenoxy, amino, lower alkanoylamino, phenyl-lower alkanoylamino or lower alkanesulfonylamino; and the variables R_1, X_1 and R_3 are as defined in each case in any one of claims 1-7; (hetero)aromatic radicals including the rings A and B each being unsubstituted or substituted by halogen, trifluoromethyl, hydroxyl, lower alkoxy, lower alkyl or hydroxy-lower alkyl, in free form or in salt form.

15. A compound according to claim 1 of the formula Ia, in which R_1 is lower alkyl, such as C_3-C_5alkyl, or lower alkenyl, such as C_3-C_5alkenyl; X_1 is CO or else SO_2; X_2 is the group of the formula Ib in which p and r are 0 or 1 and q is 1; X_4 is lower alkyl, such as C_1-C_4alkyl, or phenyl, which is unsubstituted or substituted by hydroxyl, 3- to 7-membered cycloalkyl, such as cyclohexyl, or by phenyl or imidazolyl which is unsubstituted or substituted by halogen or hydroxyl, such as 4-imidazolyl; and X_5 is hydrogen or lower alkyl, such as C_1-C_4alkyl; or X_4 and X_5 together are C_2-C_6alkylene, such as C_4-C_5alkylene; or X_2 is C_3-C_7cycloalkylene, such as C_5-C_6cycloalkylene; R_2 is carboxyl, lower alkoxycarbonyl, such as C_2-C_5alkoxycarbonyl, phenyl-lower alkoxycarbonyl such as phenyl-C_1-C_4alkoxycarbonyl, lower alkoxyl-lower alkoxycarbonyl, such as C_1-C_4alkoxy-C_2-C_5alkoxycarbonyl, hydroxyl or lower alkoxy, such as C_1-C_4alkoxy; and R_3 is carboxyl or 5-tetrazolyl; (hetero)aromatic radicals including the rings A and B each being unsubstituted or substituted by halogen, trifluoromethyl, hydroxyl, lower alkoxy, lower alkyl or hydroxy-lower alkyl, in free form or in salt form.

16. A compound according to claim 1 of the formula Ia, in which R_1 is lower alkyl, such as C_3-C_5alkyl, or lower alkenyl, such as C_3-C_5alkenyl; X_1 is CO or else SO_2; X_2 is the group of the formula Ib in which p and r are 0 or 1 and q is 1; X_4 is lower alkyl, such as C_1-C_4alkyl, or phenyl, which is unsubstituted or substituted by hydroxyl, 3- to 7-membered cycloalkyl, or by phenyl or imidazolyl which is unsubstituted or substituted by halogen or hydroxyl, such as 4-imidazolyl; and X_5 is hydrogen or lower alkyl, such as C_1-C_4alkyl; R_2 is carboxyl, lower alkoxycarbonyl, such as C_2-C_5alkoxycarbonyl, phenyl-lower alkoxycarbonyl, such as phenyl-C_1-C_4alkoxycarbonyl, lower alkoxy-lower alkoxycarbonyl, such as C_1-C_4alkoxy-C_2-C_5alkoxycarbonyl, hydroxyl or lower alkoxy, such as C_1-C_4alkoxy; and R_3 is carboxyl or 5-tetrazolyl; (hetero)aromatic radicals including the rings A and B each being unsubstituted or substituted by halogen, trifluoromethyl, hydroxyl, lower alkoxy, lower alkyl or hydroxy-lower alkyl, in free form or in salt form.

17. A compound according to claim 1 of the formula Ia, in which R_1 is lower alkyl, such as C_3-C_5alkyl, or else lower alkenyl, such as C_3-C_5alkenyl; X_1 is CO or else SO_2; X_2 is the group of the formula Ib in which p is an integer from

1 to 8 and q and r are 0; R_2 is hydroxyl, lower alkoxy, such as C_1-C_4alkoxy, phenyl-lower alkoxy, such as phenyl-C_1-C_4alkoxy, phenoxy, lower alkanoylamino, such as C_1-C_4alkanoylamino, phenyl-lower alkanoylamino, such as phenyl-C_1-C_4alkanoylamino, or lower alkanesulfonylamino, such as C_1-C_4alkanesulfonylamino; and R_3 is carboxyl or primarily 5-terrazolyl; (hetero)aromatic radicals including the rings A and B each being unsubstituted or substituted by halogen, trifluoromethyl, hydroxyl, lower alkoxy, lower alkyl or hydroxy-lower alkyl, in free form or in salt form.

18. A compound according to claim 1 of the formula Ia, in which R_1 is C_3-C_5alkyl or secondarily C_3-C_5alkenyl; X_1 is CO or else SO_2; X_2 is the group of the formula Ib in which p and r independently of one another are 0 or 1 and q is 1; X_4 is C_1-C_4alkyl, hydroxy-C_1-C_4alkyl, C_3-C_7cycloalkyl-C_1-C_4alkyl, phenyl-C_1-C_4alkyl or imidazolyl-C_1-C_4alkyl; and X_5 is hydrogen or C_1-C_4alkyl; or X_4 and X_5 together are tetramethylene or else pentamethylene; R_2 is carboxyl or C_2-C_5alkoxycarbonyl or else phenyl-C_1-C_4alkoxycarbonyl; and R_3 is carboxyl or 5-tetrazolyl, in free form or in salt form.

19. A compound according to claim 1 of the formula Ia, in which R_1 is C_3-C_5alkyl or secondarily C_3-C_5alkenyl; X_1 is CO or else SO_2; X_2 is the group of the formula Ib in which p and r are each 0 or 1 and q is 1; X_4 is C_1-C_4alkyl, hydroxy-C_1-C_4alkyl, C_3-C_7cycloalkyl-C_1-C_4alkyl, phenyl-C_1-C_4alkyl or imidazolyl-C_1-C_4alkyl; and X_5 is hydrogen; R_2 is carboxyl or C_2-C_5alkoxcarbonyl or else phenyl-C_1-C_4alkoxycarbonyl; and R_3 is carboxyl or 5-tetrazolyl, in free form or in salt form.

20. A compound according to claim 1 of the formula Ia, in which R_1 is C_3-C_5alkyl; X_1 is CO; X_2 is the group of the formula Ib in which q and r are 0 and p is 1 to 3 or in which p and q are 1 and r is 0; X_4 is C_1-C_4alkyl; X_5 is hydrogen or C_1-C_4alkyl; R_2 is carboxyl or C_2-C_5alkoxycarbonyl; and R_3 is carboxyl or 5-tetrazolyl, in free form or in salt form.

21. A compound according to any any one of claims 1-20, in which R_3 is 5-tetrazolyl, in free form or in salt form.

22. A compound according to claim 1 of the formula Ia, in which R_1 is C_3-C_5alkyl; X_1 is CO; X_2 is the group of the formula Ib in which p is 0 or 1, r is 0 and q is 1; X_4 is C_1-C_4alkyl; and X_5 is hydrogen or C_1-C_4alkyl; or X_4 and X_5 together are tetramethylene or pentamethylene; R_2 is carboxyl or C_2-C_5alkoxycarbonyl; and R_3 is 5-tetrazolyl, in free form or in salt form.

23. A compound according to claim 1 of the formula Ia, in which R_1 is C_3-C_5alkyl; X_1 is CO; X_2 is the group of the formula Ib in which p is 0 or 1, r is 0 and q is 1; X_4 and X_5 together are tetramethylene or else pentamethylene; R_2 is carboxyl or C_2-C_5alkoxycarbonyl; and R_3 is 5-tetrazolyl, in free form or in salt form.

24. A compound according to claim 1 of the formula Ia, in which R_1 is C_3-C_5alkyl; X_1 is CO; X_2 is the group of the formula Ib in which p and r are 0 or 1 and q is 1; X_4 is C_1-C_4alkyl; and X_5 is hydrogen; R_2 is carboxyl or C_2-C_5alkoxycarbonyl; and R_3 is 5-tetrazolyl, in free form or in salt form.

25. A compound of the formula Ia according to any one of claims 13-24, in which X_2 is the group of the formula Ib, q is 1 and X_4 and X_5 are defined differently, in free form or in salt form, in which the asymmetric C atom in question containing the variables X_4 and X_5 has the S configuration.

26. (S)-N-(1-Carboxy-2-methylprop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]amine, in free form or in salt form according to claim 1.

27. N-(2-Carboxy-2,2-tetramethyleneethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine, in free form or in salt form according to claim 1.

28. N-(2-Carboxy-2-ethylbut-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine, in free form or in salt form according to claim 1.

29. (S)-N-(1-Carboxy-2-methylprop-1-yl)-N-ethoxycarbonyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine, in free form or in salt form according to claim 1.

30. N-(1-Carboxycyclohexyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amine, in free form or in salt form according to claim 1.

31. A compound according to claim 1 selected from the group consisting of:
(S)-N-(1-carboxyethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,

N-(2-hydroxyethyl)-N-pentanoyl-N-(2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N-(2-ethoxycarbonyl-2,2-tetramethyleneethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N-(2-ethoxycarbonyl-2-ethylbut-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N(2-ethoxycarbonyl)-2-methylprop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]amine,
(S)-N-(1-hydroxymethyl-2-methylprop-1-yl)-N-pentanoyl-N-[2'-1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N-(2-ethoxycarbonyl-2,2-pentamethyleneethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
(S)-N-(1-carboxy-2-methylprop-1-yl)-N-propyloxycarbonyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N-(2-carboxy-2-methylpropyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N-(2-carboxy-2,2-pentamethyleneethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
(S)-N-(1-aminocarbonyl-2-methylprop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine and
(S)-N-(1-carboxy-2-methylprop-1-yl)-N-(5-oxopent-1-en-5-yl)-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine, in each case in free form or in salt form.

32. A compound according to claim 1 selected from the group consisting of:
N-carboxymethyl-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
(S)-N-(1-methoxycarbonylethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N-[1-carboxy-2-(4-fluorophenyl)ethyl]-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N-[2-(4-fluorophenyl)-1-methoxycarbonylethyl]-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N-[2-(4-fluorophenyl)-1-hydroxymethylethyl]-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N-(2'-carboxybiphenyl-4-ylmethyl)-N-[1-carboxy-2-(4-fluorophenyl)ethyl]-N-pentanoyl-amine,
N-(2'-carboxybiphenyl-4-ylmethyl)-N-[2-(4-fluorophenyl)-1-methoxycarbonylethyl]-N-pentanoylamine,
(S)-N-(2'-carboxybiphenyl-4-ylmethyl)-N-(1-hydroxymethyl-2-phenylethyl)-N-pentanoylamine,
(S)-N-(2'-carboxybiphenyl-4-ylmethyl)-N-(1-hydroxymethyl-2-imidazol-4-ylethyl)-N-pentanoylamine,
(R)-N-(1-carboxyethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
(1S),(2S)-N-(1-carboxy-2-methylbut-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
(1S),(2S)-N-(1-methoxycarbonyl-2-methylbut-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
(S)-N-(1-carboxybut-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amine,
(S)-N-(1-methoxycarbonylbut-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
(S)-N-(1-carboxyethyl)-N-hexanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
(S)-N-butanoyl-N-(1-carboxyethyl)-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
(S)-N-(1-carboxyprop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amine,
(S)-N-(1-carboxy-2-cyclohexylethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
(S)-N-(2-cyclohexyl-1-methoxycarbonylethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
(R)-N-(1-carboxy-2-methylprop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N-(2-methoxyethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N-(2-benzyloxyethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N-(3-methoxyprop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amine,
N-(3-benzyloxyprop-1-yl)-N-pentanoyl-N-[2'-1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amine,
N-(3-hydroxyprop-1-yl)-N-penanol-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amine,
N-(1-methoxycarbonyl-1-methylethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N-(2-carboxyethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine.
N-(2-carboxyprop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amine,
N-(1-carboxy-1-methylethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N-(5-hydroxypent-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N-(1-carboxyprop-2-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N-(2-ethoxycarbonyl-3-methylbut-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N-(2-carboxy-3-methylbut-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N[(3-phenoxyprop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N-[2-(4-hydroxyphenyl)ethyl]-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N-[3-(4-hydroxyphenyl)prop-1-yl]-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N-(8-hydroxyoct-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N-(2-methanesulfonylaminoethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N-(3-acetylaminoprop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amine,
N-(2-methoxy-2-oxo-1-phenylethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N-(4-hydroxybut-2-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N-(2-hydroxy-1-phenylethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N-[3-(4-hydroxybenzylcarbonylamino)prop-1-yl]-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N-(3-ethoxycarbonylcyclohexyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N-(3-carboxycyclohexyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amine,

cis-N-(4-carboxycyclohexyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
cis-N-(2-ethoxycarbonylcyclohexyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
cis-N-(2-carboxycyclohexyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine.
N-[2-[2-(4-hydroxyphenyl)ethylaminocarbonyl]-2,2-tetramethyleneethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
(S)-N-[1-[2-(4-hydroxyphenyl)ethylaminocarbonyl]-2-methylprop-1-yl]-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
(S)-N-(1-carboxy-2,2-dimethylprop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
(S)-N-(1-methoxycarbonyl-2-methylprop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N-(4-phenoxybut-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N-(2-hydroxy-1-phenyl-2-oxoethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
(S)-N-(1-benzyloxycarbonyl-2-methylprop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N-butanoyl-N-(1-carboxy-1-methylethyl)-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amine,
N-(4-hydroxybut-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
(S)-N-(1-benzyloxycarbonyl-2-methylprop-1-yl)-N-[3-bromo-2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-N-pentanoylamine,
(S)-N-[3-bromo-2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-N-(1-carboxy-2-methyl-prop-1-yl)-N-pentanoylamine,
N-(2-acetylaminoethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N-[2-(n-butoxycarbonyl)-2,2-tetramethyleneethyl]-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N-(2-benzylaminocarbonyl-2,2-tetramethyleneethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
(S)-N-butyloxycarbonyl-N-(1-carboxy-2-methylprop-1-yl)-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
(S)-N-(1-carboxy-2-methylprop-1-yl)-N-methoxycarbonyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N-(2-diethylaminocarbonyl-2,2-tetramethyleneethyl)-N-pentanoyl-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N-(2-methyl-2-morpholin-4-ylcarbonylpropyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N-(1-carboxycyclopentyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amine,
N-(1-carboxy-1-ethylprop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
(S)-N-(5-amino-1-carboxypent-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N-butanesulfonyl-N-(2-ethoxycarbonyl-2,2-pentamethyleneethyl)-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N-butanesulfonyl-N-(2-carboxy-2,2-pentamethyleneethyl)-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N-butanesulfonyl-N-(2-ethoxycarbonyl-2-methylprop-1-yl)-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N-butanesulfonyl-N-(2-carboxy-2-methylprop-1-yl)-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
(S)-N-butanesulfonyl-N-(1-tert-butoxycarbonylethyl)-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
(S)-N-butanesulfonyl-N-(1-carboxyethyl)-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amine,
(S)-N-butanesulfonyl-N-(1-carboxy-2-methylprop-1-yl)-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
(2)-N-(2-methyl-1-methylaminocarbonylprop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
(S)-N-(1-dimethylaminocarbonyl-2-methylprop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
(S)-N-(2-methyl-1-morpholin-4-ylcarbonylprop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
(S)-N-(2'-carboxybiphenyl-4-ylmethyl)-N-(1-carboxy-2-methylprop-1-yl)-N-pentanoyl-amine,
(S)-N-(1,2-dicarboxyethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amine,
(S)-N-(1-carboxy-3-phenylprop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
(S)-N-(2-cyclohexyl-1-hydroxymethylethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
(R)-N-(1-methoxycarbonyl-2-methylprop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine.
(S)-N-(2-hydroxy-1-methoxycarbonylethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N-pentanoyl-N-(1H-tetrazol-5-ylmethyl)-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amine,
N-pentanoyl-N-pyrid-3-ylmethyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
(S)-N-(1-carboxy-4-guanidinobut-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N-(2-hydroxy-1-methoxycarbonylprop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N-(1-benzyloxycarbonyl-1-methylethyl)-N-butanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
(S)-N-(1-carboxy-3-methylbut-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N-(1-carboxy-2-hydroxyethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-yl methyl]amine,
(S)-N-(1-carboxy-2-hydroxyethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
(S)-N-(2-methyl-1-(2-phenylethylaminocarbonyl)prop-1-yl]-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
(S)-N-(2-benzyloxy-1-hydroxymethylethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
(S)-N-(1-carboxy-2-methylprop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-3-ylmethyl]amine,

(S)-N-(1-carboxy-2-methylprop-1-yl)-N-pentanoyl-N-[3'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
(S)-N-[2-methyl-1-(1,2,3,4-tetrahydroquinol-1-ylcarbonyl)prop-1-yl]-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
(S)-N-(2-methyl-1-piperidin-1-ylcarbonylprop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
(S)-N-[2-methyl-1-(1,2,3,4-tetrahydroisoquinol-2-ylcarbonyl)prop-1-yl]-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N-(2-hydroxymethyl-2-methylprop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N-ethoxycarbonyl-N-(2-ethoxycarbonyl-2-methylprop-1-yl)-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine and
N-(2-carboxy-2-methylprop-1-yl)-N-ethoxycarbonyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine, in each case in free form or in salt form.

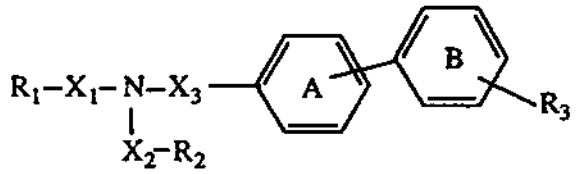
33. A compound according to any one of claims 1 to 32, in free form or in the form of a pharmaceutically utilizable salt, for use in a method for the therapeutic treatment of the human or animal body.

34. A compound according to any one of claims 1 to 33, in free form or in the form of a pharmaceutically, utilizable salt, for use as an antihypertensive.

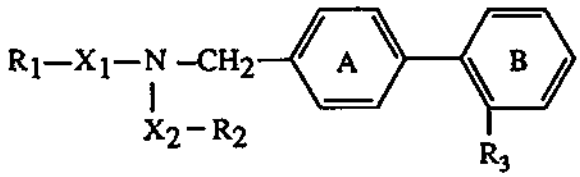
35. A pharmaceutical preparation comprising as active compound a compound according to any one of claims 1 to 34, in free form or in the form of a pharmaceutically utilizable salt, if appropriate in addition to customary pharmaceutical excipients.

36. An antihypertensive pharmaceutical preparation according to claim 35, wherein an antihypertensive active ingredient is selected.

37. A process for the preparation of a compound of the formula



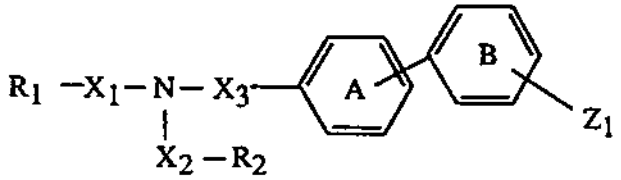
(I) or



(Ia),

in which R_1, R_2, R_3, X_1, X_2 and X_3 and the substituents of the rings A and B are as defined in each case in any one of claims 1-25; in free form or in salt form, wherein

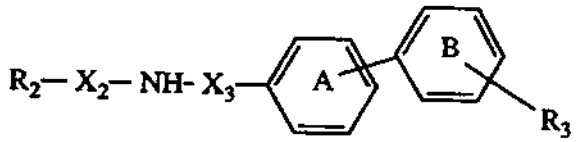
a) in a compound of the formula



(II)

or a salt thereof in which Z_1 is a radical which can be converted into R_3, Z_1 is converted to R_3 or

b) a compound of the formula R_1-X_1OH (IIIa), a reactive derivative thereof or a salt thereof is reacted with a compound of the formula



(IIIb)

or a salt thereof and in each case, if desired, a compound I in free form or in salt form obtainable according to the process or in another way is converted into another compound I, a mixture of isomers obtainable according to the process is separated and the desired isomer is isolated and/or a free compound I obtainable according to the process is converted into a salt or a salt of a compound I obtainable according to the process is converted into the free compound I or into another salt.

38. A process for the production of a pharmaceutical preparation according to claim 35 or 36, wherein the active ingredient, if appropriate with admixture of customary pharmaceutical excipients, is processed to give a pharmaceutical preparation.

39. A process according to claim 38 for the production of an antihypertensive pharmaceutical preparation according to claim 34, wherein an antihypertensive active ingredient is selected.

40. The use of a compound according to any one of claims 1 to 34, in free form or in the form of a pharmaceutically utilizable salt, for the production of a pharmaceutical preparation.

41. The use of a compound according to any one of claims 1 to 34, in free form or in the form of a pharmaceutically utilizable salt, for the production of a pharmaceutical preparation by a non-chemical route.

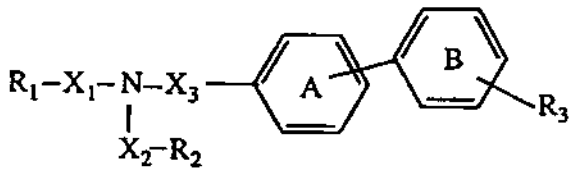
42. The use of a compound according to any one of claims 1 to 34, in free form or in the form of a pharmaceutically utilizable salt, for the production of an antihypertensive.

43. The use of a compound according to any one of claims 1 to 34, in free form or in the form of a pharmaceutically utilizable salt, for the production of a pharmaceutical preparation for the therapeutic or prophylactic treatment of cardiac insufficiency.

44. The use of a compound according to any one of claims 1 to 34, in free form or in the form of a pharmaceutically utilizable salt, for the production of a pharmaceutical preparation for the therapeutic or prophylactic treatment of disorders which are caused by angiotensin II activity.

Claims for the following Contracting States : ES, GR

1. A process for the preparation of a compound of the formula

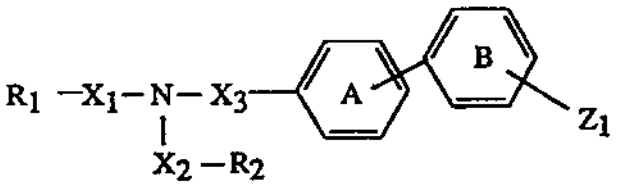


(I),

in which R_1 is lower alkyl, lower alkenyl or lower alkynyl or C_3-C_7cycloalkyl or C_3-C_7cycloalkenyl or phenyl-lower alkyl, phenyl-lower alkenyl or phenyl-lower alkynyl, each of which is unsubstituted or substituted by halogen or hydroxyl; X_1 is CO, SO_2 or -O-C(=O)-, the carbon atom of the carbonyl group being bonded to the nitrogen atom drawn in in the formula I; X_2 is C_1-C_{10}alkylene, C_2-C_{10}alkylidene or C_3-C_7cycloalkylene which is unsubstituted or substituted by hydroxyl, carboxyl, amino, guanidino, C_3-C_7cycloalkyl, C_3-C_7cycloalkenyl, phenyl or a corresponding 5- or 6-membered and monocyclic aromatic radical which has up to four identical or different heteroatoms, it being

possible for a carbon atom of C_1-C_{10}alkylene or C_2-C_{10}alkylidene additionally to be bridged by C_2-C_6alkylene, and C_3-C_7cycloalkyl or C_3-C_7cycloalkenyl being unsubstituted, monosubstituted or polysubstituted by carboxyl, carboxyl which is esterified by an alcohol which is derived from lower alkyl, phenyl-lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy-lower alkyl, lower alkoxy-lower alkenyl or lower alkoxy-lower alkynyl, carbamoyl, carbamoyl in which the amino group is monosubstituted or independently of one another disubstituted by lower alkyl, lower alkenyl, lower alkynyl, phenyl-lower alkyl, phenyl-lower alkenyl or phenyl-lower alkynyl or is disubstituted by C_1-C_{10}alkylene or C_2-C_{10}alkylidene, C_1-C_{10}alkylene or C_2-C_{10}alkylidene being uninterrupted or interrupted by -O- or being fused at two adjacent C atoms to a benzene ring, formyl, di-lower alkoxymethyl or oxy-lower alkylenoxymethylene; R_2 is carboxyl, carboxyl which is esterified by an alcohol which is derived from lower alkyl, phenyl-lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy-lower alkyl, lower alkoxy-lower alkenyl or lower alkoxy-lower alkynyl, carbamoyl, carbamoyl in which the amino group is monosubstituted or independently of one another disubstituted by lower alkyl, lower alkenyl, lower alkynyl, phenyl-lower alkyl, phenyl-lower alkenyl or phenyl-lower alkynyl or is disubstituted by C_1-C_{10}alkylene or C_2-C_{10}alkylidene, C_1-C_{10}alkylene or C_2-C_{10}alkylidene being uninterrupted or interrupted by -O- or being fused at two adjacent C atoms to a benzene ring, amino, amino which is monosubstituted or independently of one another disubstituted by lower alkyl, lower alkenyl, lower alkynyl, phenyl-lower alkyl, phenyl-lower alkenyl or phenyl-lower alkynyl or is disubstituted by C_1-C_{10}alkylene or C_2-C_{10}alkylidene, C_1-C_{10}alkylene or C_2-C_{10}alkylidene being uninterrupted or interrupted by -O- or fused at two adjacent C atoms to a benzene ring, lower alkanoyl-, phenyl-lower alkanoyl-, benzoyl-, lower alkanesulfonyl- or benzenesulfonyl-amino, formyl, di-lower alkoxymethyl, oxy-lower alkylenoxymethylene, 1H-tetrazol-5-yl, pyridyl, hydroxyl, lower alkoxy, lower alkenyloxy, phenyl-lower alkoxy, phenoxy, $S(O)_m$-R, m being 0, 1 or 2 and R being hydrogen, lower alkyl, lower alkenyl or lower alkynyl, lower alkanoyl, sulfamoyl, sulfamoyl in which the amino group is monosubstituted or independently of one another disubstituted by lower alkyl, lower alkenyl, lower alkynyl, phenyl-lower alkyl, phenyl-lower alkenyl or phenyl-lower alkynyl or is disubstituted by C_1-C_{10}alkylene or C_2-C_{10}alkylidene, C_1-C_{10}alkylene or C_2-C_{10}alkylidene being uninterrupted or interrupted by -O- or being fused at two adjacent C atoms to a benzene ring, or is PO_nH_2, n being 2 or 3; X_3 is C_1-C_{10}alkylene or C_2-C_{10}alkylidene; R_3 is carboxyl, 5-tetrazolyl, SO_3H, PO_2H_2, PO_3H_2 or halo-lower alkylsulfamoyl; and (hetero)aromatic radicals including the rings A and B independently of one another being unsubstituted or substituted by substituents selected from the group consisting of: halogen, hydroxyl, lower alkoxy, lower alkenyloxy, phenyl-lower alkoxy, phenoxy, $S(O)_m$-R and lower alkyl, lower alkenyl or lower alkynyl, each of which is unsubstituted or substituted by halogen or hydroxyl, lower alkyl, lower alkenyl or lower alkynyl being uninterrupted or interrupted by -O-, and, in the case of (hetero)aromatic radicals, additionally being unsubstituted or substituted by carboxyl, carboxyl which is esterified by an alcohol which is derived from lower alkyl, phenyl-lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy-lower alkyl, lower alkoxy-lower alkenyl or lower alkoxy-lower alkynyl, by carbamoyl, carbamoyl in which the amino group is monosubstituted or independently of one another disubstituted by lower alkyl, lower alkenyl, lower alkynyl, phenyl-lower alkyl, phenyl-lower alkenyl or phenyl-lower alkynyl or is disubstituted by C_1-C_{10}alkylene or C_2-C_{10}alkylidene, C_1-C_{10}alkylene or C_2-C_{10}alkylidene being uninterrupted or interrupted by -O- or being fused at two adjacent C atoms to a benzene ring, by formyl, di-lower alkoxymethyl or oxy-lower alkylenoxymethylene; radicals and groups designated by "lower" containing up to and including 7 carbon atoms; in free form or in salt form; wherein

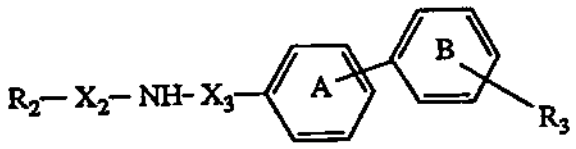
a) in a compound of the formula



(II)

or a salt thereof in which Z_1 is a radical which can be converted into R_3, Z_1 is converted to R_3 or

b) a compound of the formula R_1-X_1OH (IIIa), a reactive derivative thereof or a salt thereof is reacted with a compound of the formula



(IIIb)

or a salt thereof and in each case, if desired, a compound I in free form or in salt form obtainable according to the process or in another way is converted into another compound I, a mixture of isomers obtainable according to the process is separated and the desired isomer is isolated and/or a free compound I obtainable according to the process is converted into a salt or a salt of a compound I obtainable according to the process is converted into the free compound I or into another salt.

2. A process according to claim 1 for the preparation of a compound of the formula I, in which R_2 is other than carboxyl and R_3 is 5-tetrazolyl, wherein

(i) the starting compound used is a compound of the formula (II) in which Z_1 is cyano, and this is reacted with HN_3 or an alkali metal salt thereof, with a tri-lower alkyltin azide or triphenyltin azide; or
(ii) the starting compound used is a compound of the formula (II) in which Z_1 is 5-tetrazolyl protected by triphenylmethyl, benzyl which is unsubstituted or substituted by nitro, lower alkoxymethyl, lower alkylthiomethyl, tri-lower alkylsilyl, 2-cyanoethyl, lower alkoxy-lower alkoxymethyl, benzyloxymethyl or phenacyl, and the protective group is removed and,

if desired, a compound of the formula I in which R_2 is other than carboxyl and R_3 is 5-tetrazolyl obtainable according to the process is converted into a compound of the formula I in which R_2 is carboxyl.

3. A process according to claim 1 or 2 for the preparation of a compound of the formula I, in which R_1 is lower alkyl, lower alkenyl or lower alkynyl or C_3-C_7cycloalkyl or C_3-C_7cycloalkenyl or phenyl-lower alkyl, phenyl-lower alkenyl or phenyl-lower alkynyl, each of which is unsubstituted or substituted by halogen or hydroxyl; X_1 is CO or SO_2; X_2 is C_1-C_{10}alkylene or C_2-C_{10}alkylidene or C_3-C_7cycloalkylene which is unsubstituted or substituted by hydroxyl, C_3-C_7cycloalkyl or C_3-C_7cycloalkenyl or phenyl or a corresponding 5- or 6-membered and monocyclic aromatic radical which has up to 4 identical or different heteroatoms, it being possible for a carbon atom of C_1-C_{10}alkylene or C_2-C_{10}alkylidene additionally to be bridged by C_2-C_6alkylene, and C_3-C_7cycloalkylene being unsubstituted, monosubstituted or polysubstituted by carboxyl, carboxyl which is esterified by an alcohol which is derived from lower alkyl, phenyl-lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy-lower alkyl, lower alkoxy-lower alkenyl or lower alkoxy-lower alkynyl, carbamoyl, carbamoyl in which the amino group is monosubstituted or independently of one another disubstituted by lower alkyl, lower alkenyl, lower alkynyl, phenyl-lower alkyl, phenyl-lower alkenyl or phenyl-lower alkynyl or is disubstituted by C_1-C_{10}alkylene or C_2-C_{10}alkylidene, C_1-C_{10}alkylene or C_2-C_{10}alkylidene being uninterrupted or interrupted by -O-, formyl, di-lower alkoxymethyl or oxy-lower alkylenoxymethylene; R_2 is carboxyl, carboxyl which is esterified by an alcohol which is derived from lower alkyl, phenyl-lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy-lower alkyl, lower alkoxy-lower alkenyl or lower alkoxy-lower alkynyl, carbamoyl, carbamoyl in which the amino group is monosubstituted or independently of one another disubstituted by lower alkyl lower alkenyl lower alkynyl, phenyl-lower alkyl, phenyl-lower alkenyl or phenyl-lower alkynyl or is disubstituted by C_1-C_{10}alkylene or C_2-C_{10}alkylidene, C_1-C_{10}alkylene or C_2-C_{10}alkylidene being uninterrupted or interrupted by -O-, amino, amino which is monosubstituted or independently of one another disubstituted by lower alkyl, lower alkenyl, lower alkynyl, phenyl-lower alkyl, phenyl-lower alkenyl or phenyl-lower alkynyl or is disubstituted by C_1-C_{10}alkylene or C_2-C_{10}alkylidene, C_1-C_{10}alkylene or C_2-C_{10}alkylidene being uninterrupted or interrupted by -O-, lower alkanoyl-, phenyl-lower alkanoyl-, benzoyl-, lower alkanesulfonyl- or benzenesulfonyl-amino, formyl, di-lower alkoxymethyl, oxy-lower alkylenoxymethylene, hydroxyl, lower alkoxy, lower alkenyloxy, phenyl-lower alkoxy, phenoxy, $S(O)_m$-R, m being 0, 1 or 2 and R being hydrogen, lower alkyl, lower alkenyl or lower alkynyl, lower alkanoyl, sulfamoyl, sulfamoyl in which the amino group is monosubstituted or independently of one another disubstituted by lower alkyl, lower alkenyl, lower alkynyl, phenyl-lower alkyl, phenyl-lower alkenyl or phenyl-lower alkynyl or is disubstituted by C_1-C_{10}alkylene or C_2-C_{10}alkylidene, C_1-C_{10}alkylene or C_2-C_{10}alkylidene being uninterrupted or interrupted by -O-, or is PO_nH_2, n being 2 or 3; X_3 is C_1-C_{10}alkylene or C_2-C_{10}alkylidene; R_3 is carboxyl, 5-tetrazolyl, SO_3H, PO_2H_2, PO_3H_2 or halo-lower alkylsulfamoyl; (hetero)aromatic radicals including the rings A and B independently of one another being

unsubstituted or substituted by substituents selected from the group consisting of: halogen, hydroxyl, lower alkoxy, lower alkenyloxy, phenyl-lower alkoxy, phenoxy, $S(O)_m$-R and lower alkyl, lower alkenyl or lower alkynyl, each of which is unsubstituted or substituted by halogen or hydroxyl, lower alkyl, lower alkenyl or lower alkynyl being uninterrupted or interrupted by -O-, and, in the case of (hetero)aromatic radicals, additionally unsubstituted or substituted by carboxyl, carboxyl which is esterified by an alcohol which is derived from lower alkyl, phenyl-lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy-lower alkyl, lower alkoxy-lower alkenyl or lower alkoxy-lower alkynyl, by carbamoyl, carbamoyl in which the amino group is monosubstituted or independently of one another disubstituted by lower alkyl, lower alkenyl, lower alkynyl, phenyl-lower alkyl, phenyl-lower alkenyl or phenyl-lower alkynyl or is disubstituted by C_1-C_{10}alkylene or C_2-C_{10}alkylidene, C_1-C_{10}alkylene or C_2-C_{10}alkylidene being uninterrupted or interrupted by -O-, by formyl, di-lower alkoxymethyl or oxy-lower alkylenoxymethylene; in free form or in salt form.

4. A process according to claim 1 or 2 for the preparation of a compound of the formula I, in which R_1 is lower alkyl, lower alkenyl or lower alkynyl or C_3-C_7cycloalkyl or C_3-C_7cycloalkenyl or phenyl-lower alkyl phenyl-lower alkenyl or phenyl-lower alkynyl, each of which is unsubstituted or substituted by halogen or hydroxyl; X_1 is CO or SO_2; X_2 is C_1-C_{10}alkylene or C_2-C_{10}alkylidene which is unsubstituted or substituted by hydroxyl, C_3-C_7cycloalkyl or C_3-C_7cycloalkenyl or phenyl or a corresponding 5- or 6-membered and monocyclic aromatic radical which has up to 4 identical or different heteroatoms; R_2 is carboxyl, carboxyl which is esterified by an alcohol which is derived from lower alkyl, phenyl-lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy-lower alkyl, lower alkoxy-lower alkenyl or lower alkoxy-lower alkynyl, carbamoyl, carbamoyl in which the amino group is monosubstituted or independently of one another disubstituted by lower alkyl, lower alkenyl, lower alkynyl, phenyl-lower alkyl, phenyl-lower alkenyl or phenyl-lower alkynyl or is disubstituted by C_1-C_{10}alkylene or C_2-C_{10}alkylidene, C_1-C_{10}alkylene or C_2-C_{10}alkylidene being uninterrupted or interrupted by -O-, amino, amino which is monosubstituted or independently of one another disubstituted by lower alkyl, lower alkenyl, lower alkynyl, phenyl-lower alkynyl, phenyl-lower alkenyl or phenyl-lower alkynyl or is disubstituted by C_1-C_{10}alkylene or C_2-C_{10}alkylidene, C_1-C_{10}alkylene or C_2-C_{10}alkylidene being uninterrupted or interrupted by -O-, lower alkanoyl-, phenyl-lower alkanoyl-, benzoyl-, lower alkanesulfonyl- or benzenesulfonyl-amino, formyl, di-lower alkoxymethyl, oxy-lower alkylenoxymethylene, hydroxyl, lower alkoxy, lower alkenyloxy, phenyl-lower alkoxy or phenoxy, $S(O)_m$-R, m being 0, 1 or 2 and R being hydrogen, lower alkyl, lower alkenyl or lower alkynyl, lower alkanoyl, sulfamoyl, sulfamoyl in which the amino group is monosubstituted or independently of one another disubstituted by lower alkyl, lower alkenyl, lower alkynyl, phenyl-lower alkyl, phenyl-lower alkenyl or phenyl-lower alkynyl or is disubstituted by C_1-C_{10}alkylene or C_2-C_{10}alkylidene, C_1-C_{10}alkylene or C_2-C_{10}alkylidene being uninterrupted or interrupted by -O-, or is PO_nH_2, n being 2 or 3; X_3 is $-CH_2-$; R_3 is carboxyl, 5-tetrazolyl, SO_3H, PO_2H_2, PO_3H_2 or halo-lower alkylsulfamoyl; and (hetero)aromatic radicals including the rings A and B independently of one another being unsubstituted or substituted by substituents selected from the group consisting of: halogen, hydroxyl, lower alkoxy, lower alkenyloxy, phenyl-lower alkoxy, phenoxy, $S(O)_m$-R and lower alkyl, lower alkenyl or lower alkynyl, each of which is unsubstituted or substituted by halogen or hydroxyl, lower alkyl, lower alkenyl or lower alkynyl being uninterrupted or interrupted by -O-, and, in the case of (hetero)aromatic radicals, additionally unsubstituted or substituted by carboxyl, carboxyl which is esterified by an alcohol which is derived from lower alkyl, phenyl-lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy-lower alkyl, lower alkoxy-lower alkenyl or lower alkoxy-lower alkynyl, by carbamoyl, carbamoyl in which the amino group is monosubstituted or independently of one another disubstituted by lower alkyl, lower alkenyl, lower alkynyl, phenyl-lower alkyl, phenyl-lower alkenyl or phenyl-lower alkynyl or is disubstituted by C_1-C_{10}alkylene or C_1-C_{10}alkylidene, C_1-C_{10}alkylene or C_2-C_{10}alkylidene being uninterrupted or interrupted by -O-, by formyl, di-lower alkoxymethyl or oxy-lower alkylenoxymethylene; in free form or in salt form.

5. A process according to claim 1 or 2 for the preparation of a compound of the formula I, in which R_1 is lower alkyl, lower alkenyl, lower alkynyl, halo-lower alkyl, -lower alkenyl or -lower alkynyl, hydroxy-lower alkyl, -lower alkenyl or -lower alkynyl, C_3-C_7cycloalkyl, C_3-C_7cycloalkenyl, phenyl-lower alkyl, phenyl-lower alkenyl or phenyl-lower alkynyl: X_1 is CO or SO_2; X_2 is C_1-C_{10}alkylene or C_2-C_{10}alkylidene, each of which is unsubstituted or substituted by hydroxyl a C_3-C_7cycloalkyl, C_3-C_7cycloalkenyl or a phenyl radical or a 5- or 6-membered, monocyclic heteroaromatic radical having up to four identical or different heteroatoms, the cyclic radicals for their part being unsubstituted or substituted by carboxyl which can be esterified with an alcohol which is derived from lower alkyl, phenyl-lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy-lower alkyl, -lower alkenyl or -lower alkynyl, carbamoyl in which the amino group is unsubstituted, monosubstituted or independently of one another disubstituted by lower alkyl, lower alkenyl, lower alkynyl, phenyl-lower alkyl, phenyl-lower alkenyl or phenyl-lower alkynyl or is disubstituted by lower alkylene or lower alkylenoxy-lower alkylene, formyl, di-lower alkoxymethyl or oxy-lower alkylenoxymethylene; R_2 is carboxyl which can be esterified with an alcohol which is derived from lower alkyl, phenyl-lower alkyl, lower alkenyl, lower alkynyl, or lower alkoxy-lower alkyl, -lower alkenyl or -lower alkynyl, carbamoyl in which the amino group is unsubstituted, monosubstituted or independently of one another disubstituted by lower alkyl, lower alkenyl, lower alkynyl, phenyl-lower alkyl, phenyl-lower alkenyl or phenyl-lower alkynyl or is disubstituted by lower alkylene- or lower alkylenoxy-

lower alkylene, amino in which the amino group is unsubstituted, monosubstituted or independently of one another disubstituted by lower alkyl, lower alkenyl, lower alkynyl, phenyl-lower alkyl, phenyl-lower alkenyl or phenyl-lower alkynyl or is disubstituted by lower alkylene- or lower-alkylenoxy-lower alkylene, lower alkanoyl-, phenyl-lower alkanoyl-, benzoyl-, lower alkanesulfonyl- or benzenesulfonyl-amino, formyl, di-lower alkoxymethyl, oxy-lower alkylenoxymethylene, hydroxyl lower alkoxy, lower alkenyloxy, phenyl-lower alkoxy, phenoxy, $S(O)_m$-R, m being 0, 1 or 2 and R being hydrogen, lower alkyl, lower alkenyl or lower alkynyl, lower alkanoyl, sulfamoyl in which the amino group is unsubstituted, monosubstituted or independentiy of one another disubstituted by lower alkyl, lower alkenyl, lower alkynyl, phenyl-lower alkyl, phenyl-lower alkenyl or phenyl-lower alkynyl or is disubstituted by lower alkylene- or lower alkylenoxy-lower alkylene, or is PO_nH_2, n being 2 or 3; X_3 is $-CH_2-$; and R_3 is carboxyl, 5-tetrazolyl, SO_3H, PO_2H_2, PO_3H_2 or halo-lower alkylsulfamoyl; (hetero)aromatic radicals including the rings A and B independently of one another each being unsubstituted or substituted by one or more substituents selected from halogen, hydroxyl lower alkoxy, lower alkenyloxy, or lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy-lower alkyl, -lower alkenyl or -lower alkynyl, lower alkenyloxy-lower alkyl, -lower alkenyl and -lower alkynyl, each of which is unsubstituted or substituted by halogen or hydroxyl, in free form or in salt form.

6. A process according to claim 1 or 2 for the preparation of a compound of the formula I, in which X_2 is C_1-C_{10}alkylene or C_2-C_{10}alkylidene, each of which is unsubstituted or substituted by hydroxyl, a C_3-C_7cycloalkyl, C_3-C_7cycloalkenyl or a phenyl radical or a 5-or 6-membered, monocyclic heteroaromatic radical having up to four identical or different heteroatoms, it being possible for a C atom of C_1-C_{10}alkylene or C_2-C_{10}alkylidene to be bridged by C_2-C_6alkylene and the cyclic radicals for their part being unsubstituted or substituted by carboxyl which can be esterified with an alcohol which is derived from lower alkyl, phenyl-lower alkyl, lower alkenyl, lower alkynyl, or lower alkoxy, -lower alkyl-lower alkenyl or -lower alkynyl, carbamoyl in which the amino group is unsubstituted, monosubstituted or independently of one another disubstituted by lower alkyl, lower alkenyl, lower alkynyl, phenyl-lower alkyl, phenyl-lower alkenyl or phenyl-lower alkynyl or is disubstituted by lower alkylene- or lower alkylenoxy-lower alkylene, formyl, di-lower alkoxymethyl or by oxy-lower alkylenoxymethylene, or X_2 is C_3-C_7cycloalkylene; X_3 is lower alkylene or lower alkylidene; the variables X_1, R_1, R_2 and R_3 are as defined in claim 5; and the (hetero)aromatic rings including the rings A and B can be substituted as indicated in claim 5, in free form or in salt form.

7. A process according to claim 1 or 2 for the preparation of a compound of the formula I, in which R_1 is lower alkyl, lower alkenyl, halo-lower alkyl or -lower alkenyl, hydroxy-lower alkyl, 3- to 7-membered cycloalkyl or phenyl-lower alkyl; X_1 is CO, SO_2 or
-O-C(=O)-, the carbon atom of the carbonyl group being bonded to the nitrogen atom drawn in in the formula I; X_2 is C_1-C_{10}alkylene or C_1-C_7alkylidene, each of which is unsubstituted or substituted by hydroxyl, carboxyl, amino, guanidino, a 3- to 7-membered cycloalkyl, 3- to 7-membered cycloalkenyl, phenyl, pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, furyl, thienyl or pyridyl radical which for its part can additionally be unsubstituted or substituted by carboxyl, lower alkoxycarbonyl, phenyl-lower alkoxycarbonyl, carbamoyl in which the amino group is unsubstituted, monosubstituted or independently of one another disubstituted by lower alkyl or phenyl-lower alkyl, formyl, di-lower alkoxymethyl or oxy-lower alkylenoxymethylene; R_2 is carboxyl, lower alkoxy-, phenyl-lower alkoxy-, lower alkenyloxy- or lower alkoxy-lower alkoxy-carbonyl, carbamoyl in which the amino group is unsubstituted, monosubstituted or independently of one another disubstituted by lower alkyl or phenyl-lower alkyl or is disubstituted by lower alkylene which can be fused at two adjacent carbon atoms to a benzene ring, or lower alkylenoxy-lower alkylene, amino in which the amino group is unsubstituted, monosubstituted or independently of one another disubstituted by lower alkyl or phenyl-lower alkyl or is disubstituted by lower alkylene- or lower alkylenoxy-lower alkylene, lower alkanoyl-, phenyl-lower alkanoyl-, benzoyl-, lower alkanesulfonyl- or benzenesulfonyl-amino, formyl, di-lower alkoxymethyl, oxy-lower alkylenoxymethylene, hydroxyl, lower alkoxy, phenyl-lower alkoxy, phenoxy, $S(O)_m$-R, m being 0, 1 or 2 and R being lower alkyl, lower alkanoyl, sulfamoyl in which the amino group is unsubstituted, monosubstituted or independently of one another disubstituted by lower alkyl or phenyl-lower alkyl, or is PO_nH_2, n being 2 or 3; X_3 is methylene; R_3 is carboxyl, 5-tetrazolyl, SO_3H, PO_2H_2, PO_3H_2 or halo-lower alkylsulfamoyl; and (hetero)aromatic radicals including the rings A and B are each additionally unsubstituted or substituted by one or more substituents selected from halogen, hydroxyl, lower alkoxy, or lower alkyl or lower alkoxy-lower alkyl, each of which is unsubstituted or substituted by halogen or hydroxyl, in free form or in salt form.

8. A process according to claim 1 or 2 for the preparation of a compound of the formula I, in which R_1 is lower alkyl, lower alkenyl, halo-lower alkyl or -lower alkenyl, hydroxy-lower alkyl, 3- to 7-membered cycloalkyl or phenyl-lower alkyl; X_1 is CO or SO_2; X_2 is C_1-C_{10}alkylene or C_1-C_7alkylidene, each of which is unsubstituted or substituted by hydroxyl, a 3- to 7-membered cycloalkyl, 3- to 7-membered cycloalkenyl, phenyl, pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, furyl, thienyl or pyridyl radical which for its part can additionally be unsubstituted or substituted by carboxyl, lower alkoxycarbonyl, phenyl-lower alkoxycarbonyl, carbamoyl in which the amino group is unsubstituted, monosubstituted or independently of one another disubstituted by lower alkyl or phenyl-lower alkyl, formyl, di-lower

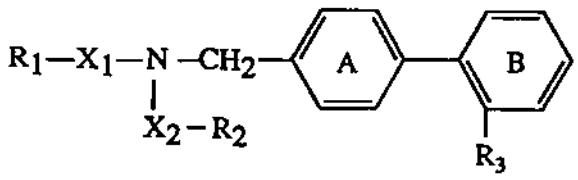
alkoxymethyl or oxy-lower alkylenoxymethylene; R_2 is carboxyl, lower alkoxy-, phenyl-lower alkoxy-, lower alkenyloxy- or lower alkoxy-lower alkoxy-carbonyl, carbamoyl in which the amino group is unsubstituted, monosubstituted or independently of one another disubstituted by lower alkyl or phenyl-lower alkyl or is disubstituted by lower alkylene- or lower alkylenoxy-lower alkylene, amino in which the amino group is unsubstituted, monosubstituted or independently of one another disubstituted by lower alkyl or phenyl-lower alkyl or is disubstituted by lower alkylene- or lower alkylenoxy-lower alkylene, lower alkanoyl, phenyl-lower alkanoyl-, benzoyl-, lower alkanesulfonyl- or benzenesulfonyl-amino, formyl, di-lower alkoxymethyl, oxy-lower alkylenoxymethylene, hydroxyl, lower alkoxy, phenyl-lower alkoxy, phenoxy, $S(O)_m$-R, m being 0, 1 or 2 and R being lower alkyl, lower alkanoyl, sulfamoyl in which the amino group is unsubstituted, monosubstituted or independently of one another disubstituted by lower alkyl or phenyl-lower alkyl, or is PO_nH_2, n being 2 or 3; X_3 is methylene; R_3 is carboxyl, 5-tetrazolyl, SO_3H, PO_2H_2, PO_3H_2 or halo-lower alkylsulfamoyl; and (hetero)aromatic radicals including the rings A and B are in each case additionally unsubstituted or substituted by one or more substituents selected from halogen, hydroxyl, lower alkoxy, or lower alkyl or lower alkoxy-lower alkyl, each of which is unsubstituted or substituted by halogen or hydroxyl, in free form or in salt form.

9. A process according to claim 1 or 2 for the preparation of a compound of the formula I, in which X_2 is C_1-C_{10}alkylene or C_1-C_7alkylidene, each of which is unsubstituted or substituted by hydroxyl, a 3- to 7-membered cycloalkyl, 3- to 7-membered cycloalkenyl, phenyl, pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, furyl, thienyl or pyridyl radical which for its part can additionally be substituted by carboxyl, lower alkoxycarbonyl, phenyl-lower alkoxycarbonyl, carbamoyl in which the amino group is unsubstituted, monosubstituted or independently of one another disubstituted by lower alkyl or phenyl-lower alkyl, formyl, di-lower alkoxymethyl or by oxy-lower alkylenoxymethylene, it being possible for a C atom of C_1-C_{10}alkylene or C_1-C_7alkylidene to be bridged by C_2-C_6alkylene, or X_2 is C_3-C_7cycloalkylene; X_3 is lower alkylene or lower alkylidene; the variables X_1, R_1, R_2 and R_3 are as defined in claim 8; and the (hetero)aromatic rings including the rings A and B can be substituted as indicated in claim 8, in free form or in salt form.

10. A process according to claim 1 or 2 for the preparation of a compound of the formula I, in which the variables R_1,X_1 and R_3 are as defined in each case in any one of claims 1-8; X_2 is lower alkylene or lower alkylidene, each of which is unsubstituted or substituted by hydroxyl, 3- to 7-membered cycloalkyl, phenyl or imidazolyl and R_2 is carboxyl, lower alkoxy-, phenyl-lower alkoxy- or lower alkoxy-lower alkoxy-carbonyl, carbamoyl which is unsubstituted, monosubstituted or independently of one another disubstituted by lower alkyl or phenyl-lower alkyl, amino, lower alkanoyl-, phenyl-lower alkanoyl- or lower alkanesulfonylamino, hydroxyl, lower alkoxy, phenyl-lower alkoxy or phenoxy; X_3 is -CH_2-; (hetero)aromatic radicals including the rings A and B each being unsubstituted or substituted by one or more substituents selected from halogen, trifluoromethyl, hydroxyl, lower alkoxy, lower alkyl, hydroxy-lower alkyl or lower alkoxy-lower alkyl, in free form or in salt form.

11. A process according to claim 1 or 2 for the preparation of a compound of the formula I, in which X_2 is lower alkylene or lower alkylidene which is unsubstituted or substituted by hydroxyl, 3- to 7-membered cycloalkyl, 7-membered cycloalkenyl, phenyl or imidazolyl, where a C atom of lower alkylene or lower alkylidene can be bridged by C_2-C_6alkylene, or X_2 is C_3-C_7cycloalkylene; the variables X_1, X_3, R_1, R_2 and R_3 are as defined in claim 8 to 10; and the rings A and B can be substituted as indicated in claim 10, in free form or in salt form.

12. A process according to claim 1 or 2 for the preparation of a compound of the formula



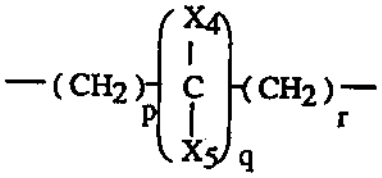
(Ia),

in which the variables R_1, X_1, X_2, R_2 and R_3 are as defined in each case in any one of claims 1 or 3-11 and the rings A and B can be substituted as indicated in claim 11, in free form or in salt form.

13. A process according to claim 1 or 2 for the preparation of a compound of the formula Ia, in which X_2 is lower alkylene or lower alkylidene, which is unsubstituted or substituted by hydroxyl or 3- to 7-membered cycloalkyl, it being possible for a C atom of lower alkylene or lower alkylidene to be bridged by C_2-C_6alkylene, or in which X_2 is C_3-

C_7cycloalkylene; the variables R_1,X_1, R_2 and R_3 are as defined in each case in any one of claims 1 or 3-11; and the rings A and B can be substituted as indicated in claim 11, in free form or in salt form.

14. A process according to claim 1 or 2 for the preparation of a compound of the formula Ia, in which X_2 is the group of the formula



(Ib)

in which p is 0 or 1, q is 1 and r is 0 or 1 or in which p is 1 to 8 and q and r are in each case 0; X_4 is lower alkyl or phenyl which is unsubstituted or substituted by hydroxyl, 3- to 7-membered cycloalkyl, phenyl or imidazolyl; and X_5 is hydrogen or lower alkyl; R_2 is carboxyl, lower alkoxycarbonyl, phenyl-lower alkoxycarbonyl, lower alkoxy-lower alkoxycarbonyl, hydroxyl, lower alkoxy, phenyl-lower alkoxy, phenoxy, amino, lower alkanoylamino, phenyl-lower alkanoylamino or lower alkanesulfonylamino; and the variables R_1, X_1 and R_3 are as defined in each case in any one of claims 1 or 3-8; (hetero)aromatic radicals including the rings A and B each being unsubstituted or substituted by halogen, trifluoromethyl, hydroxyl, lower alkoxy, lower alkyl or hydroxy-lower alkyl, in free form or in salt form.

15. A process according to claim 1 or 2 for the preparation of a compound of the formula Ia, in which X_2 is the group of the formula Ib in which p is 0 or 1, q is 1 and r is 0 or 1 or in which p is 1 to 8 and q and r are each 0; X_4 is lower alkyl or phenyl, which is unsubstituted or substituted by hydroxyl, 3- to 7-membered cycloalkyl, phenyl or imidazolyl; and X_5 is hydrogen or lower alkyl; or X_4 and X_5 together are C_2-C_6alkylene, such as C_4-C_5alkylene; or X_2 is C_3-C_7cycloalkylene such as C_5-C_6cycloalkylene; R_2 is carboxyl, lower alkoxycarbonyl, phenyl-lower alkoxycarbonyl, lower alkoxy-lower alkoxycarbonyl, hydroxyl, lower alkoxy, phenyl-lower alkoxy, phenoxy, amino, lower alkanoylamino, phenyl-lower alkanoylamino or lower alkanesulfonylamino; and the variables R_1, X_1 and R_3 are as defined in each case in any one of claims 1 or 3-8; (hetero)aromatic radicals including the rings A and B each being unsubstituted or substituted by halogen, trifluoromethyl, hydroxyl, lower alkoxy, lower alkyl or hydroxy-lower alkyl, in free form or in salt form.

16. A process according to claim 1 or 2 for the preparation of a compound of the formula Ia, in which R_1 is lower alkyl, such as C_3-C_5alkyl, or lower alkenyl, such as C_3-C_5alkenyl; X_1 is CO or else SO_2; X_2 is the group of the formula Ib in which p and r are 0 or 1 and q is 1; X_4 is lower alkyl, such as C_1-C_4alkyl, or phenyl, which is unsubstituted or substituted by hydroxyl, 3- to 7-membered cycloalkyl, such as cyclohexyl, or by phenyl or imidazolyl which is unsubstituted or substituted by halogen or hydroxyl, such as 4-imidazolyl; and X_5 is hydrogen or lower alkyl, such as C_1-C_4alkyl; or X_4 and X_5 together are C_2-C_6alkylene, such as C_4-C_5alkylene; or X_2 is C_3-C_7cycloalkylene, such as C_5-C_6cycloalkylene; R_2 is carboxyl, lower alkoxycarbonyl, such as C_2-C_5alkoxycarbonyl, phenyl-lower alkoxycarbonyl, such as phenyl-C_1-C_4alkoxycarbonyl, lower alkoxy-lower alkoxycarbonyl, such as C_1-C_4alkoxy-C_2-C_5alkoxycarbonyl, hydroxyl or lower alkoxy, such as C_1-C_4alkoxy; and R_3 is carboxyl or 5-tetrazolyl; (hetero)aromatic radicals including the rings A and B each being unsubstituted or substituted by halogen, trifluoromethyl, hydroxyl, lower alkoxy, lower alkyl or hydroxy-lower alkyl, in free form or in salt form.

17. A process according to claim 1 or 2 for the preparation of a compound of the formula Ia, in which R_1 is lower alkyl, such as C_3-C_5alkyl, or lower alkenyl, such as C_3-C_5alkenyl; X_1 is CO or else SO_2; X_2 is the group of the formula Ib in which p and r are 0 or 1 and q is 1; X_4 is lower alkyl, such as C_1-C_4alkyl, or phenyl, which is unsubstituted or substituted by hydroxyl, 3- to 7-membered cycloalkyl, or by phenyl or imidazolyl which is unsubstituted or substituted by halogen or hydroxyl, such as 4-imidazolyl; and X_5 is hydrogen or lower alkyl, such as C_1-C_4alkyl; R_2 is carboxyl, lower alkoxycarbonyl, such as C_2-C_5alkoxycarbonyl, phenyl-lower alkoxycarbonyl, such as phenyl-C_1-C_4alkoxycarbonyl, lower alkoxy-lower alkoxycarbonyl, such as C_1-C_4alkoxy-C_2-C_5alkoxycarbonyl, hydroxyl or lower alkoxy, such as C_1-C_4alkoxy; and R_3 is carboxyl or 5-tetrazolyl; (hetero)aromatic radicals including the rings A and B each being unsubstituted or substituted by halogen, trifluoromethyl, hydroxyl, lower alkoxy, lower alkyl or hydroxy-lower alkyl, in free form or in salt form.

18. A process according to claim 1 or 2 for the preparation of a compound of the formula Ia, in which R_1 is lower alkyl, such as C_3-C_5alkyl, or else lower alkenyl, such as C_3-C_5alkenyl; X_1 is CO or else SO_2; X_2 is the group of the formula Ib in which p is an integer from 1 to 8 and q and r are 0; R_2 is hydroxyl, lower alkoxy, such as C_1-C_4alkoxy, phenyl-

lower alkoxy, such as phenyl-C_1-C_4alkoxy, phenoxy, lower alkanoylamino, such as C_1-C_4alkanoylamino, phenyl-lower alkanoylamino, such as phenyl-C_1-C_4alkanoylamino, or lower alkanesulfonylamino, such as C_1-C_4alkanesulfonylamino; and R_3 is carboxyl or primarily 5-tetrazolyl; (hetero)aromatic radicals including the rings A and B each being unsubstituted or substituted by halogen, trifluoromethyl, hydroxyl, lower alkoxy, lower alkyl or hydroxy-lower alkyl, in free form or in salt form.

19. A process according to claim 1 or 2 for the preparation of a compound of the formula Ia, in which R_1 is C_3-C_5alkyl or secondarily C_3-C_5alkenyl; X_1 is CO, also SO_2; X_2 is the group of the formula Ib in which p and r independently of one another are 0 or 1 and q is 1; X_4 is C_1-C_4alkyl, hydroxy-C_1-C_4alkyl, C_3-C_7cycloalkyl-C_1-C_4alkyl, phenyl-C_1-C_4alkyl or imidazolyl-C_1-C_4alkyl; and X_5 is hydrogen or C_1-C_4alkyl; or X_4 and X_5 together are tetramethylene, and also pentamethylene; R_2 is carboxyl or C_2-C_5alkoxycarbonyl, and also phenyl-C_1-C_4alkoxycarbonyl; and R_3 is carboxyl or 5-tetrazolyl, in free form or in salt form.

20. A process according to claim 1 or 2 for the preparation of a compound of the formula Ia, in which R_1 is C_3-C_5alkyl or secondarily C_3-C_5alkenyl; X_1 is CO, and also SO_2; X_2 is the group of the formula Ib in which p and r are each 0 or 1 and q is 1; X_4 is C_1-C_4alkyl, hydroxy-C_1-C_4alkyl, C_3-C_7cycloalkyl-C_1-C_4alkyl, phenyl-C_1-C_4alkyl or imidazolyl-C_1-C_4alkyl; and X_5 is hydrogen; R_2 is carboxyl or C_2-C_5alkoxycarbonyl, and also phenyl-C_1-C_4alkoxycarbonyl; and R_3 is carboxyl or 5-tetrazolyl, in free form or in salt form.

21. A process according to claim 1 or 2 for the preparation of a compound of the formula Ia, in which R_1 is C_3-C_5alkyl; X_1 is CO; X_2 is the group of the formula Ib in which q and r are 0 and p is 1 to 3 or in which p and q are 1 and r is 0; X_4 is C_1-C_4alkyl; X_5 is hydrogen or C_1-C_4alkyl; R_2 is carboxyl or C_2-C_5alkoxycarbonyl; and R_3 is carboxyl or 5-tetrazolyl, in free form or in salt form.

22. A process according to claim 1 or 2 for the preparation of a compound of the formula Ia, in which R_3 is 5-tetrazolyl, in free form or in salt form.

23. A process according to claim 1 or 2 for the preparation of a compound of the formula Ia, in which R_1 is C_3-C_5alkyl; X_1 is CO; X_2 is the group of the formula Ib in which p is 0 or 1, r is 0 and q is 1; X_4 is C_1-C_4alkyl; and X_5 is hydrogen or C_1-C_4alkyl; or X_4 and X_5 together are tetramethylene or pentamethylene; R_2 is carboxyl or C_2-C_5alkoxycarbonyl; and R_3 is 5-tetrazolyl, in free form or in salt form.

24. A process according to claim 1 or 2 for the preparation of a compound of the formula Ia, in which R_1 is C_3-C_5alkyl; X_1 is CO; X_2 is the group of the formula Ib in which p is 0 or 1, r is 0 and q is 1; X_4 and X_5 together are tetramethylene, and also pentamethylene; R_2 is carboxyl or C_2-C_5alkoxycarbonyl; and R_3 is 5-tetrazolyl, in free form or in salt form.

25. A process according to claim 1 or 2 for the preparation of a compound of the formula Ia, in which R_1 is C_3-C_5alkyl; X_1 is CO; X_2 is the group of the formula Ib in which p and r are 0 or 1 and q is 1; X_4 is C_1-C_4alkyl; and X_5 is hydrogen; R_2 is carboxyl or C_2-C_5alkoxycarbonyl; and R_3 is 5-tetrazolyl, in free form or in salt form.

26. A process according to claim 1 or 2 for the preparation of a compound of the formula Ia according to any one of claims 14-25, in which X_2 is the group of the formula Ib, q is 1 and X_4 and X_5 are defined differently, in free form or in salt form, in which the asymmetric C atom in question containing the variables X_4 and X_5 has the S configuration.

27. A process according to claim 1 or 2 for the preparation of (S)-N-(1-carboxy-2-methylprop-1-yl)-N-pentanoyl-N-[2'-(1H-te trazol-5-yl)biphenyl-4-yl-methyl]amine, in free form or in salt form according to claim 1.

28. A process according to claim 1 or 2 for the preparation of N-(2-carboxy-2,2-tetramethyleneethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine, in free form or in salt form according to claim 1.

29. A process according to claim 1 or 2 for the preparation of N-(2-carboxy-2-ethylbut-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine, in free form or in salt form according to claim 1.

30. A processs according to claim 1 or 2 for the preparation of (S)-N-(1-carboxy-2-methylprop-1-yl)-N-ethoxycarbonyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine, in free form or in salt form according to claim 1.

31. A process according to claim 1 or 2 for the preparation of N-(1-carboxycyclohexyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amine, in free form or in salt form according to claim 1.

32. A process according to claim 1 or 2 for the preparation of a compound according to claim 1 selected from the group consisting of:
(S)-N-(1-carboxyethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N-(2-hydroxyethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N-(2-ethoxycarbonyl-2,2-tetramethyleneethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N-(2-ethoxycarbonyl-2-ethylbut-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N(2-ethoxycarbonyl)-2-methylprop-1-yl)-N-pentamoyl-N-[2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]amine,
(S)-N-(1-hydroxymethyl-2-methylprop-1-yl)-N-pentanoyl-N-[2'-1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N-(2-ethoxycarbonyl-2,2-pentamethyleneethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
(S)-N-(1-carboxy-2-methylprop-1-yl)-N-propyloxycarbonyl-N-[2'-1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N-(2-carboxy-2-methylpropyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N-(2-carboxy-2,2-pentamethyleneethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
(S)-N-(1-aminocarbonyl-2-methylprop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine and
(S)-N-(1-carboxy-2-methylprop-1-yl)-N-(5-oxopent-1-en-5-yl)-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine, in each case in free form or in salt form.

33. A process according to claim 1 or 2 for the preparation of a compound according to claim 1 selected from the group consisting of:
N-carboxymethyl-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
(S)-N-(1-methoxycarbonylethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N-[1-carboxy-2-(4-fluorophenyl)ethyl]-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N-[2-(4-fluorophenyl)-1-methoxycarbonylethyl]-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N-[2-(4-fluorophenyl)-1-hydroxymethylethyl]-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N-(2'-carboxybiphenyl-4-ylmethyl)-N-[1-carboxy-2-(4-fluorop henyl)ethyl]-N-pentanyol-amine,
N-(2'-carboxybiphenyl-4-ylmethyl)-N-[2-(4-fluorophenyl)-1-methoxycarbonyethyl]-N-pentanoylamine,
(S)-N-(2'-carboxybiphenyl-4-ylmethyl)-N-(1-hydroxymethyl-2-phenylethyl)-N-pentanoylamine,
(S)-N-(2'-carboxybiphenyl-4-ylmethyl)-N-(1-hydroxymethyl-2-imidazol-4-ylethyl)N-pentanoylamine,
(R)-N-(1-carboxyethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
(1S),(2S)-N-(1-carboxy-2-methylbut-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
(1S),(2S)-N-(1-methoxycarbonyl-2-methylbut-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
(S)-N-(1-carboxybut-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amine,
(S)-N-(1-methoxycarbonylbut-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
(S)-N-(1-carboxyethyl-N-hexanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
(S)-N-butanoyl-N-(1-carboxyethyl)-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
(S)-N-(1-carboxyprop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amine,
(S)-N-(1-carboxy-2-cyclohexylethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
(S)-N-(2-cyclohexyl-1-methoxycarbonylethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
(R)-N-(1-carboxy-2-methylprop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N-(2-methoxyethyl-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N-(2-benzyloxyethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N-(3-methoxyprop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amine,
N-(3-benzyloxyprop-1-yl)-N-pentanoyl-N-[2'-1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amine,
N-(3-hydroxyprop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amine,
N-(1-methoxycarbonyl-1-methylethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N-(2-carboxyethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N-(2-carboxyprop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amine,
N-(1-carboxy-1-methylethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N-(5-hydroxypent-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N-(1-carboxyprop-2-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N-(2-ethoxycarbonyl-3-methylbut-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N-(2-carboxy-3-methylbut-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N[(3-phenoxyprop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N-[2-(4-hydroxyphenyl)ethyl]-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N-[3-(4-hydroxyphenyl)prop-1-yl]-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N-(8-hydroxyoct-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N-(2-methanesulfonylaminoethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N-(3-acetylaminoprop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amine,
N-(2-methoxy-2-oxo-1-phenylethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N-(4-hydroxybut-2-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,

N-(2-hydroxyl-1-phenylethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N-[3-(4-hydroxybenzylcarbonylamino)prop-1-yl]-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N-(3-ethoxycarbonylcyclohexyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N-(3-carboxycyclohexyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-methyl]-amine,
cis-N-(4-carboxycyclohexyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
cis-N-(2-ethoxycarbonylcyclohexyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
cis-N-(2-carboxycyclohexyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N-{2-[2-(4-hydroxyphenyl)ethylaminocarbonyl]-2,2-tetramethyleneethyl}-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
(S)-N-{1-[2-(4-hydroxyphenyl)ethylaminocarbonyl]-2-methylprop-1-yl}-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
(S)-N-(1-carboxy-2,2-dimethylprop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
(S)-N-(1-methoxycarbonyl-2-methylprop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N-(4-phenoxybut-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N-(2-hydroxy-1-phenyl-2-oxoethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
(S)-N-(1-benzyloxycarbonyl-2-methylprop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N-butanoyl-N-(1-carboxy-1-methylethyl)-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amine,
N-(4-hydroxybut-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
(S)-N-(1-benzyloxycarbonyl-2-methylprop-1-yl)-N-[3-bromo-2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-N-pentanoylamine,
(S)-N-[3-bromo-2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-N-(1-carboxy-2-methylprop-1-yl)-N-pentanoylamine,
N-(2-acetylaminoethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N-[2-(n-butoxycarbonyl)-2,2-tetramethyleneethyl]-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N-(2-benzylaminocarbonyl-2,2-tetramethyleneethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
(S)-N-butyloxycarbonyl-N-(1-carboxy-2-methylprop-1-yl)-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
(S)-N-(1-carboxy-2-methylprop-1-yl)-N-methoxycarbonyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N-(2-diethylaminocarbonyl-2,2-tetramethyleneethyl)-N-pentanoyl-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N-(2-methyl-2-morpholin-4-ylcarbonylpropyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N-(1-carboxycyclopentyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amine,
N-(1-carboxy-1-ethylprop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
(S)-N-(5-amino-1-carboxypent-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N-butanesulfonyl-N-(2-ethoxycarbonyl-2,2-pentamethyleneethyl)-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N-butanesulfonyl-N-(2-carboxy-2,2-pentamethyleneethyl)-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N-butanesulfonyl-N-(2-ethoxycarbonyl-2-methylprop-1-yl)-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N-butanesulfonyl-N-(2-carboxy-2-methylprop-1-yl)-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
(S)-N-butanesulfonyl-N-(1-tert-butoxycarbonylethyl)-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
(S)-N-butanesulfonyl-N-(1-carboxyethyl)-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amine,
(S)-N-butanesulfonyl-N-(1-carboxy-2-methylprop-1-yl)-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
(S)-N-(2-methyl-1-methylaminocarbonylprop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
(S)-N-(1-dimethylaminocarbonyl-2-methylprop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
(S)-N-(2-methyl-1-morpholin-4-ylcarbonylprop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
(S)-N-(2'-carboxybiphenyl-4-ylmethyl)-N-(1-carboxy-2-methylprop-1-yl)-N-pentanoyl-amine,
(S)-N-(1,2-dicarboxyethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-amine,
(S)-N-(1-carboxy-3-phenylprop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
(S)-N-(2-cyclohexyl-1-hydroxymethylethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
(R)-N-(1-methoxycarbonyl-2-methylprop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
(S)-N-(2-hydroxy-1-methoxycarbonylethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N-pentanoyl-N-(1H-tetrazol-5-ylmethyl)-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amine,
N-pentanoyl-N-pyrid-3-ylmethyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
(S)-N-(1-carboxy-4-guanidinobut-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N-(2-hydroxy-1-methoxycarbonylprop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N-(1-benzyloxycarbonyl-1-methylethyl)-N-butanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine, (S)-N-(1-carboxy-3-methylbut-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N-(1-carboxy-2-hydroxyethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-yl-methyl]amine,
(S)-N-(1-carboxy-2-hydroxyethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,

(S)-N-(2-methyl-1-(2-phenylethylaminocarbonyl)prop-1-yl]-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
(S)-N-(2-benzyloxy-1-hydroxymethylethyl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
(S)-N-(1-carboxy-2-methylprop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-3-ylmethyl]amine,
(S)-N-(1-carboxy-2-methylprop-1-yl)-N-pentanoyl-N-[3'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
(S)-N-[2-methyl-1-(1,2,3,4-tetrahydroquinol-1-ylcarbonyl)prop-1-yl]-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
(S)-N-(2-methyl-1-piperidin-1-ylcarbonylprop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
(S)-N-[2-methyl-1-(1,2,3,4-tetrahydroisoquinol-2-ylcarbonyl)prop-1-yl]-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine,
N-(2-hydroxymethyl-2-methylprop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]amine,
N-ethoxycarbonyl-N-(2-ethoxycarbonyl-2-methylprop-1-yl)-N-[2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]amine and
N-(2-carboxy-2-methylprop-1-yl)-N-ethoxycarbonyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine, in each case in free form or in salt form.

34. A process for the production of a pharmaceutical preparation comprising as active ingredient a compound according to any one of claims 1 or 3 to 33, in free form or in the form of a pharmaceutically utilizable salt, if appropriate in addition to customary pharmaceutical excipients, wherein the active ingredient, if appropriate with admixture of customary pharmaceutical excipients, is processed to give a pharmaceutical preparation.

35. The use of a compound according to any one of claims 1 or 3 to 33, in free form or in the form of a pharmaceutically utilizable salt, for the production of an antihypertensive.

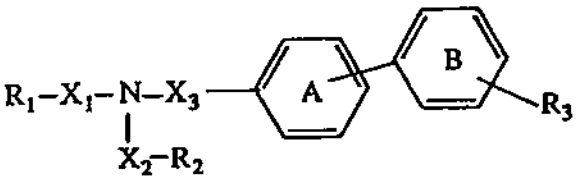
36. The use of a compound according to any one of claims 1 or 3 to 33, in free form or in the form of a pharmaceutically utilizable salt, for the production of a pharmaceutical preparation for the therapeutic or prophylactic treatment of cardiac insufficiency.

37. The use of a compound according to any one of claims 1 or 3 to 33, in free form or in the form of a pharmaceutically utilizable salt, for the production of a pharmaceutical preparation for the therapeutic or prophylactic treatment of disorders which are caused by angiotensin II activity.

Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE

1. Composé de formule



(I),

dans laquelle R_1 représente un radical alkyle inférieur, alcényle inférieur ou alcynyle inférieur, éventuellement substitué par un atome d'halogène ou par le groupe hydroxy, ou un radical cycloalkyle en C_3-C_7 ou cycloalcényle en C_3-C_7 ou phényl-alkyle inférieur, phényl-alcényle inférieur ou phényl-alcynyle inférieur; X_1 représente CO, SO_2 ou -O-C(=O)-, l'atome de carbone du groupe carbonyle étant lié à l'atome d'azote indiqué dans la formule I; X_2 représente un radical alkylène en C_1-C_{10}, alkylidène en C_2-C_{10} ou cycloalkylène en C_3-C_7, éventuellement substitué par un groupe hydroxy, carboxy, amino, guanidino, cycloalkyle en C_3-C_7, cycloalcényle en C_3-C_7, phényle ou par un groupe aromatique monocyclique et à 5 ou 6 chaînons correspondant, qui comporte jusqu'à 4 hétéroatomes identiques ou différents, un atome de carbone du radical alkylène en C_1-C_{10} ou alkylidène en C_2-C_{10} pouvant en outre être ponté par un groupe alkylène en C_2-C_6, et un radical cycloalkyle en C_3-C_7 ou cycloalcényle en C_3-C_7 étant éventuellement une ou plusieurs fois substitué par un ou des groupes carboxy, carboxy estérifié par un alcool dérivant d'un reste alkyle inférieur, phényl-alkyle inférieur, alcényle inférieur, alcynyle inférieur, (alcoxy inférieur)-alkyle inférieur, (alcoxy inférieur)-alcényle inférieur ou (alcoxy inférieur)-alcynyle inférieur, ou par un ou des groupes carbamoyle, carbamoyle dont le fragment amino est monosubstitué ou disubstitué, indépendamment l'un de l'autre, par un ou des groupes alkyle inférieur, alcényle inférieur, alcynyle inférieur, phényl-alkyle inférieur, phényl-alcényle inférieur ou

phényl-alcynyle inférieur, ou disubstitué par des radicaux alkylène en C_1-C_{10} ou alkylidène en C_2-C_{10}, les radicaux alkylène en C_1-C_{10} ou alkylidène en C_2-C_{10} étant éventuellement interrompus par -O- ou condensés, au niveau de deux atomes de carbone contigus, avec un cycle benzénique, ou par un ou des groupes formyle, di-(alcoxy inférieur)-méthyle ou oxy-(alkylène-oxy inférieur)-méthylène; R_2 représente le groupe carboxy ou un groupe carboxy qui est estérifié par un alcool dérivant d'un reste alkyle inférieur, phényl-alkyle inférieur, alcényle inférieur, alcynyle inférieur, (alcoxy inférieur)-alkyle inférieur, (alcoxy inférieur)-alcényle inférieur ou (alcoxy inférieur)-alcynyle inférieur, le groupe carbamoyle ou un groupe carbamoyle dans lequel le fragment amino est monosubstitué ou disubstitué, indépendamment l'un de l'autre, par un ou des groupes alkyle inférieur, alcényle inférieur, alcynyle inférieur, phényl-alkyle inférieur, phényl-alcényle inférieur ou phényl-alcynyle inférieur, ou disubstitué par des groupes alkylène en C_1-C_{10} ou alkylidène en C_2-C_{10}, les groupes alkylène en C_1-C_{10} ou alkylidène en C_2-C_{10} étant éventuellement interrompus par -O- ou condensés, au niveau de deux atomes de carbone contigus, avec un cycle benzénique, le groupe amino ou un groupe amino qui est monosubstitué ou disubstitué, indépendamment l'un de l'autre, par un ou des radicaux alkyle inférieur, alcényle inférieur, alcynyle inférieur, phényl-alkyle inférieur, phényl-alcényle inférieur ou phényl-alcynyle inférieur, ou disubstitué par des radicaux alkylène en C_1-C_{10} ou alkylidène en C_2-C_{10}, les radicaux alkylène en C_1-C_{10} ou alkylidène en C_2-C_{10} étant éventuellement interrompus par -O- ou condensés, au niveau de deux atomes de carbone contigus, avec un cycle benzénique, un groupe alcanoyle inférieur, phényl-(alcanoyl inférieur)-, benzoyl-, (alcane inférieur)-sulfonyl-, benzènesulfonyl-amino, formyle, di-(alcoxy inférieur)-méthyle, oxy-(alkylène-oxy inférieur)-méthylène, 1H-tétrazol-5-yle, pyridyle, hydroxy, alcoxy inférieur, alcényloxy inférieur, phényl-alcoxy inférieur, phénoxy, $S(O)_m$-R, m étant 0, 1 ou 2 et R représentant un atome d'hydrogène ou un radical alkyle inférieur, alcényle inférieur ou alcynyle inférieur, ou représente un groupe alcanoyle inférieur, sulfamoyle, sulfamoyle dans lequel le fragment amino est monosubstitué ou disubstitué, indépendamment l'un de l'autre, par un ou des groupes alkyle inférieur, alcényle inférieur, alcynyle inférieur, phényl-alkyle inférieur, phényl-alcényle inférieur ou phényl-alcynyle inférieur, ou disubstitué par des groupes alkylène en C_1-C_{10} ou alkylidène en C_2-C_{10}, les groupes alkylène en C_1-C_{10} ou alkylidène en C_2-C_{10} étant éventuellement interrompus par -O- ou condensés, au niveau de deux atomes de carbone contigus, avec un cycle benzénique, ou représente PO_nH_2, n étant 2 ou 3; X_3 représente un groupe alkylène en C_1-C_{10} ou alkylidène en C_2-C_{10}; R_3 est le groupe carboxy, 5-tétrazolyle, SO_3H, PO_2H_2, PO_3H_2 ou un groupe halogéno-(alkyl inférieur)-sulfamoyle; et les radicaux (hétéro)aromatiques, y compris les cycles A et B, étant éventuellement substitués, indépendamment les uns des autres, par des substituants choisis parmi des atomes d'halogène et des groupes hydroxy, alcoxy inférieur, alcényloxy inférieur, phényl-alcoxy inférieur, phénoxy, $S(O)_m$-R et des groupes alkyle inférieur, alcényle inférieur ou alcynyle inférieur éventuellement substitués par un atome d'halogène ou par le groupe hydroxy, les radicaux alkyle inférieur, alcényle inférieur ou alcynyle inférieur étant éventuellement interrompus par -O-, ainsi que, dans le cas de radicaux (hétéro)aromatiques, éventuellement substitués en outre par le groupe carboxy ou un groupe carboxy estérifié par un alcool dérivant d'un reste alkyle inférieur, phényl-alkyle inférieur, alcényle inférieur, alcynyle inférieur, (alcoxy inférieur)-alkyle inférieur, (alcoxy inférieur)-alcényle inférieur ou (alcoxy inférieur)-alcynyle inférieur, par le groupe carbamoyle ou un groupe carbamoyle dans lequel le fragment amino est monosubstitué ou disubstitué, indépendamment l'un de l'autre, par un ou des groupes alkyle inférieur, alcényle inférieur, alcynyle inférieur, phényl-alkyle inférieur, phényl-alcényle inférieur ou phényl-alcynyle inférieur, ou disubstitué par des groupes alkylène en C_1-C_{10} ou alkylidène en C_2-C_{10}, les groupes alkylène en C_1-C_{10} ou alkylidène en C_2 -C_{10} étant éventuellement interrompus par -O- ou condensés, au niveau de deux atomes de carbone contigus, avec un cycle benzénique, par le groupe formyle ou par un groupe di-(alcoxy inférieur)-méthyle ou oxy(alkylène-oxy inférieur)-méthylène; les radicaux et groupes désignés par "inférieur" contenant jusqu'à 7 atomes de carbone; sous forme libre ou sous forme de sel.

2. composé selon la revendication 1, de formule I, dans lequel R_1 représente un radical alkyle inférieur, alcényle inférieur ou alcynyle inférieur éventuellement substitué par un atome d'halogène ou par le groupe hydroxy, ou un radical cycloalkyle en C_3-C_7 ou cycloalcényle en C_3-C_7 ou phényl-alkyle inférieur, phényl-alcényle inférieur ou phényl-alcynyle inférieur; X_1 représente CO ou SO_2; X_2 représente un radical alkylène en C_1-C_{10} ou alkylidène en C_2-C_{10} ou cycloalkylène en C_3-C_7, éventuellement substitué par un groupe hydroxy, cycloalkyle en C_3-C_7 ou cycloalcényle en C_3-C_7 ou phényle ou par un radical aromatique correspondant, monocyclique à 5 ou 6 chaînons, qui comporte jusqu'à 4 hétéroatomes identiques ou différents, un atome de carbone du radical alkylène en C_1-C_{10} ou alkylidène en C_2-C_{10} pouvant en outre être ponté par des groupes alkylène en C_2-C_6, et les groupes cycloalkylène en C_3-C_7 étant éventuellement substitués une ou plusieurs fois par un ou plusieurs groupes carboxy, carboxy estérifié par un alcool dérivant d'un reste alkyle inférieur, phényl-alkyle inférieur, alcényle inférieur, alcynyle inférieur, (alcoxy inférieur)-alkyle inférieur, (alcoxy inférieur)-alcényle inférieur ou (alcoxy inférieur)-alcynyle inférieur, ou par le groupe carbamoyle ou un groupe carbamoyle dans lequel le fragment amino est monosubstitué ou disubstitué, indépendamment l'un de l'autre, par un ou des groupes alkyle inférieur, alcényle inférieur, alcynyle inférieur, phényl-alkyle inférieur, phényl-alcényle inférieur ou phényl-alcynyle inférieur, ou disubstitué par des radicaux alkylène en C_1-C_{10} ou alkylidène en C_2-C_{10}, les radicaux alkylène en C_1-C_{10} ou alkylidène en C_2-C_{10} étant éventuellement interrompus par -O-, le groupe formyle, un groupe di(alcoxy inférieur)-méthyle ou oxy-(alkylène-oxy inférieur)-méthylène; R_2

représente le radical carboxy ou un radical carboxy estérifié par un alcool dérivant d'un reste alkyle inférieur, phényl-alkyle inférieur, alcényle inférieur, alcynyle inférieur, (alcoxy inférieur)-alkyle inférieur, (alcoxy inférieur)-alcényle inférieur ou (alcoxy inférieur)-alcynyle inférieur, ou le radical carbamoyle ou un radical carbamoyle dans lequel le fragment amino est monosubstitué ou disubstitué, indépendamment l'un de l'autre, par un ou des groupes alkyle inférieur, alcényle inférieur, alcynyle inférieur, phényl-alkyle inférieur, phényl-alcényle inférieur ou phényl-alcynyle inférieur, ou disubstitué par des radicaux alkylène en C_1-C_{10} ou alkylidène en C_2-C_{10}, les radicaux alkylène en C_1-C_{10} ou alkylidène en C_2-C_{10} étant éventuellement interrompus par -O-, le radical amino ou un radical amino qui est monosubstitué ou disubstitué, indépendamment l'un de l'autre, par un ou des groupes alkyle inférieur, alcényle inférieur, alcynyle inférieur, phényl-alkyle inférieur, phényl-alcényle inférieur ou phényl-alcynyle inférieur, ou disubstitué par des radicaux alkylène en C_1-C_{10} ou alkylidène en C_2-C_{10}, les radicaux alkylène en C_1-C_{10} ou alkylidène en C_2-C_{10} étant éventuellement interrompus par -O-, ou représente un radical (alcanoyl inférieur)-, phényl-(alcanoyl inférieur)-, benzoyl-, (alcane inférieur)-sulfonyl-, benzènesulfonyl-amino, formyle, di-(alcoxy inférieur)-méthyle, oxy-(alkylène-oxy inférieur)-méthylène, hydroxy, alcoxy inférieur, alcényloxy inférieur, phényl-alcoxy inférieur, phénoxy, $S(O)_m$-R, m représentant 0, 1 ou 2 et R représentant un atome d'hydrogène ou un groupe alkyle inférieur, alcényle inférieur ou alcynyle inférieur, un radical alcanoyle inférieur, le radical sulfamoyle ou un radical sulfamoyle dans lequel le fragment amino est monosubstitué ou disubstitué, indépendamment l'un de l'autre, par un ou des radicaux alkyle inférieur, alcényle inférieur, alcynyle inférieur, phényl-alkyle inférieur, phényl-alcényle inférieur ou phényl-alcynyle inférieur, ou disubstitué par des radicaux alkylène en C_1-C_{10} ou alkylidène en C_2-C_{10}, les radicaux alkylène en C_1-C_{10} ou alkylidène en C_2-C_{10} étant éventuellement interrompus par -O-, ou représente PO_nH_2, n représentant 2 ou 3; X_3 représente un radical alkylène en C_1-C_{10} ou alkylidène en C_2-C_{10}; R_3 est le groupe carboxy, 5-tétrazolyle, SO_3H, PO_2H_2, PO_3H_2 ou un groupe halogéno(alkyl inférieur)-sulfamoyle; les radicaux (hétéro)aromatiques, y compris les cycles A et B, étant éventuellement substitués, indépendamment les uns des autres, par des substituants choisis parmi des atomes d'halogène et des groupes hydroxy, alcoxy inférieur, alcényloxy inférieur, phényl-alcoxy inférieur, phénoxy, $S(O)_m$-R et des radicaux alkyle inférieur, alcényle inférieur ou alcynyle inférieur éventuellement substitués par un atome d'halogène ou par le groupe hydroxy, les radicaux alkyle inférieur, alcényle inférieur ou alcynyle inférieur étant éventuellement interrompus par -O-, ainsi que, dans le cas des radicaux (hétéro)aromatiques, éventuellement substitués en outre par le groupe carboxy, un groupe carboxy estérifié par un alcool dérivant d'un reste alkyle inférieur, phényl-alkyle inférieur, alcényle inférieur, alcynyle inférieur, (alcoxy inférieur)-alkyle inférieur, (alcoxy inférieur)-alcényle inférieur ou (alcoxy inférieur)-alcynyle inférieur, par le groupe carbamoyle, par un groupe carbamoyle dans lequel le fragment amino est monosubstitué ou disubstitué, indépendamment l'un de l'autre, par un ou des groupes alkyle inférieur, alcényle inférieur, alcynyle inférieur, phényl-alkyle inférieur, phényl-alcényle inférieur ou phényl-alcynyle inférieur, ou disubstitué par des radicaux alkylène en C_1-C_{10} ou alkylidène en C_2-C_{10}, les radicaux alkylène en C_1-C_{10} ou alkylidène en C_2-C_{10} étant éventuellement interrompus par -O-, ou par le groupe formyle, un groupe di-(alcoxy inférieur)-méthyle ou oxy(alkylène-oxy inférieur)-méthylène; sous forme libre ou sous forme de sel.

3. Composé selon la revendication 1, de formule I, dans lequel R_1 représente un radical alkyle inférieur, alcényle inférieur ou alcynyle inférieur éventuellement substitué par un atome d'halogène ou par le groupe hydroxy, ou un radical cycloalkyle en C_3-C_7 ou cycloalcényle en C_3-C_7 ou phényl-alkyle inférieur, phényl-alcényle inférieur ou phényl-alcynyle inférieur; X_1 représente CO ou SO_2; X_2 représente un radical alkylène en C_1-C_{10} ou alkylidène en C_2-C_{10} éventuellement substitué par un groupe hydroxy, cycloalkyle en C_3-C_7 ou cycloalcényle en C_3-C_7 ou phényle ou par un radical aromatique correspondant, monocyclique et à 5 ou 6 chaînons, qui comporte jusqu'à 4 hétéroatomes identiques ou différents; R_2 représente le groupe carboxy ou un groupe carboxy estérifié par un alcool dérivant d'un reste alkyle inférieur, phényl-alkyle inférieur, alcényle inférieur, alcynyle inférieur, (alcoxy inférieur)-alkyle inférieur, (alcoxy inférieur)-alcényle inférieur ou (alcoxy inférieur)-alcynyle inférieur, le groupe carbamoyle ou un groupe carbamoyle dans lequel le fragment amino est mono-substitué ou disubstitué, indépendamment l'un de l'autre, par un ou des groupes alkyle inférieur, alcényle inférieur, alcynyle inférieur, phényl-alkyle inférieur, phényl-alcényle inférieur ou phényl-alcynyle inférieur, ou disubstitué par des radicaux alkylène en C_1-C_{10} ou alkylidène en C_2-C_{10}, les radicaux alkylène en C_1-C_{10} ou alkylidène en C_2-C_{10} étant éventuellement interrompus par -O-, ou représente le groupe amino ou un groupe amino qui est monosubstitué ou disubstitué, indépendamment l'un de l'autre, par un ou des radicaux alkyle inférieur, alcényle inférieur, alcynyle inférieur, phényl-alkyle inférieur, phényl-alcényle inférieur ou phényl-alcynyle inférieur, ou disubstitué par des radicaux alkylène en C_1-C_{10} ou alkylidène en C_2-C_{10}, les radicaux alkylène en C_1-C_{10} ou alkylidène en C_2-C_{10} étant éventuellement interrompus par -O-, ou représente un groupe (alcanoyl inférieur)-, phényl-(alcanoyl inférieur)-, benzoyl-, (alcane inférieur)-sulfonyl-, benzènesulfonylamino, formyle, di-(alcoxy inférieur)-méthyle, oxy-(alkylène-oxy inférieur)-méthylène, hydroxy, alcoxy inférieur, alcényloxy inférieur, phényl-alcoxy inférieur ou phénoxy, $S(O)_m$-R, m représentant 0, 1 ou 2 et R représentant un atome d'hydrogène ou un groupe alkyle inférieur, alcényle inférieur ou alcynyle inférieur, un radical alcanoyle inférieur, ou représente le radical sulfamoyle ou un radical sulfamoyle dans lequel le fragment amino est monosubstitué ou disubstitué, indépendamment l'un de l'autre, par un ou des groupes alkyle inférieur, alcényle inférieur, alcynyle

inférieur, phényl-alkyle inférieur, phényl-alcényle inférieur ou phényl-alcynyle inférieur, ou disubstitué par des groupes alkylène en C_1-C_{10} ou alkylidène en C_2-C_{10}, les groupes alkylène en C_1-C_{10} ou alkylidène en C_2-C_{10} étant éventuellement interrompus par -O-, ou représente PO_nH_2, n étant 2 ou 3; X_3 représente $-CH_2-$; R_3 est le groupe carboxy, 5-tétrazolyle, SO_3H, PO_2H_2, PO_3H_2 ou un groupe halogéno-(alkyl inférieur)-sulfamoyle; et les radicaux (hétéro)aromatiques, y compris les cycles A et B, étant éventuellement substitués, indépendamment les uns des autres, par des substituants choisis parmi des atomes d'halogène et des groupes hydroxy, alcoxy inférieur, alcényloxy inférieur, phényl-alcoxy inférieur, phénoxy, $S(O)_m$-R et des radicaux alkyle inférieur, alcényle inférieur ou alcynyle inférieur éventuellement substitués par un atome d'halogène ou par le groupe hydroxy, les radicaux alkyle inférieur, alcényle inférieur ou alcynyle inférieur étant éventuellement interrompus par -O-, et, dans le cas de radicaux (hétéro)aromatiques, étant éventuellement substitués en outre par le groupe carboxy ou par un groupe carboxy estérifié par un alcool dérivant d'un reste alkyle inférieur, phényl-alkyle inférieur, alcényle inférieur, alcynyle inférieur, (alcoxy inférieur)-alkyle inférieur, (alcoxy inférieur)-alcényle inférieur ou (alcoxy inférieur)-alcynyle inférieur, par le groupe carbamoyle ou par un groupe carbamoyle dans lequel le fragment amino est monosubstitué ou disubstitué, indépendamment l'un de l'autre, par un ou des groupes alkyle inférieur, alcényle inférieur, alcynyle inférieur, phényl-alkyle inférieur, phényl-alcényle inférieur ou phényl-alcynyle inférieur, ou disubstitué par des radicaux alkylène en C_1-C_{10} ou alkylidène en C_2-C_{10}, les radicaux alkylène en C_1-C_{10} ou alkylidène en C_2-C_{10} étant éventuellement interrompus par -O-, ou par le groupe formyle, un groupe di-(alcoxy inférieur)-méthyle ou oxy-(alkylène-oxy inférieur)-méthylène; sous forme libre ou sous forme de sel.

4. Composé selon la revendication 1, de formule I, dans lequel R_1 représente un radical alkyle inférieur, alcényle inférieur, alcynyle inférieur, halogéno-alkyle inférieur, -alcényle inférieur, -alcynyle inférieur, hydroxyalkyle inférieur, -alcényle inférieur, -alcynyle inférieur, cycloalkyle en C_3-C_7, cycloalcényle en C_3-C_7, phényl-alkyle inférieur, phényl-alcényle inférieur ou phényl-alcynyle inférieur; X_1 représente CO ou SO_2; X_2 représente un radical alkylène en C_1-C_{10} ou alkylidène en C_2-C_{10} qui sont éventuellement substitués par le groupe hydroxy ou par un radical cycloalkyle en C_3-C_7, cycloalcényle en C_3-C_7, phényle ou par un radical hétéroaromatique monocyclique à 5 ou 6 chaînons, comportant jusqu'à 4 hétéroatomes identiques ou différents, les radicaux cycliques étant pour leur part éventuellement substitués par un groupe carboxy éventuellement estérifié par un alcool dérivant d'un reste alkyle inférieur, phényl-alkyle inférieur, alcényle inférieur, alcynyle inférieur, (alcoxy inférieur)-alkyle inférieur, -alcényle inférieur ou -alcynyle inférieur, ou par un groupe carbamoyle dans lequel le fragment amino est éventuellement monosubstitué ou disubstitué, indépendamment l'un de l'autre, par un ou des radicaux alkyle inférieur, alcényle inférieur, alcynyle inférieur, phényl-alkyle inférieur, phényl-alcényle inférieur, phényl-alcynyle inférieur, ou disubstitué par des radicaux (alkylène inférieur)- ou (alkylène-oxy inférieur)-alkylène inférieur, le radical formyle, di-(alcoxy inférieur)-méthyle, oxy-(alkylène-oxy inférieur)-méthylène; R_2 représente un groupe carboxy éventuellement estérifié par un alcool dérivant d'un reste alkyle inférieur, phényl-alkyle inférieur, alcényle inférieur, alcynyle inférieur, (alcoxy inférieur)-alkyle inférieur, -alcényle inférieur ou -alcynyle inférieur, un radical carbamoyle dans lequel le fragment amino est éventuellement monosubstitué ou disubstitué, indépendamment l'un de l'autre, par un ou des groupes alkyle inférieur, alcényle inférieur, alcynyle inférieur, phényl-alkyle inférieur, phényl-alcényle inférieur, phényl-alcynyle inférieur, ou disubstitué par des radicaux (alkylène inférieur)- ou (alkylène-oxy inférieur)-alkylène inférieur, un radical amino dans lequel le fragment amino est éventuellement monosubstitué ou disubstitué, indépendamment l'un de l'autre, par un ou des radicaux alkyle inférieur, alcényle inférieur, alcynyle inférieur, phényl-alkyle inférieur, phényl-alcényle inférieur, phényl-alcynyle inférieur, ou disubstitué par des radicaux (alkylène inférieur)- ou (alkylène-oxy inférieur)-alkylène inférieur, un groupe (alcanoyl inférieur)-, phényl-(alcanoyl inférieur)-, benzoyl-, (alcane inférieur)-sulfonyl-, benzènesulfonyl-amino, formyle, di-(alcoxy inférieur)-méthyle, oxy-(alkylène-oxy inférieur)-méthylène, hydroxy, alcoxy inférieur, alcényloxy inférieur, phényl-alcoxy inférieur, phénoxy, $S(O)_m$-R, m représentant 0, 1 ou 2 et R représentant un atome d'hydrogène ou un groupe alkyle inférieur, alcényle inférieur ou alcynyle inférieur, un radical alcanoyle inférieur, sulfamoyle, dans lequel le fragment amino est éventuellement monosubstitué ou disubstitué, indépendamment l'un de l'autre, par un ou des groupes alkyle inférieur, alcényle inférieur, alcynyle inférieur, phényl-alkyle inférieur, phényl-alcényle inférieur ou phényl-alcynyle inférieur, ou disubstitué par des radicaux (alkylène inférieur)- ou (alkylène-oxy inférieur)-alkylène inférieur, ou représente PO_nH_2, n représentant 2 ou 3; X_3 représente $-CH_2-$; R_3 est le groupe carboxy, 5-tétrazolyle, SO_3H, PO_2H_2, PO_3H_2 ou un groupe halogéno-(alkyl inférieur)-sulfamoyle; les radicaux (hétéro)aromatiques, y compris les cycles A et B, étant éventuellement substitués, indépendamment les uns des autres, par un ou plusieurs substituants choisis parmi des atomes d'halogène et des groupes hydroxy, alcoxy inférieur, alcényloxy inférieur, des radicaux alkyle inférieur, alcényle inférieur, alcynyle inférieur, (alcoxy inférieur)-alkyle inférieur, -alcényle inférieur, -alcynyle inférieur, (alcényloxy inférieur)-alkyle inférieur, -alcényle inférieur et -alcynyle inférieur, éventuellement substitués chacun par un atome d'halogène ou par le groupe hydroxy, sous forme libre ou sous forme de sel.

5. Composé selon la revendication 1, de formule I, dans lequel X_2 représente un radical alkylène en C_1-C_{10} ou alkylidène en C_2-C_{10} qui sont éventuellement substitués par le groupe hydroxy ou par un groupe cycloalkyle en C_3-C_7,

cycloalcényle en C_3-C_7, phényle ou par un radical hétéroaromatique monocyclique à 5 ou 6 chaînons, comportant jusqu'à 4 hétéroatomes identiques ou différents, un atome de carbone d'un radical alkylène en C_1-C_{10} ou alkylidène en C_2-C_{10} pouvant être ponté par un groupe alkylène en C_2-C_6, et les radicaux cycliques étant pour leur part éventuellement substitués par un groupe carboxy éventuellement estérifié par un alcool dérivant d'un reste alkyle inférieur, phényl-alkyle inférieur, alcényle inférieur, alcynyle inférieur, (alcoxy inférieur)-alkyle inférieur, -alcényle inférieur ou -alcynyle inférieur, par un groupe carbamoyle dans lequel le fragment amino est éventuellement monosubstitué ou disubstitué, indépendamment l'un de l'autre, par un ou des groupes alkyle inférieur, alcényle inférieur, alcynyle inférieur, phényl-alkyle inférieur, phényl-alcényle inférieur, phényl-alcynyle inférieur, ou disubstitué par des radicaux (alkylène inférieur)- ou (alkylène-oxy inférieur)-alkylène inférieur, par le groupe formyle, par un groupe di-(alcoxy inférieur)-méthyle, ou par un groupe oxy-(alkylène-oxy inférieur)-méthylène, ou X_2 représente un groupe cycloalkylène en C_3-C_7; X_3 représente un groupe alkylène inférieur ou alkylidène inférieur; les variables X_1, R_1, R_2, R_3 ont les significations indiquées dans la revendication 4; et les cycles (hétéro)aromatiques, y compris les cycles A et B, peuvent être substitués comme indiqué dans la revendication 4, sous forme libre ou sous forme de sel.

6. Composé selon la revendication 1, de formule I, dans lequel R_1 représente un radical alkyle inférieur, alcényle inférieur, halogéno-alkyle inférieur, -alcényle inférieur, hydroxy-alkyle inférieur, un radical cycloalkyle à 3-7 chaînons ou phényl-alkyle inférieur; X_1 représente CO, SO_2 ou -O-C(=O)-, l'atome de carbone du groupe carbonyle étant lié à l'atome d'azote indiqué dans la formule I; X_2 représente un radical alkylène en C_1-C_{10} ou alkylidène en C_1-C_7, qui sont éventuellement substitués par le groupe hydroxy, carboxy, amino, guanidino, un radical cycloalkyle à 3-7 chaînons, cycloalcényle à 3- 7 chaînons, phényle, pyrrolyle, pyrazolyle, imidazolyle, triazolyle, tétrazolyle, furyle, thiényle ou pyridyle, qui pour leur part peuvent être éventuellement substitués en outre par un radical carboxy, (alcoxy inférieur)-carbonyle, phényl-(alcoxy inférieur)-carbonyle, par un radical carbamoyle dans lequel le fragment amino peut éventuellement être monosubstitué ou disubstitué, indépendamment l'un de l'autre, par un ou des groupes alkyle inférieur ou phényl-alkyle inférieur, ou un radical formyle, di-(alcoxy inférieur)-méthyle ou oxy-(alkylène-oxy inférieur)-méthylène; R_2 représente un groupe carboxy, (alcoxy inférieur)-, phényl-(alcoxy inférieur)-, (alcényloxy inférieur)-, (alcoxy inférieur)-(alcoxy inférieur)-carbonyle, un radical carbamoyle dans lequel le fragment amino est éventuellement monosubstitué ou disubstitué, indépendamment l'un de l'autre, par un ou des radicaux alkyle inférieur ou phényl-alkyle inférieur, ou est disubstitué par des radicaux alkylène inférieur, éventuellement condensés, au niveau de deux atomes de carbone contigus, avec un cycle benzénique, ou par des radicaux (alkylène-oxy inférieur)-alkylène inférieur, un radical amino dans lequel le fragment amino est éventuellement monosubstitué ou disubstitué, indépendamment l'un de l'autre, par un ou des radicaux alkyle inférieur ou phényl-alkyle inférieur, ou est disubstitué par des radicaux (alkylène inférieur)- ou (alkylène-oxy inférieur)-alkylène inférieur, un groupe (alcanoyl inférieur)-, phényl-(alcanoyl inférieur)-, benzoyl-, (alcane inférieur)-sulfonyl-, benzènesulfonylamino, formyle, di-(alcoxy inférieur)-méthyle, oxy-(alkylène-oxy inférieur)-méthylène, hydroxy, alcoxy inférieur, phényl-alcoxy inférieur, phénoxy, $S(O)_m$-R, m représentant 0, 1 ou 2 et R représentant un groupe alkyle inférieur, alcanoyle inférieur, sulfamoyle, dans lequel le fragment amino est éventuellement monosubstitué ou disubstitué, indépendamment l'un de l'autre, par un ou des groupes alkyle inférieur ou phényl-alkyle inférieur, ou représente PO_nH_2, n représentant 2 ou 3; X_3 est le groupe méthylène; R_3 représente le groupe carboxy, 5-tétrazolyle, SO_3H, PO_2H_2, PO_3H_2 ou un groupe halogéno-(alkyl inférieur)-sulfamoyle; et les radicaux (hétéro)aromatiques, y compris les cycles A et B, sont éventuellement substitués chacun en outre par un ou plusieurs substituants choisis parmi des atomes d'halogène et des groupes hydroxy, alcoxy inférieur, et des radicaux alkyle inférieur ou (alcoxy inférieur)-alkyle inférieur éventuellement substitués chacun par un atome d'halogène ou par le groupe hydroxy, sous forme libre ou sous forme de sel.

7. Composé selon la revendication 1, de formule I, dans lequel R_1 représente un radical alkyle inférieur, alcényle inférieur, halogéno-alkyle inférieur, -alcényle inférieur, hydroxy-alkyle inférieur, un radical cycloalkyle à 3-7 chaînons ou phényl-alkyle inférieur; X_1 représente CO ou SO_2; X_2 représente un radical alkylène en C_1-C_{10} ou alkylidène en C_1-C_7, qui sont éventuellement substitués par un groupe hydroxy, un radical cycloalkyle à 3-7 chaînons, cycloalcényle à 3-7 chaînons, phényle, pyrrolyle, pyrazolyle, imidazolyle, triazolyle, tétrazolyle, furyle, thiényle ou pyridyle, qui peuvent pour leur part être éventuellement substitués en outre par un groupe carboxy, (alcoxy inférieur)-carbonyle, phényl-(alcoxy inférieur)-carbonyle, carbamoyle dans lequel le fragment amino est éventuellement monosubstitué ou disubstitué, indépendamment l'un de l'autre, par un ou des groupes alkyle inférieur ou phényl-alkyle inférieur, le radical formyle, un radical di-(alcoxy inférieur)-méthyle ou oxy-(alkylène-oxy inférieur)-méthylène; R_2 représente un radical carboxy, (alcoxy inférieur)-, phényl-(alcoxy inférieur)-, (alcényloxy inférieur)-, (alcoxy inférieur)-(alcoxy inférieur)-carbonyle, un radical carbamoyle dans lequel le fragment amino est éventuellement monosubstitué ou disubstitué, indépendamment l'un de l'autre, par un ou des groupes alkyle inférieur, phényl-alkyle inférieur, ou disubstitué par des radicaux (alkylène inférieur)-, ou (alkylène-oxy inférieur)- alkylène inférieur, un radical amino dans lequel le fragment amino est éventuellement monosubstitué ou disubstitué, indépendamment l'un de l'autre, par un ou des groupes alkyle inférieur, phényl-alkyle inférieur, ou disubstitué par des radicaux (alkylène inférieur)-

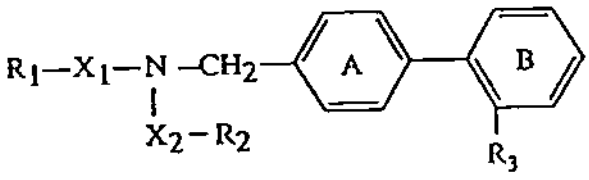
ou (alkylène-oxy inférieur)-alkylène inférieur, un groupe (alcanoyl inférieur)-, phényl-(alcanoyl inférieur)-, benzoyl-, (alcane inférieur)-sulfonyl-, benzènesulfonylamino, formyle, di-(alcoxy inférieur)-méthyle, oxy-(alkylène-oxy inférieur)-méthylène, hydroxy, alcoxy inférieur, phényl-alcoxy inférieur, phénoxy, $S(O)_m$-R, m représentant 0, 1 ou 2 et R représentant un groupe alkyle inférieur, un radical alcanoyle inférieur, sulfamoyle dans lequel le groupe amino est éventuellement monosubstitué ou disubstitué, indépendamment l'un de l'autre, par des groupes alkyle inférieur, phényl-alkyle inférieur, ou représente PO_nH_2, n représentant 2 ou 3; X_3 est le groupe méthylène; R_3 représente le groupe carboxy, 5-tétrazolyle, SO_3H, PO_2H_2, PO_3H_2 ou un groupe halogéno-(alkyl inférieur)-sulfamoyle; et les radicaux (hétéro)aromatiques, y compris les cycles A et B, sont éventuellement substitués chacun en outre par un ou plusieurs substituants choisis parmi des atomes d'halogène et des groupes hydroxy, alcoxy inférieur, des groupes alkyle inférieur ou (alcoxy inférieur)-alkyle inférieur éventuellement substitués chacun par un atome d'halogène ou par le groupe hydroxy, sous forme libre ou sous forme de sel.

8. Composé selon la revendication 1, de formule I, dans lequel X_2 représente un radical alkylène en C_1-C_{10} ou alkylidène en C_1-C_7, qui sont éventuellement substitués par un groupe hydroxy, un radical cycloalkyle à 3-7 chaînons, cycloalcényle à 3-7 chaînons, phényle, pyrrolyle, pyrazolyle, imidazolyle, triazolyle, tétrazolyle, furyle, thiényle ou pyridyle, qui peuvent pour leur part être éventuellement substitués en outre par un groupe carboxy, (alcoxy inférieur)-carbonyle, phényl-(alcoxy inférieur)-carbonyle, carbamoyle dans lequel le fragment amino est éventuellement monosubstitué ou disubstitué, indépendamment l'un de l'autre, par un ou des groupes alkyle inférieur ou phényl-alkyle inférieur, ou peuvent être substitués par le groupe formyle, par un groupe di-(alcoxy inférieur)-méthyle, ou par un groupe oxy-(alkylène-oxy inférieur)-méthylène, un atome de carbone d'un radical alkylène en C_1-C_{10} ou alkylidène en C_1-C_7 pouvant être ponté par un groupe alkylène en C_2-C_6, ou X_2 représente un groupe cycloalkylène en C_3-C_7; X_3 représente un groupe alkylène inférieur ou alkylidène inférieur; les variables X_1, R_1, R_2, R_3 ont les significations indiquées dans la revendication 7, et les cycles (hétéro)-aromatiques, y compris les cycles A et B, peuvent être substitués comme indiqué dans la revendication 7, sous forme libre ou sous forme de sel.

9. Composé selon la revendication 1, de formule I, dans lequel les variables R_1, X_1, R_3 ont les significations indiquées respectivement dans les revendications 1 à 7; X_2 représente un radical alkylène inférieur ou alkylidène inférieur éventuellement substitué par un groupe hydroxy, cycloalkyle à 3-7 chaînons, phényle ou imidazolyle; et R_2 représente un radical carboxy, (alcoxy inférieur)-, phényl-(alcoxy inférieur)-, (alcoxy inférieur)-(alcoxy inférieur)carbonyle, un radical carbamoyle qui est éventuellement monosubstitué ou disubstitué, indépendamment l'un de l'autre, par un ou des groupes alkyle inférieur ou phényl-alkyle inférieur, un radical amino, (alcanoyl inférieur)-, phényl-(alcanoyl inférieur)-, (alcane inférieur)-sulfonyl-amino, hydroxy, alcoxy inférieur, phényl-alcoxy inférieur ou phénoxy; X_3 représente -CH_2-; les radicaux (hétéro)aromatiques, y compris les cycles A et B, étant éventuellement substitués chacun par un ou plusieurs substituants choisis parmi des atomes d'halogène et des groupes trifluorométhyle, hydroxy, alcoxy inférieur, alkyle inférieur, hydroxyalkyle inférieur ou (alcoxy inférieur)-alkyle inférieur, sous forme libre ou sous forme de sel.

10. Composé selon la revendication 1, de formule I, dans lequel X_2 représente un radical alkylène inférieur ou alkylidène inférieur éventuellement substitué par un groupe hydroxy, cycloalkyle à 3-7 chaînons, cycloalcényle à 7 chaînons, phényle ou imidazolyle, un atome de carbone d'un radical alkylène inférieur ou alkylidène inférieur pouvant être ponté par un groupe alkylène en C_2-C_6, ou X_2 représente un groupe cycloalkylène en C_3-C_7; les variables X_1, X_3, R_1, R_2, R_3 ont les significations indiquées dans les revendications 7 à 9; et les cycles A et B, peuvent être substitués comme indiqué dans la revendication 9, sous forme libre ou sous forme de sel.

11. Composé selon la revendication 1, de formule

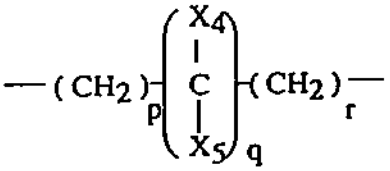


(Ia),

dans laquelle les variables R_1, X_1, X_2, R_2 et R_3 ont les significations données chacune dans l'une des revendications 1 à 10, et les cycles A et B, peuvent être substitués comme indiqué dans la revendication 10, sous forme libre ou sous forme de sel.

12. Composé selon la revendication 1, de formule Ia, dans lequel X_2 représente un radical alkylène inférieur ou alkylidène inférieur éventuellement substitué par un groupe hydroxy ou par un groupe cycloalkyle à 3-7 chaînons, un atome de carbone d'un radical alkylène inférieur ou alkylidène inférieur pouvant être ponté par un groupe alkylène en C_2-C_6, ou dans lequel X_2 représente un groupe cycloalkylène en C_3-C_7, et les variables R_1, X_1, R_2 et R_3 ont les significations indiquées chacune dans l'une des revendications 1 à 10, et les cycles A et B peuvent être substitués comme indiqué dans la revendication 10, sous forme libre ou sous forme de sel.

13. Composé selon la revendication 1, de formule Ia, dans lequel X_2 représente le groupe de formule



(Ib)

dans laquelle p représente 0 ou 1, q représente 1 et r représente 0 ou 1, ou dans laquelle p représente 1 à 8 et q ainsi que r représentent chacun 0; X_4 représente un radical phényle ou alkyle inférieur éventuellement substitué par un groupe hydroxy, cycloalkyle à 3-7 chaînons, phényle ou imidazolyle; et X_5 représente un atome d'hydrogène ou un groupe alkyle inférieur; R_2 représente un radical carboxy, (alcoxy inférieur)-carbonyle, phényl-(alcoxy inférieur)-carbonyle, (alcoxy inférieur)-(alcoxy inférieur)-carbonyle, hydroxy, alcoxy inférieur, phényl-alcoxy inférieur, phénoxy, amino, alcanoylamino inférieur, phénylalcanoylamino inférieur ou (alcane inférieur)-sulfonylamino; et les variables R_1, X_1 et X_3 ont les significations indiquées respectivement dans l'une des revendications 1 à 7; les radicaux (hétéro)-aromatiques, y compris les cycles A et B, étant éventuellement substitués chacun par un atome d'halogène ou par un groupe trifluorométhyle, hydroxy, alcoxy inférieur, alkyle inférieur ou hydroxyalkyle inférieur, sous forme libre ou sous forme de sel.

14. Composé selon la revendication 1, de formule Ia, dans lequel X_2 représente le groupe de formule Ib, dans lequel p représente 0 ou 1, q représente 1 et r représente 0 ou 1, ou dans lequel p représente 1 à 8 et q ainsi que r représentent chacun 0; X_4 représente un radical phényle ou alkyle inférieur éventuellement substitué par un groupe hydroxy, cycloalkyle à 3-7 chaînons, phényle ou imidazolyle; et X_5 représente un atome d'hydrogène ou un groupe alkyle inférieur; ou X_4 et X_5 forment ensemble un radical alkylène en C_2-C_6, tel qu'alkylène en C_4-C_5, ou X_2 représente un radical cycloalkylène en C_3-C_7, tel que cycloalkylène en C_5-C_6; R_2 représente un radical carboxy, (alcoxy inférieur)-carbonyle, phényl-(alcoxy inférieur)-carbonyle, (alcoxy inférieur)-(alcoxy inférieur)-carbonyle, hydroxy, alcoxy inférieur, phényl-alcoxy inférieur, phénoxy, amino, alcanoylamino inférieur, phényl-alcanoylamino inférieur ou (alcane inférieur)-sulfonylamino; et les variables R_1, X_1 et R_3 ont les significations indiquées respectivement dans l'une des revendications 1 à 7; les radicaux (hétéro)aromatiques, y compris les cycles A et B, étant éventuellement substitués chacun par un atome d'halogène ou par un groupe trifluorométhyle, hydroxy, alcoxy inférieur, alkyle inférieur ou hydroxyalkyle inférieur, sous forme libre ou sous forme de sel.

15. Composé selon la revendication 1, de formule Ia, dans lequel R_1 représente un radical alkyle inférieur, tel qu'un radical alkyle en C_3-C_5, ou un radical alcényle inférieur, tel qu'un radical alcényle en C_3-C_5; X_1 représente CO ou SO_2; X_2 représente le groupe de formule Ib, dans lequel p et r représentent 0 ou 1, et q représente 1; X_4 représente un radical alkyle inférieur, tel qu'un radical alkyle en C_1-C_4, ou phényle, éventuellement substitué par un groupe hydroxy, cycloalkyle à 3-7 chaînons tel que cyclohexyle, par un groupe phényle ou imidazolyle, tel que 4-imidazolyle, éventuellement substitué par un atome d'halogène ou par le groupe hydroxy; et X_5 représente un atome d'hydrogène ou un groupe alkyle inférieur, tel qu'un groupe alkyle en C_1-C_4; ou X_4 et X_5 représentent ensemble un groupe alkylène en C_2-C_6, tel qu'un groupe alkylène en C_4-C_5; ou X_2 représente un radical cycloalkylène en C_3-C_7, tel qu'un radical cycloalkylène en C_5-C_6,; R_2 représente un radical carboxy, (alcoxy inférieur)-carbonyle tel qu'un groupe alcoxy(C_2-C_5)-carbonyle, phényl-(alcoxy inférieur)-carbonyle, tel que phényl-alcoxy-(C_1-C_4)-carbonyle, un radical (alcoxy inférieur)-(alcoxy inférieur)-carbonyle, tel qu'un radical alcoxy(C_1-C_4)-alcoxy(C_2-C_5)-carbonyle, un groupe hydroxy ou alcoxy inférieur, tel qu'un groupe alcoxy en C_1-C_4; et R_3 représente le groupe carboxy ou 5-tétrazolyle; les radicaux (hétéro)aromatiques, y compris les cycles A et B, étant éventuellement substitués chacun par un atome d'halogène ou par un groupe trifluorométhyle, hydroxy, alcoxy inférieur, alkyle inférieur ou hydroxyalkyle inférieur, sous forme libre ou sous forme de sel.

16. Composé selon la revendication 1, de formule Ia, dans lequel R_1 représente un radical alkyle inférieur, tel qu'alkyle en C_3-C_5, ou alcényle inférieur, tel qu'alcényle en C_3-C_5; X_1 représente CO ou SO_2; X_2 représente le groupe de

formule Ib, dans lequel p et r représentent 0 ou 1 et q représente 1; X_4 représente un radical alkyle inférieur, tel qu'un radical alkyle en C_1-C_4, ou phényle, éventuellement substitué par un groupe hydroxy, cycloalkyle à 3-7 chaînons, phényle ou imidazolyle, tel que 4-imidazolyle, éventuellement substitué par un atome d'halogène ou par le groupe hydroxy; et X_5 représente un atome d'hydrogène ou un groupe alkyle inférieur, tel qu'un groupe alkyle en C_1-C_4; R_2 représente un groupe carboxy, (alcoxy inférieur)-carbonyle, tel qu'un groupe alcoxy(C_2-C_5)-carbonyle, phényl-(alcoxy inférieur)-carbonyle, tel que phényl-alcoxy(C_1-C_4)-carbonyle, (alcoxy inférieur)-(alcoxy inférieur)-carbonyle tel qu'un groupe alcoxy(C_1-C_4)-alcoxy-(C_2-C_5)-carbonyle, un groupe hydroxy ou alcoxy inférieur tel qu'un groupe alcoxy en C_1-C_4; et R_3 représente le groupe carboxy ou 5-tétrazolyle; les radicaux (hétéro)aromatiques, y compris les cycles A et B, étant éventuellement substitués chacun par un atome d'halogène ou par un groupe trifluorométhyle, hydroxy, alcoxy inférieur, alkyle inférieur ou hydroxyalkyle inférieur, sous forme libre ou sous forme de sel.

17. Composé selon la revendication 1, de formule Ia, dans lequel R_1 représente un radical alkyle inférieur, tel qu'un radical alkyle en C_3-C_5, ou bien un radical alcényle inférieur, tel qu'alcényle en C_3-C_5; X_1 représente CO ou SO_2; X_2 représente le groupe de formule Ib dans lequel p représente un nombre entier allant de 1 à 8 et q ainsi que r représentent 0; R_2 représente un groupe hydroxy, alcoxy inférieur tel qu'alcoxy en C_1-C_4, phényl-alcoxy inférieur tel que phényl-alcoxy(C_1-C_4), phénoxy, un groupe alcanoyl-amino inférieur, tel qu'alcanoyl(C_1-C_4)-amino, un groupe phényl-(alcanoyl inférieur)-amino, tel que phényl-alcanoyl(C_1-C_4)-amino, un groupe (alcane inférieur)-sulfonylamino, tel qu'un groupe alcane(C_1-C_4)-sulfonylamino; et R_3 représente le groupe carboxy ou, en premier lieu, 5-tétrazolyle; les radicaux (hétéro)aromatiques, y compris les cycles A et B, étant éventuellement substitués chacun par un atome d'halogène ou par un groupe trifluorométhyle, hydroxy, alcoxy inférieur, alkyle inférieur ou hydroxyalkyle inférieur, sous forme libre ou sous forme de sel.

18. Composé selon la revendication 1, de formule Ia, dans lequel R_1 représente un radical alkyle en C_3-C_5 ou, en second lieu, un radical alcényle en C_3-C_5; X_1 représente CO ou SO_2; X_2 représente un groupe de formule Ib dans lequel p et r représentent, indépendamment l'un de l'autre, 0 ou 1, et q représente 1; X_4 représente un groupe alkyle en C_1-C_4, hydroxyalkyle en C_1-C_4, cycloalkyl(C_3-C_7)-alkyle(C_1-C_4), phényl-alkyle(C_1-C_4), ou imidazolyl-alkyle(C_1-C_4); et X_5 représente un atome d'hydrogène ou un groupe alkyle en C_1-C_4; ou X_4 et X_5 représentent ensemble le groupe tétraméthylène ou pentaméthylène; R_2 représente un groupe carboxy ou alcoxy-(C_2-C_5)-carbonyle, ainsi qu'un groupe phényl-alcoxy(C_1-C_4)-carbonyle; et R_3 représente le groupe carboxy ou 5-tétrazolyle, sous forme libre ou sous forme de sel.

19. Composé selon la revendication 1, de formule Ia, dans lequel R_1 représente un groupe alkyle en C_3-C_5 ou, en second lieu, un groupe alcényle en C_3-C_5; X_1 représente CO ou SO_2; X_2 représence un groupe de formule Ib dans lequel p et r représentent chacun 0 ou 1 et q représente 1; X_4 représente un groupe alkyle en C_1-C_4, hydroxyalkyle en C_1-C_4, cycloalkyl(C_3-C_7)-alkyle(C_1-C_4), phényl-alkyle(C_1-C_4), ou imidazolyl-alkyle(C_1-C_4); et X_5 représente un atome d'hydrogène; R_2 représente un groupe carboxy ou alcoxy(C_2-C_5)-carbonyle, ou un groupe phényl-alcoxy(C_1-C_4)-carbonyle; et R_3 représente le groupe carboxy ou 5-tétrazolyle, sous forme libre ou sous forme de sel.

20. Composé selon la revendication 1, de formule Ia, dans lequel R_1 représente un groupe alkyle en C_3-C_5; X_1 représente CO; X_2 représente un groupe de formule Ib dans lequel q et r représentent 0 et p représente 1 à 3, ou dans lequel p et q représentent 1 et r représente 0; X_4 représente un groupe alkyle en C_1-C_4; X_5 représente un atome d'hydrogène ou un groupe alkyle en C_1-C_4; R_2 représente un groupe carboxy, alcoxy(C_2-C_5)-carbonyle; et R_3 représente le groupe carboxy ou 5-tétrazolyle, sous forme libre ou sous forme de sel.

21. Composé selon l'une des revendications 1 à 20, dans lequel R_3 représente le groupe 5-tétrazolyle, sous forme libre ou sous forme de sel.

22. Composé selon la revendication 1, de formule Ia, dans lequel R_1 représente un groupe alkyle en C_3-C_5; X_1 représente CO; X_2 représente un groupe de formule Ib dans lequel p représente 0 ou 1, r représente 0 et q représente 1; X_4 représente un groupe alkyle en C_1-C_4; et X_5 représente un atome d'hydrogène ou un groupe alkyle en C_1-C_4; ou X_4 et X_5 représentent ensemble le groupe tétraméthylène ou pentaméthylène; R_2 représente un groupe carboxy ou alcoxy(C_2-C_5)-carbonyle; et R_3 représente le groupe 5-tétrazolyle, sous forme libre ou sous forme de sel.

23. Composé selon la revendication 1, de formule Ia, dans lequel R_1 représente un groupe alkyle en C_3-C_5; X_1 représente CO; X_2 représente un groupe de formule Ib dans lequel p représente 0 ou 1, r représente 0 et q représente 1; X_4 et X_5 représentent ensemble le groupe tétraméthylène ou pentaméthylène; R_2 représente un groupe carboxy ou alcoxy(C_2-C_5)-carbonyle; et R_3 représente le groupe tétrazolyle, sous forme libre ou sous forme de sel.

24. Composé selon la revendication 1, de formule Ia, dans lequel R_1 représente un groupe alkyle en C_3-C_5; X_1 représente CO; X_2 représente un groupe de formule Ib dans lequel p et r représentent 0 ou 1 et q représente 1: X_4 représente un groupe alkyle en C_1-C_4; et X_5 représente un atome d'hydrogène; R_2 représente un groupe carboxy ou alcoxy(C_2-C_5)-carbonyle; et R_3 représente le groupe 5-tétrazolyle, sous forme libre ou sous forme de sel.

25. Composé de formule Ia selon l'une des revendications 13 à 24, dans lequel X_2 représente un groupe de formule Ib, q représente 1 et X_4 et X_5 ont des significations différentes, sous forme libre ou sous forme de sel, et dans lequel l'atome de carbone asymétrique concerné, portant les variables X_4 et X_5, a la configuration S.

26. (S)-N-(1-carboxy-2-méthylprop-1-yl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine, sous forme libre ou sous forme de sel, selon la revendication 1.

27. N-(2-carboxy-2,2-tétraméthylène-éthyl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine, sous forme libre ou sous forme de sel, selon la revendication 1.

28. N-[2-carboxy-2-éthylbut-1-yl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine, sous forme libre ou sous forme de sel, selon la revendication 1.

29. (S)-N-(1-carboxy-2-méthylprop-1-yl)-N-éthoxycarbonyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine, sous forme libre ou sous forme de sel, selon la revendication 1.

30. N-(1-carboxycyclohexyl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine, sous forme libre ou sous forme de sel, selon la revendication 1.

31. Composé selon la revendication 1, choisi parmi les suivants:
(S)-N-(1-carboxyéthyl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-(2-hydroxyéthyl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-(2-éthoxycarbonyl-2,2-tétraméthylène-éthyl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-(2-éthoxycarbonyl-2-éthylbut-1-yl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-(2-éthoxycarbonyl-2-méthylprop-1-yl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
(S)-N-(1-hydroxyméthyl-2-méthylprop-1-yl)-N-pentanoyl-N-[2'-1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-(2-éthoxycarbonyl-2,2-pentaméthylène-éthyl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
(S)-N-(1-carboxy-2-méthylprop-1-yl)-N-propyloxycarbonyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-(2-carboxy-2-méthylpropyl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-(2-carboxy-2,2-pentaméthylène-éthyl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
(S)-N-(1-aminocarbonyl-2-méthylprop-1-yl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine
et
(S)-N-(1-carboxy-2-méthylprop-1-yl)-N-5-oxopent-N-5-yl)-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
chacun sous forme libre ou sous forme de sel.

32. Composé selon la revendication 1, choisi parmi les suivants:
N-carboxyméthyl-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
(S)-N-(1-méthoxycarbonyléthyl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-[1-carboxy-2-(4-fluorophényl)éthyl]-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-[2-(4-fluorophényl)-1-méthoxycarbonyléthyl]-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-[2-(4-fluorophényl)-1-hydroxyméthyléthyl]-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-(2'-carboxybiphényl-4-ylméthyl)-N-[1-carboxy-2-(4-fluorophényl)éthyl]-N-pentanoylamine,
N-(2'-carboxybiphényl-4-ylméthyl)-N-[2-(4-fluorophényl)-1-méthoxycarbonyléthyl]-N-pentanoylamine,
(S)-N-(2'-carboxybiphényl-4-ylméthyl)-N-(1-hydroxyméthyl-2-phényléthyl)-N-pentanoylamine,
(S)-N-(2'-carboxybiphényl-4-ylméthyl)-N-(1-hydroxyméthyl-2-imidazol-4-yléthyl)-N-pentanoylamine,
(R)-N-(1-carboxyéthyl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
(1S),(2S)-N-(1-carboxy-2-méthylbut-1-yl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
(1S),(2S)-N-(1-méthoxycarbonyl-2-méthylbut-1-yl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]-amine,
(S)-N-(1-carboxybut-1-yl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,

(S)-N-(1-méthoxycarbonylbut-1-yl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
(S)-N-(1-carboxyéthyl)-N-hexanoyl-N-[2'-(1H-tétrazol-5-yl)-biphényl-4-ylméthyl]amine,
(S)-N-butanoyl-N-(1-carboxyéthyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
(S)-N-(1-carboxyprop-1-yl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)-biphényl-4-ylméthyl]amine,
(S)-N-(1-carboxy-2-cyclohexyléthyl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)-biphényl-4-ylméthyl]amine,
(S)-N-(2-cyclohexyl-1-méthoxycarbonyléthyl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)-biphényl-4-ylméthyl]amine,
(R)-N-(1-carboxy-2-méthylprop-1-yl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)-biphényl-4-ylméthyl]amine,
N-(2-méthoxyéthyl)-N-pentanoyl-N-[2'-1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-(2-benzyloxyéthyl)-N-pentanoyl-N-[2'-1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-(3-méthoxyprop-1-yl)-N-pentanoyl-N-[2'-1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-(3-benzyloxyprop-1-yl)-N-pentanoyl-N-[2'-1H-tétrazol-5-yl)-biphényl-4-ylméthyl]amine,
N-(3-hydroxyprop-1-yl)-N-pentanoyl-N-[2'-1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-(1-méthoxycarbonyl-1-méthyléthyl)-N-pentanoyl-N-[2'-1H-tétrazol-5-yl)-biphényl-4-ylméthyl]amine,
N-(2-carboxyéthyl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-(2-carboxyprop-1-yl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-(1-carboxy-1-méthyléthyl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-(5-hydroxypent-1-yl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-(1-carboxyprop-2-yl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-(2-éthoxycarbonyl-3-méthylbut-1-yl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl)amine,
N-(2-carboxy-3-méthylbut-1-yl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-(3-phénoxyprop-1-yl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-[2-(4-hydroxyphényl)éthyl]-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-[3-(4-hydroxyphényl)prop-1-yl]-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-[8-hydroxyoct-1-yl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-[2-méthanesulfonylaminoéthyl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-(3-acétylaminoprop-1-yl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-(2-méthoxy-2-oxo-1-phényléthyl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-(4-hydroxybut-2-yl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-(2-hydroxy-1-phényléthyl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-[3-(4-hydroxybenzylcarbonylamino)prop-1-yl]-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-(3-éthoxycarbonylcyclohexyl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-(3-carboxycyclohexyl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
cis-N-(4-carboxycyclohexyl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
cis-N-(2-éthoxycarbonylcyclohexyl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
cis-N-(2-carboxycyclohexyl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-[2-[2-(4-hydroxyphényl)éthylaminocarbonyl]-2,2-tétraméthylène-éthyl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
(S)-N-(1-[2-(4-hydroxyphényl)éthylaminocarbonyl]-2-méthylprop-1-yl)]-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
(S)-N-(1-carboxy-2,2-diméthylprop-1-yl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
(S)-N-(1-méthoxycarbonyl-2-méthylprop-1-yl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-(4-phénoxybut-1-yl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-(2-hydroxy-1-phényl-2-oxoéthyl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
(S)-N-(1-benzyloxycarbonyl-2-méthylprop-1-yl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-butanoyl-N-(1-carboxy-1-méthyléthyl)-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-(4-hydroxybut-1-yl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
(S)-N-(1-benzyloxycarbonyl-2-méthylprop-1-yl)-N-[3-bromo-2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]-N-pentanoylamine,
(S)-N-[3-bromo-2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]-N-(1-carboxy-2-méthylprop-1-yl)-N-pentanoylamine,
N-(2-acétylaminoéthyl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-[2-(n-butoxycarbonyl)-2,2-tétraméthylène-éthyl]-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-(2-benzylaminocarbonyl-2,2-tétraméthylène-éthyl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,

(S)-N-butyloxycarbonyl-N-(1-carboxy-2-méthylprop-1-yl)-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
(S)-N-(1-carboxy-2-méthylprop-1-yl)-N-méthoxycarbonyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-(2-diéthylaminocarbonyl-2,2-tétraméthylène-éthyl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-(2-méthyl-2-morpholine-4-ylcarbonylpropyl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-(1-carboxycyclopentyl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-(1-carboxy-1-éthylprop-1-yl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl-)biphényl-4-ylméthyl]amine,
(S)-N-(5-amino-1-carboxypent-1-yl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-butanesulfonyl-N-(2-éthoxycarbonyl-2,2-pentaméthylène-éthyl)-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-butanesulfonyl-N-(2-carboxy-2,2-pentaméthylène-éthyl)-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-butanesulfonyl-N-(2-éthoxycarbonyl-2-méthylprop-1-yl)-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-butanesulfonyl-N-(2-carboxy-2-méthylprop-1-yl)-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
(S)-N-butanesulfonyl-N-(1-tert-butoxycarbonyléthyl)-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
(S)-N-butanesulfonyl-N-(1-carboxyéthyl)-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
(S)-N-butanesulfonyl-N-(1-carboxy-2-méthylprop-1-yl)-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
(S)-N-(2-méthyl-1-méthylaminocarbonylprop-1-yl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
(S)-N-(1-diméthylaminocarbonyl-2-méthylprop-1-yl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
(2)-N-(2-méthyl-1-morpholine-4-ylcarbonylprop-1-yl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
(S)-N-(2'-carboxybiphényl-4-ylméthyl)-N-(1-carboxy-2-méthyl-prop-1-yl)-N-pentanoylamine,
(S)-N-(1,2-dicarboxyéthyl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
(S)-N-(1-carboxy-3-phénylprop-1-yl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
(S)-N-(2-cyclohexyl-1-hydroxyméthyl-éthyl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
(R)-N-(1-méthoxycarbonyl-2-méthylprop-1-yl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
(S)-N-(2-hydroxy-1-méthoxycarbonyl-éthyl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-pentanoyl-N-(1H-tétrazol-5-ylméthyl)-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-pentanoyl-N-pyrid-3-ylméthyl)-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
(S)-N-(1-carboxy-4-guanidinobut-1-yl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-(2-hydroxy-1-méthoxycarbonylprop-1-yl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-(1-benzyloxycarbonyl-1-méthyléthyl)-N-butanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
(S)-N-(1-carboxy-3-méthylbut-1-yl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-(1-carboxy-2-hydroxyéthyl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
(S)-N-(1-carboxy-2-hydroxyéthyl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
(S)-N-(2-méthyl-1-(2-phényléthylaminocarbonyl)prop-1-yl]-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
(S)-N-(2-benzyloxy-1-hydroxyméthyléthyl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
(S)-N-(1-carboxy-2-méthylprop-1-yl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-3-ylméthyl]amine,
(S)-N-(1-carboxy-2-méthylprop-1-yl)-N-pentanoyl-N-[3'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
(S)-N-[2-méthyl-1-(1,2,3,4-tétrahydroquinol-1-ylcarbonyl)prop-1-yl]-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
(S)-N-(2-méthyl-1-pipéridine-1-ylcarbonylprop-1-yl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
(2)-N-[2-méthyl-1-(1,2,3,4-tétrahydroisoquinol-2-yl-carbonyl)prop-1-yl]-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-(2-hydroxyméthyl-2-méthylprop-1-yl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-éthoxycarbonyl-N-(2-éthoxycarbonyl-2-méthylprop-1-yl)-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine et
N-(2-carboxy-2-méthylprop-1-yl)-N-éthoxycarbonyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,

chacun sous forme libre ou sous forme de sel.

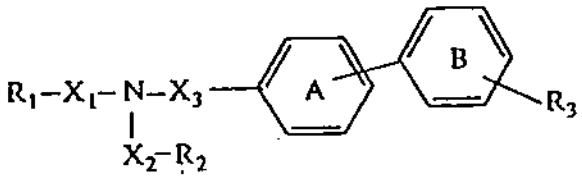
33. Composé selon l'une des revendications 1 à 32, sous forme libre ou sous forme d'un sel pharmaceutiquement utilisable, pour utilisation dans un procédé destiné au traitement thérapeutique de l'organisme humain ou animal.

34. Composé selon l'une des revendications 1 à 33, sous forme libre ou sous forme d'un sel pharmaceutiquement utilisable, pour utilisation en tant qu'antihypertenseur.

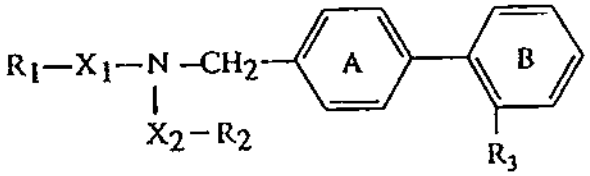
35. Composition pharmaceutique, contenant en tant que substance active un composé selon l'une des revendications 1 à 34, sous forme libre ou sous forme d'un sel pharmaceutiquement utilisable, éventuellement en plus d'adjuvants pharmaceutiques usuels.

36. Composition pharmaceutique à effet antihypertenseur selon la revendication 35, caractérisée en ce que l'on choisit une substance active à effet antihypertenseur.

37. Procédé pour la préparation d'un composé de formule



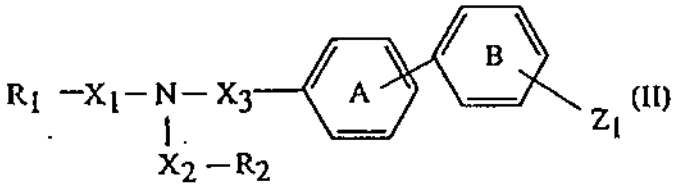
(I) ou



(Ia),

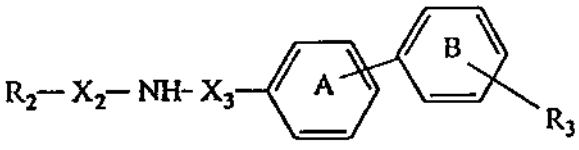
formules dans lesquelles R_1, R_2, R_3, X_1, X_2 et X_3 ainsi que les substituants des cyles A et B ont les significations indiquées chacune dans l'une des revendications 1 à 25, sous forme libre ou sous forme de sel, caractérisé en ce que

a) dans un composé de formule



(II)

ou un sel de celui-ci, dans lequel Z_1 représente un radical pouvant être converti en R_3, on convertit Z_1 en R_3, ou b) on fait réagir un composé de formule R_1-X_1OH (IIIa), un dérivé réactif de celui-ci ou un sel de celui-ci, avec un composé de formule



(IIIb)

ou un sel de celui-ci, et, si on le désire, on convertit dans chaque cas un composé I sous forme libre ou sous forme de sel, pouvant être obtenu conformément au procédé ou d'une autre façon, en un autre composé I, on scinde un mélange d'isomères, pouvant être obtenu conformément au procédé, et on isole les isomères recherchés, et/ou on convertit un composé I libre, pouvant être obtenu conformément au procédé, en un sel, ou on convertit un sel d'un composé I, pouvant être obtenu conformément au procédé, en le composé I libre ou en un autre sel.

38. Procédé pour la préparation d'une composition pharmaceutique selon la revendication 35 ou 36, caractérisé en ce que l'on met la substance active, éventuellement avec addition d'adjuvants pharmaceutiques usuels, sous forme d'une composition pharmaceutique.

39. Procédé selon la revendication 38, pour la préparation d'une composition pharmaceutique à effet antihypertenseur selon la revendication 34, caractérisé en ce que l'on choisit une substance active à effet antihypertenseur.

40. Utilisation d'un composé selon l'une des revendications 1 à 34, sous forme libre ou sous forme d'un sel pharmaceutiquement utilisable, pour la préparation d'une composition pharmaceutique.

41. Utilisation d'un composé selon l'une des revendications 1 à 34, sous forme libre ou sous forme d'un sel pharmaceutiquement utilisable, pour la préparation d'une composition pharmaceutique par voie non chimique.

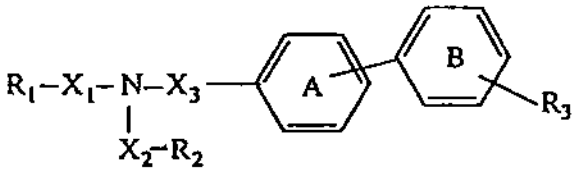
42. Utilisation d'un composé selon l'une des revendications 1 à 34, sous forme libre ou sous forme d'un sel pharmaceutiquement utilisable, pour la préparation d'un agent antihypertenseur.

43. Utilisation d'un composé selon l'une des revendications 1 à 34, sous forme libre ou sous forme d'un sel pharmaceutiquement utilisable, pour la préparation d'une composition pharmaceutique destinée au traitement thérapeutique ou prophylactique de l'insuffisance cardiaque.

44. Utilisation d'un composé selon l'une des revendications 1 à 34, sous forme libre ou sous forme d'un sel pharmaceutiquement utilisable, pour la préparation d'une composition pharmaceutique destinée au traitement thérapeutique ou prophylactique de maladies qui sont provoquées par l'activité de l'angiotensine II.

Revendications pour les Etats contractants suivants : ES, GR

1. Procédé pour la préparation d'un composé de formule

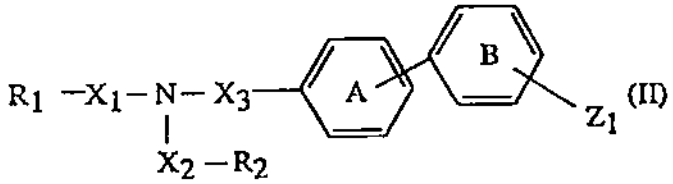


(I),

dans laquelle R_1 représente un radical alkyle inférieur, alcényle inférieur ou alcynyle inférieur, éventuellement substitué par un atome d'halogène ou par le groupe hydroxy, ou un radical cycloalkyle en C_3-C_7 ou cycloalcényle en C_3-C_7 ou phényl-alkyle inférieur, phényl-alcényle inférieur ou phényl-alcynyle inférieur; X_1 représente CO, SO_2 ou -O-C(=O)-, l'atome de carbone du groupe carbonyle étant lié à l'atome d'azote indiqué dans la formule I; X_2 représente un radical alkylène en C_1-C_{10}, alkylidène en C_2-C_{10} ou cycloalkylène en C_3-C_7, éventuellement substitué par un groupe hydroxy, carboxy, amino, guanidino, cycloalkyle en C_3-C_7, cycloalcényle en C_3-C_7, phényle ou par un groupe aromatique monocyclique et à 5 ou 6 chaînons correspondant, qui comporte jusqu'à 4 hétéroatomes identiques ou différents, un atome de carbone du radical alkylène en C_1-C_{10} ou alkylidène en C_2-C_{10} pouvant en outre être ponté par un groupe alkylène en C_2-C_6, et un radical cycloalkyle en C_3-C_7 ou cycloalcényle en C_3-C_7 étant éventuellement une ou plusieurs fois substitué par un ou des groupes carboxy, carboxy estérifié par un alcool dérivant d'un reste alkyle inférieur, phényl-alkyle inférieur, alcényle inférieur, alcynyle inférieur, (alcoxy inférieur)-alkyle inférieur, (alcoxy inférieur)-alcényle inférieur ou (alcoxy inférieur)-alcynyle inférieur, ou par un ou des groupes carbamoyle, carbamoyle dont le fragment amino est monosubstitué ou disubstitué, indépendamment l'un de l'autre, par un ou des groupes alkyle inférieur, alcényle inférieur, alcynyle inférieur, phényl-alkyle inférieur, phényl-alcényle inférieur ou phényl-alcynyle inférieur, ou disubstitué par des radicaux alkylène en C_1-C_{10} ou alkylidène en C_2-C_{10}, les radicaux alkylène en C_1-C_{10} ou alkylidène en C_2-C_{10} étant éventuellement interrompus par -O- ou condensés, au niveau de deux atomes de carbone contigus, avec un cycle benzénique, ou par un ou des groupes formyle, di-(alcoxy inférieur)-méthyle ou oxy-(alkylène-oxy inférieur)-méthylène; R_2 représente le groupe carboxy ou un groupe carboxy qui est estérifié par un alcool dérivant d'un reste alkyle inférieur, phényl-alkyle inférieur, alcényle inférieur, alcynyle inférieur, (alcoxy inférieur)-alkyle inférieur, (alcoxy inférieur)-alcényle inférieur ou (alcoxy inférieur)-alcynyle inférieur, le groupe carbamoyle ou un groupe carbamoyle dans lequel le fragment amino est monosubstitué ou disubstitué, indépendamment l'un de l'autre, par un ou des groupes alkyle inférieur, alcényle inférieur, alcynyle inférieur, phényl-alkyle inférieur, phényl-alcényle inférieur ou phényl-alcynyle inférieur, ou disubstitué par des groupes alkylène en

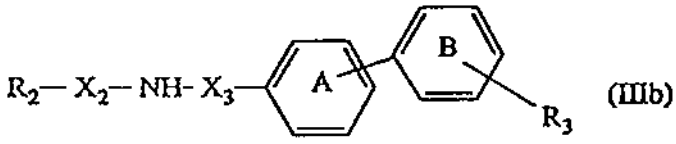
C_1-C_{10} ou alkylidène en C_2-C_{10}, les groupes alkylène en C_1-C_{10} ou alkylidène en C_2-C_{10} étant éventuellement interrompus par -O- ou condensés, au niveau de deux atomes de carbone contigus, avec un cycle benzénique, le groupe amino ou un groupe amino qui est monosubstitué ou disubstitué, indépendamment l'un de l'autre, par un ou des radicaux alkyle inférieur, alcényle inférieur, alcynyle inférieur, phényl-alkyle inférieur, phényl-alcényle inférieur ou phényl-alcynyle inférieur, ou disubstitué par des radicaux alkylène en C_1-C_{10} ou alkylidène en C_2-C_{10}, les radicaux alkylène en C_1-C_{10} ou alkylidène en C_2-C_{10} étant éventuellement interrompus par -O- ou condensés, au niveau de deux atomes de carbone contigus, avec un cycle benzénique, un groupe alcanoyle inférieur, phényl-(alcanoyl inférieur)-, benzoyl-, (alcane inférieur)-sulfonyl-, benzènesulfonyl-amino, formyle, di-(alcoxy inférieur)-méthyle, oxy-(alkylène-oxy inférieur)-méthylène, 1H-tétrazol-5-yle, pyridyle, hydroxy, alcoxy inférieur, alcényloxy inférieur, phényl-alcoxy inférieur, phénoxy, $S(O)_m$-R, m étant 0, 1 ou 2 et R représentant un atome d'hydrogène ou un radical alkyle inférieur, alcényle inférieur ou alcynyle inférieur, ou représente un groupe alcanoyle inférieur, sulfamoyle, sulfamoyle dans lequel le fragment amino est monosubstitué ou disubstitué, indépendamment l'un de l'autre, par un ou des groupes alkyle inférieur, alcényle inférieur, alcynyle inférieur, phényl-alkyle inférieur, phényl-alcényle inférieur ou phényl-alcynyle inférieur, ou disubstitué par des groupes alkylène en C_1-C_{10} ou alkylidène en C_2-C_{10}, les groupes alkylène en C_1-C_{10} ou alkylidène en C_2-C_{10} étant éventuellement interrompus par -O- ou condensés, au niveau de deux atomes de carbone contigus, avec un cycle benzénique, ou représente PO_nH_2, n étant 2 ou 3; X_3 représente un groupe alkylène en C_1-C_{10} ou alkylidène en C_2-C_{10}; R_3 est le groupe carboxy, 5-tétrazolyle, SO_3H, PO_2H_2, PO_3H_2 ou un groupe halogéno-(alkyl inférieur)-sulfamoyle; et les radicaux (hétéro)aromatiques, y compris les cycles A et B, étant éventuellement substitués, indépendamment les uns des autres, par des substituants choisis parmi des atomes d'halogène et des groupes hydroxy, alcoxy inférieur, alcényloxy inférieur, phényl-alcoxy inférieur, phénoxy, $S(O)_m$-R et des groupes alkyle inférieur, alcényle inférieur ou alcynyle inférieur éventuellement substitués par un atome d'halogène ou par le groupe hydroxy, les radicaux alkyle inférieur, alcényle inférieur ou alcynyle inférieur étant éventuellement interrompus par -O-, ainsi que, dans le cas de radicaux (hétéro)aromatiques, éventuellement substitués en outre par le groupe carboxy ou un groupe carboxy estérifié par un alcool dérivant d'un reste alkyle inférieur, phényl-alkyle inférieur, alcényle inférieur, alcynyle inférieur, (alcoxy inférieur)-alkyle inférieur, (alcoxy inférieur)-alcényle inférieur ou (alcoxy inférieur)-alcynyle inférieur, par le groupe carbamoyle ou un groupe carbamoyle dans lequel le fragment amino est monosubstitué ou disubstitué, indépendamment l'un de l'autre, par un ou des groupes alkyle inférieur, alcényle inférieur, alcynyle inférieur, phényl-alkyle inférieur, phényl-alcényle inférieur ou phényl-alcynyle inférieur, ou disubstitué par des groupes alkylène en C_1-C_{10} ou alkylidène en C_2-C_{10}, les groupes alkylène en C_1-C_{10} ou alkylidène en C_2-C_{10} étant éventuellement interrompus par -O- ou condensés, au niveau de deux atomes de carbone contigus, avec un cycle benzénique, par le groupe formyle ou par un groupe di-(alcoxy inférieur)-méthyle ou oxy(alkylène-oxy inférieur)-méthylène; les radicaux et groupes désignés par "inférieur" contenant jusqu'à 7 atomes de carbone; sous forme libre ou sous forme de sel;
caractérisé en ce que

a) dans un composé de formule



(II)

ou un sel de celui-ci, dans lequel Z_1 représente un radical pouvant être converti en R_3, on convertit Z_1 en R_3, ou
b) on fait réagir un composé de formule R_1-X_1OH (IIIa), un dérivé réactif de celui-ci ou un sel de celui-ci, avec un composé de formule



(IIIb)

ou un sel de celui-ci, et, si on le désire, on convertit dans chaque cas un composé I sous forme libre ou sous forme de sel, pouvant être obtenu conformément au procédé ou d'une autre façon, en un autre composé I, on scinde un mélange d'isomères, pouvant être obtenu conformément au procédé, et on isole les isomères recher-

chés, et/ou on convertit un composé I libre, pouvant être obtenu conformément au procédé, en un sel, ou on convertit un sel d'un composé I, pouvant être obtenu conformément au procédé, en le composé I libre ou en un autre sel.

2. Procédé selon la revendication 1, pour la préparation d'un composé de formule I dans lequel R_2 est différent d'un groupe carboxy et R_3 représente le groupe 5-tétrazolyle, caractérisé en ce que

(I) on part d'un composé de formule (II) dans lequel Z_1 représente le groupe cyano, et on le fait réagir avec HN_3 ou un sel alcalin de celui-ci, avec un azide de tri-(alkyl inférieur)-étain ou un azide de triphénylétain; ou

(II) on part d'un composé de formule (II) dans lequel Z_1 représente un groupe 5-tétrazolyle protégé par un groupe triphénylméthyle, benzyle éventuellement substitué par le radical nitro, un groupe (alcoxy inférieur)-méthyle, (alkyl inférieur)-thiométhyle, tri-(alkyl inférieur)-silyle, 2-cyanoéthyle, (alcoxy inférieur)-(alcoxy inférieur)-méthyle, benzyloxyméthyle ou phénacyle, et on élimine le groupe protecteur,

et, si on le désire, on convertit un composé de formule I, pouvant être obtenu selon le procédé, dans lequel R_2 est différent d'un groupe carboxy et R_3 représente le groupe 5-tétrazolyle, en un composé de formule I dans lequel R_2 est le groupe carboxy.

3. Procédé selon la revendication 1 ou 2 pour la préparation d'un composé de formule I dans lequel R_1 représente un radical alkyle inférieur, alcényle inférieur ou alcynyle inférieur éventuellement substitué par un atome d'halogène ou par le groupe hydroxy, ou un radical cycloalkyle en C_3-C_7 ou cycloalcényle en C_3-C_7 ou phényl-alkyle inférieur, phényl-alcényle inférieur ou phényl-alcynyle inférieur; X_1 représente CO ou SO_2; X_2 représente un radical alkylène en C_1-C_{10} ou alkylidène en C_2-C_{10} ou cycloalkylène en C_3-C_7, éventuellement substitué par un groupe hydroxy, cycloalkyle en C_3-C_7 ou cycloalcényle en C_3-C_7 ou phényle ou par un radical aromatique correspondant, monocyclique à 5 ou 6 chaînons, qui comporte jusqu'à 4 hétéroatomes identiques ou différents, un atome de carbone du radical alkylène en C_1-C_{10} ou alkylidène en C_2-C_{10} pouvant en outre être ponté par des groupes alkylène en C_2-C_6, et les groupes cycloalkylène en C_3-C_7 étant éventuellement substitués une ou plusieurs fois par un ou plusieurs groupes carboxy, carboxy estérifié par un alcool dérivant d'un reste alkyle inférieur, phényl-alkyle inférieur, alcényle inférieur, alcynyle inférieur, (alcoxy inférieur)-alkyle inférieur, (alcoxy inférieur)-alcényle inférieur ou (alcoxy inférieur)-alcynyle inférieur, ou par le groupe carbamoyle ou un groupe carbamoyle dans lequel le fragment amino est monosubstitué ou disubstitué, indépendamment l'un de l'autre, par un ou des groupes alkyle inférieur, alcényle inférieur, alcynyle inférieur, phényl-alkyle inférieur, phényl-alcényle inférieur ou phényl-alcynyle inférieur, ou disubstitué par des radicaux alkylène en C_1-C_{10} ou alkylidène en C_2-C_{10}, les radicaux alkylène en C_1-C_{10} ou alkylidène en C_2-C_{10} étant éventuellement interrompus par -O-, le groupe formyle, un groupe di(alcoxy inférieur)-méthyle ou oxy-(alkylène-oxy inférieur)-méthylène; R_2 représente le radical carboxy ou un radical carboxy estérifié par un alcool dérivant d'un reste alkyle inférieur, phényl-alkyle inférieur, alcényle inférieur, alcynyle inférieur, (alcoxy inférieur)-alkyle inférieur, (alcoxy inférieur)-alcényle inférieur ou (alcoxy inférieur)-alcynyle inférieur, ou le radical carbamoyle ou un radical carbamoyle dans lequel le fragment amino est monosubstitué ou disubstitué, indépendamment l'un de l'autre, par un ou des groupes alkyle inférieur, alcényle inférieur, alcynyle inférieur, phényl-alkyle inférieur, phényl-alcényle inférieur ou phényl-alcynyle inférieur, ou disubstitué par des radicaux alkylène en C_1-C_{10} ou alkylidène en C_2-C_{10}, les radicaux alkylène en C_1-C_{10} ou alkylidène en C_2-C_{10} étant éventuellement interrompus par -O-, le radical amino ou un radical amino qui est monosubstitué ou disubstitué, indépendamment l'un de l'autre, par un ou des groupes alkyle inférieur, alcényle inférieur, alcynyle inférieur, phényl-alkyle inférieur, phényl-alcényle inférieur ou phényl-alcynyle inférieur, ou disubstitué par des radicaux alkylène en C_1-C_{10} ou alkylidène en C_2-C_{10}, les radicaux alkylène en C_1-C_{10} ou alkylidène en C_2-C_{10} étant éventuellement interrompus par -O-, ou représente un radical (alcanoyl inférieur)-, phényl-(alcanoyl inférieur)-, benzoyl-, (alcane inférieur)-sulfonyl-, benzènesulfonyl-amino, formyle, di-(alcoxy inférieur)-méthyle, oxy-(alkylène-oxy inférieur)-méthylène, hydroxy, alcoxy inférieur, alcényloxy inférieur, phényl-alcoxy inférieur, phénoxy, $S(O)_m$-R, m représentant 0, 1 ou 2 et R représentant un atome d'hydrogène ou un groupe alkyle inférieur, alcényle inférieur ou alcynyle inférieur, un radical alcanoyle inférieur, le radical sulfamoyle ou un radical sulfamoyle dans lequel le fragment amino est monosubstitué ou disubstitué, indépendamment l'un de l'autre, par un ou des radicaux alkyle inférieur, alcényle inférieur, alcynyle inférieur, phényl-alkyle inférieur, phényl-alcényle inférieur ou phényl-alcynyle inférieur, ou disubstitué par des radicaux alkylène en C_1-C_{10} ou alkylidène en C_2-C_{10}, les radicaux alkylène en C_1-C_{10} ou alkylidène en c_2-C_{10} étant éventuellement interrompus par -O-, ou représente PO_nH_2, n représentant 2 ou 3; X_3 représente un radical alkylène en C_1-C_{10} ou alkylidène en C_2-C_{10}; R_3 est le groupe carboxy, 5-tétrazolyle, SO_3H, PO_2H_2, PO_3H_2 ou un groupe halogéno-(alkyl inférieur)-sulfamoyle; les radicaux (hétéro)aromatiques, y compris les cycles A et B, étant éventuellement substitués, indépendamment les uns des autres, par des substituants choisis parmi des atomes d'halogène et des groupes hydroxy, alcoxy inférieur, alcényloxy inférieur, phényl-alcoxy inférieur, phénoxy, $S(O)_m$-R et des radicaux alkyle inférieur, alcényle inférieur ou alcynyle inférieur éventuellement substitués par un atome d'halogène ou par le groupe hydroxy,

les radicaux alkyle inférieur, alcényle inférieur ou alcynyle inférieur étant éventuellement interrompus par -O-, ainsi que, dans le cas des radicaux (hétéro)aromatiques, éventuellement substitués en outre par le groupe carboxy, un groupe carboxy estérifié par un alcool dérivant d'un reste alkyle inférieur, phényl-alkyle inférieur, alcényle inférieur, alcynyle inférieur, (alcoxy inférieur)-alkyle inférieur, (alcoxy inférieur)-alcényle inférieur ou (alcoxy inférieur)-alcynyle inférieur, par le groupe carbamoyle, par un groupe carbamoyle dans lequel le fragment amino est monosubstitué ou disubstitué, indépendamment l'un de l'autre, par un ou des groupes alkyle inférieur, alcényle inférieur, alcynyle inférieur, phényl-alkyle inférieur, phényl-alcényle inférieur ou phényl-alcynyle inférieur, ou disubstitué par des radicaux alkylène en C_1-C_{10} ou alkylidène en C_2-C_{10}, les radicaux alkylène en C_1-C_{10} ou alkylidène en C_2-C_{10} étant éventuellement interrompus par -O-, ou par le groupe formyle, un groupe di-(alcoxy inférieur)-méthyle ou oxy(alkylène-oxy inférieur)-méthylène; sous forme libre ou sous forme de sel.

4. Procédé selon la revendication 1 ou 2 pour la préparation d'un composé de formule I dans lequel R_1 représente un radical alkyle inférieur, alcényle inférieur ou alcynyle inférieur éventuellement substitué par un atome d'halogène ou par le groupe hydroxy, ou un radical cycloalkyle en C_3-C_7 ou cycloalcényle en C_3-C_7 ou phényl-alkyle inférieur, phényl-alcényle inférieur ou phényl-alcynyle inférieur; X_1 représente CO ou SO_2; X_2 représente un radical alkylène en C_1-C_{10} ou alkylidène en C_2-C_{10} éventuellement substitué par un groupe hydroxy, cycloalkyle en C_3-C_7 ou cycloalcényle en C_3-C_7 ou phényle ou par un radical aromatique correspondant, monocyclique et à 5 ou 6 chaînons, qui comporte jusqu'à 4 hétéroatomes identiques ou différents; R_2 représente le groupe carboxy ou un groupe carboxy estérifié par un alcool dérivant d'un reste alkyle inférieur, phényl-alkyle inférieur, alcényle inférieur, alcynyle inférieur, (alcoxy inférieur)-alkyle inférieur, (alcoxy inférieur)-alcényle inférieur ou (alcoxy inférieur)-alcynyle inférieur, le groupe carbamoyle ou un groupe carbamoyle dans lequel le fragment amino est monosubstitué ou disubstitué, indépendamment l'un de l'autre, par un ou des groupes alkyle inférieur, alcényle inférieur, alcynyle inférieur, phényl-alkyle inférieur, phényl-alcényle inférieur ou phényl-alcynyle inférieur, ou disubstitué par des radicaux alkylène en C_1-C_{10} ou alkylidène en C_2-C_{10}, les radicaux alkylène en C_1-C_{10} ou alkylidène en C_2-C_{10} étant éventuellement interrompus par -O-, ou représente le groupe amino ou un groupe amino qui est monosubstitué ou disubstitué, indépendamment l'un de l'autre, par un ou des radicaux alkyle inférieur, alcényle inférieur, alcynyle inférieur, phényl-alkyle inférieur, phényl-alcényle inférieur ou phényl-alcynyle intérieur, ou disubstitué par des radicaux alkylène en C_1-C_{10} ou alkylidène en C_2-C_{10}, les radicaux alkylène en C_1-C_{10} ou alkylidène en C_2-C_{10} étant éventuellement interrompus par -O-, ou représente un groupe (alcanoyl inférieur)-, phényl-(alcanoyl inférieur)-, benzoyl-, (alcane inférieur)-sulfonyl-, benzènesulfonylamino, formyle, di-(alcoxy inférieur)-méthyle, oxy-(alkylène-oxy inférieur)-méthylène, hydroxy, alcoxy inférieur, alcényloxy inférieur, phényl-alcoxy inférieur ou phénoxy, $S(O)_m$-R, m représentant 0, 1 ou 2 et R représentant un atome d'hydrogène ou un groupe alkyle inférieur, alcényle inférieur ou alcynyle inférieur, un radical alcanoyle inférieur, ou représente le radical sulfamoyle ou un radical sulfamoyle dans lequel le fragment amino est monosubstitué ou disubstitué, indépendamment l'un de l'autre, par un ou des groupes alkyle inférieur, alcényle inférieur, alcynyle inférieur, phényl-alkyle inférieur, phényl-alcényle inférieur ou phényl-alcynyle inférieur, ou disubstitué par des groupes alkylène en C_1-C_{10} ou alkylidène en C_2-C_{10}, les groupes alkylène en C_1-C_{10} ou alkylidène en C_2-C_{10} étant éventuellement interrompus par -O-, ou représente PO_nH_2, n étant 2 ou 3; X_3 représente -CH_2-; R_3 est le groupe carboxy, 5-tétrazolyle, SO_3H, PO_2H_2, PO_3H_2 ou un groupe halogéno-(alkyl inférieur)-sulfamoyle; et les radicaux (hétéro)aromatiques, y compris les cycles A et B, étant éventuellement substitués, indépendamment les uns des autres, par des substituants choisis parmi des atomes d'halogène et des groupes hydroxy, alcoxy inférieur, alcényloxy inférieur, phényl-alcoxy inférieur, phénoxy, $S(O)_m$-R et des radicaux alkyle inférieur, alcényle inférieur ou alcynyle inférieur éventuellement substitués par un atome d'halogène ou par le groupe hydroxy, les radicaux alkyle inférieur, alcényle inférieur ou alcynyle inférieur étant éventuellement interrompus par -O-, et, dans le cas de radicaux (hétéro)aromatiques, étant éventuellement substitués en outre par le groupe carboxy ou par un groupe carboxy estérifié par un alcool dérivant d'un reste alkyle inférieur, phényl-alkyle inférieur, alcényle inférieur, alcynyle inférieur, (alcoxy inférieur)-alkyle inférieur, (alcoxy inférieur)-alcényle inférieur ou (alcoxy inférieur)-alcynyle inférieur, par le groupe carbamoyle ou par un groupe carbamoyle dans lequel le fragment amino est monosubstitué ou disubstitué, indépendamment l'un de l'autre, par un ou des groupes alkyle inférieur, alcényle inférieur, alcynyle inférieur, phényl-alkyle inférieur, phényl-alcényle inférieur ou phényl-alcynyle inférieur, ou disubstitué par des radicaux alkylène en C_1-C_{10} ou alkylidène en C_2-C_{10}, les radicaux alkylène en C_1-C_{10} ou alkylidène en C_2-C_{10} étant éventuellement interrompus par -O-, ou par le groupe formyle, un groupe di-(alcoxy inférieur)-méthyle ou oxy-(alkylène-oxy inférieur)-méthylène; sous forme libre ou sous forme de sel.

5. Procédé selon la revendication 1 ou 2 pour la préparation d'un composé de formule I dans lequel R_1 représente un radical alkyle inférieur, alcényle inférieur, alcynyle inférieur, halogéno-alkyle inférieur, -alcényle inférieur, -alcynyle inférieur, hydroxy-alkyle inférieur, -alcényle inférieur, -alcynyle inférieur, cycloalkyle en C_3-C_7, cycloalcényle en C_3-C_7, phényl-alkyle inférieur, phényl-alcényle inférieur ou phényl-alcynyle inférieur; X_1 représente CO ou SO_2; X_2 représente un radical alkylène en C_1-C_{10} ou alkylidène en C_2-C_{10} qui sont éventuellement substitués par le groupe hydroxy ou par un radical cycloalkyle en C_3-C_7, cycloalcényle en C_3-C_7, phényle ou par un radical hétéroaromatique

monocyclique à 5 ou 6 chaînons, comportant jusqu'à 4 hétéroatomes identiques ou différents, les radicaux cycliques étant pour leur part éventuellement substitués par un groupe carboxy éventuellement estérifié par un alcool dérivant d'un reste alkyle inférieur, phényl-alkyle inférieur, alcényle inférieur, alcynyle inférieur, (alcoxy inférieur)-alkyle inférieur, -alcényle inférieur ou -alcynyle inférieur, ou par un groupe carbamoyle dans lequel le fragment amino est éventuellement monosubstitué ou disubstitué, indépendamment l'un de l'autre, par un ou des radicaux alkyle inférieur, alcényle inférieur, alcynyle inférieur, phényl-alkyle inférieur, phényl-alcényle inférieur, phényl-alcynyle inférieur, ou disubstitué par des radicaux (alkylène inférieur)- ou (alkylène-oxy inférieur)-alkylène inférieur, le radical formyle, di-(alcoxy inférieur)-méthyle, oxy-(alkylène-oxy inférieur)-méthylène; R_2 représente un groupe carboxy éventuellement estérifié par un alcool dérivant d'un reste alkyle inférieur, phényl-alkyle inférieur, alcényle inférieur, alcynyle inférieur, (alcoxy inférieur)-alkyle inférieur, -alcényle inférieur ou -alcynyle inférieur, un radical carbamoyle dans lequel le fragment amino est éventuellement monosubstitué ou disubstitué, indépendamment l'un de l'autre, par un ou des groupes alkyle inférieur, alcényle inférieur, alcynyle inférieur, phényl-alkyle inférieur, phényl-alcényle inférieur, phényl-alcynyle inférieur, ou disubstitué par des radicaux (alkylène inférieur)- ou (alkylène-oxy inférieur)-alkylène inférieur, un radical amino dans lequel le fragment amino est éventuellement monosubstitué ou disubstitué, indépendamment l'un de l'autre, par un ou des radicaux alkyle inférieur, alcényle inférieur, alcynyle inférieur, phényl-alkyle inférieur, phényl-alcényle inférieur, phényl-alcynyle inférieur, ou disubstitué par des radicaux (alkylène inférieur)- ou (alkylène-oxy inférieur)-alkylène inférieur, un groupe (alcanoyl inférieur)-, phényl-(alcanoyl inférieur)-, benzoyl-, (alcane inférieur)-sulfonyl-, benzènesulfonyl-amino, formyle, di-(alcoxy inférieur)-méthyle, oxy-(alkylène-oxy inférieur)-méthylène, hydroxy, alcoxy inférieur, alcényloxy inférieur, phényl-alcoxy inférieur, phénoxy, $S(O)_m$-R, m représentant 0, 1 ou 2 et R représentant un atome d'hydrogène ou un groupe alkyle inférieur, alcényle inférieur ou alcynyle inférieur, un radical alcanoyle inférieur, sulfamoyle, dans lequel le fragment amino est éventuellement monosubstitué ou disubstitué, indépendamment l'un de l'autre, par un ou des groupes alkyle inférieur, alcényle inférieur, alcynyle inférieur, phényl-alkyle inférieur, phényl-alcényle inférieur ou phényl-alcynyle inférieur, ou disubstitué par des radicaux (alkylène inférieur)- ou (alkylène-oxy inférieur)-alkylène inférieur, ou représente PO_nH_2, n représentant 2 ou 3; X_3 représente $-CH_2-$; R_3 est le groupe carboxy, 5-tétrazolyle, SO_3H, PO_2H_2, PO_3H_2 ou un groupe halogéno-(alkyl inférieur)-sulfamoyle; les radicaux (hétéro)aromatiques, y compris les cycles A et B, étant éventuellement substitués, indépendamment les uns des autres, par un ou plusieurs substituants choisis parmi des atomes d'halogène et des groupes hydroxy, alcoxy inférieur, alcényloxy inférieur, des radicaux alkyle inférieur, alcényle inférieur, alcynyle inférieur, (alcoxy inférieur)-alkyle inférieur, -alcényle inférieur, -alcynyle inférieur, (alcényloxy inférieur)-alkyle inférieur, -alcényle inférieur et -alcynyle inférieur, éventuellement substitués chacun par un atome d'halogène ou par le groupe hydroxy, sous forme libre ou sous forme de sel.

6. Procédé selon la revendication 1 ou 2 pour la préparation d'un composé de formule I dans lequel X_2 représente un radical alkylène en C_1-C_{10} ou alkylidène en C_2-C_{10} qui sont éventuellement substitués par le groupe hydroxy ou par un groupe cycloalkyle en C_3-C_7, cycloalcényle en C_3-C_7, phényle ou par un radical hétéroaromatique monocyclique à 5 ou 6 chaînons, comportant jusqu'à 4 hétéroatomes identiques ou différents, un atome de carbone d'un radical alkylène en C_1-C_{10} ou alkylidène en C_2-C_{10} pouvant être ponté par un groupe alkylène en C_2-C_6, et les radicaux cycliques étant pour leur part éventuellement substitués par un groupe carboxy éventuellement estérifié par un alcool dérivant d'un reste alkyle inférieur, phényl-alkyle inférieur, alcényle inférieur, alcynyle inférieur, (alcoxy inférieur)-alkyle inférieur, -alcényle inférieur ou -alcynyle inférieur, par un groupe carbamoyle dans lequel le fragment amino est éventuellement monosubstitué ou disubstitué, indépendamment l'un de l'autre, par un ou des groupes alkyle inférieur, alcényle inférieur, alcynyle inférieur, phényl-alkyle inférieur, phényl-alcényle inférieur, phényl-alcynyle inférieur, ou disubstitué par des radicaux (alkylène inférieur)- ou (alkylène-oxy inférieur)-alkylène inférieur, par le groupe formyle, par un groupe di-(alcoxy inférieur)-méthyle, ou par un groupe oxy-(alkylène-oxy inférieur)-méthylène, ou X_2 représente un groupe cycloalkylène en C_3-C_7; X_3 représente un groupe alkylène inférieur ou alkylidène inférieur; les variables X_1, R_1, R_2, R_3 ont les significations indiquées dans la revendication 5; et les cycles (hétéro)aromatiques, y compris les cycles A et B, peuvent être substitués comme indiqué dans la revendication 5, sous forme libre ou sous forme de sel.

7. Procédé selon la revendication 1 ou 2 pour la préparation d'un composé de formule I dans lequel R_1 représente un radical alkyle inférieur, alcényle inférieur, halogéno-alkyle inférieur, -alcényle inférieur, hydroxy-alkyle inférieur, un radical cycloalkyle à 3-7 chaînons ou phényl-alkyle inférieur; X_1 représente CO, SO_2 ou -O-C(=O)-, l'atome de carbone du groupe carbonyle étant lié à l'atome d'azote indiqué dans la formule I; X_2 représente un radical alkylène en C_1-C_{10} ou alkylidène en C_1-C_7, qui sont éventuellement substitués par le groupe hydroxy, carboxy, amino, guanidino, un radical cycloalkyle à 3-7 chaînons, cyclo-alcényle à 3-7 chaînons, phényle, pyrrolyle, pyrazolyle, imidazolyle, triazolyle, tétrazolyle, furyle, thiényle ou pyridyle, qui pour leur part peuvent être éventuellement substitués en outre par un radical carboxy, (alcoxy inférieur)-carbonyle, phényl-(alcoxy inférieur)-carbonyle, par un radical carbamoyle dans lequel le fragment amino peut éventuellement être monosubstitué ou disubstitué, indépendamment l'un de l'autre, par un ou des groupes alkyle inférieur ou phényl-alkyle inférieur, ou un radical formyle, di-(alcoxy

inférieur)-méthyle ou oxy-(alkylène-oxy inférieur)-méthylène; R_2 représente un groupe carboxy, (alcoxy inférieur)-, phényl-(alcoxy inférieur)-, (alcényloxy inférieur)-, (alcoxy inférieur)-(alcoxy inférieur)-carbonyle, un radical carbamoyle dans lequel le fragment amino est éventuellement monosubstitué ou disubstitué, indépendamment l'un de l'autre, par un ou des radicaux alkyle inférieur ou phényl-alkyle inférieur, ou est disubstitué par des radicaux alkylène inférieur, éventuellement condensés, au niveau de deux atomes de carbone contigus, avec un cycle benzénique, ou par des radicaux (alkylène-oxy inférieur)-alkylène inférieur, un radical amino dans lequel le fragment amino est éventuellement monosubstitué ou disubstitué, indépendamment l'un de l'autre, par un ou des radicaux alkyle inférieur ou phényl-alkyle inférieur, ou est disubstitué par des radicaux (alkylène inférieur)- ou (alkylène-oxy inférieur)-alkylène inférieur, un groupe (alcanoyl inférieur)-, phényl-(alcanoyl inférieur)-, benzoyl-, (alcane inférieur)-sulfonyl-, benzènesulfonylamino, formyle, di-(alcoxy inférieur)-méthyle, oxy-(alkylène-oxy inférieur)-méthylène, hydroxy, alcoxy inférieur, phényl-alcoxy inférieur, phénoxy, $S(O)_m$-R, m représentant 0, 1 ou 2 et R représentant un groupe alkyle inférieur, alcanoyle inférieur, sulfamoyle, dans lequel le fragment amino est éventuellement monosubstitué ou disubstitué, indépendamment l'un de l'autre, par un ou des groupes alkyle inférieur ou phényl-alkyle inférieur, ou représente PO_nH_2, n représentant 2 ou 3; X_3 est le groupe méthylène; R_3 représente le groupe carboxy, 5-tétrazolyle, SO_3H, PO_2H_2, PO_3H_2 ou un groupe halogéno-(alkyl inférieur)-sulfamoyle; et les radicaux (hétéro)aromatiques, y compris les cycles A et B, sont éventuellement substitués chacun en outre par un ou plusieurs substituants choisis parmi des atomes d'halogène et des groupes hydroxy, alcoxy inférieur, et des radicaux alkyle inférieur ou (alcoxy inférieur)-alkyle inférieur éventuellement substitués chacun par un atome d'halogène ou par le groupe hydroxy, sous forme libre ou sous forme de sel.

8. Procédé selon la revendication 1 ou 2 pour la préparation d'un composé de formule I dans lequel R_1 représente un radical alkyle inférieur, alcényle inférieur, halogéno-alkyle inférieur, -alcényle inférieur, hydroxy-alkyle inférieur, un radical cycloalkyle à 3-7 chaînons ou phényl-alkyle inférieur; X_1 représente CO ou SO_2; X_2 représente un radical alkylène en C_1-C_{10} ou alkylidène en C_1-C_7, qui sont éventuellement substitués par un groupe hydroxy, un radical cycloalkyle à 3-7 chaînons, cycloalcényle à 3-7 chaînons, phényle, pyrrolyle, pyrazolyle, imidazolyle, triazolyle, tétrazolyle, furyle, thiényle ou pyridyle, qui peuvent pour leur part être éventuellement substitués en outre par un groupe carboxy, (alcoxy inférieur)-carbonyle, phényl-(alcoxy inférieur)-carbonyle, carbamoyle dans lequel le fragment amino est éventuellement monosubstitué ou disubstitué, indépendamment l'un de l'autre, par un ou des groupes alkyle inférieur ou phényl-alkyle inférieur, le radical formyle, un radical di-(alcoxy inférieur)-méthyle ou oxy-(alkylène-oxy inférieur)-méthylène; R_2 représente un radical carboxy, (alcoxy inférieur)-, phényl-(alcoxy inférieur)-, (alcényloxy inférieur)-, (alcoxy inférieur)-(alcoxy inférieur)-carbonyle, un radical carbamoyle dans lequel le fragment amino est éventuellement monosubstitué ou disubstitué, indépendamment l'un de l'autre, par un ou des groupes alkyle inférieur, phényl-alkyle inférieur, ou disubstitué par des radicaux (alkylène inférieur)-, ou (alkylène-oxy inférieur)-alkylène inférieur, un radical amino dans lequel le fragment amino est éventuellement monosubstitué ou disubstitué, indépendamment l'un de l'autre, par un ou des groupes alkyle inférieur, phényl-alkyle inférieur, ou disubstitué par des radicaux (alkylène inférieur)- ou (alkylène-oxy inférieur)-alkylène inférieur, un groupe (alcanoyl inférieur)-, phényl-(alcanoyl inférieur)-, benzoyl-, (alcane inférieur)-sulfonyl-, benzènesulfonylamino, formyle, di-(alcoxy inférieur)-méthyle, oxy-(alkylène-oxy inférieur)-méthylène, hydroxy, alcoxy inférieur, phényl-alcoxy inférieur, phénoxy, $S(O)_m$-R, m représentant 0, 1 ou 2 et R représentant un groupe alkyle inférieur, un radical alcanoyle inférieur, sulfamoyle dans lequel le groupe amino est éventuellement monosubstitué ou disubstitué, indépendamment l'un de l'autre, par des groupes alkyle inférieur, phényl-alkyle inférieur, ou représente PO_nH_2, n représentant 2 ou 3; X_3 est le groupe méthylène; R_3 représente le groupe carboxy, 5-tétrazolyle, SO_3H, PO_2H_2, PO_3H_2 ou un groupe halogéno-(alkyl inférieur)-sulfamoyle; et les radicaux (hétéro)aromatiques, y compris les cycles A et B, sont éventuellement substitués chacun en outre par un ou plusieurs substituants choisis parmi des atomes d'halogène et des groupes hydroxy, alcoxy inférieur, des groupes alkyle inférieur ou (alcoxy inférieur)-alkyle inférieur éventuellement substitués chacun par un atome d'halogène ou par le groupe hydroxy, sous forme libre ou sous forme de sel.

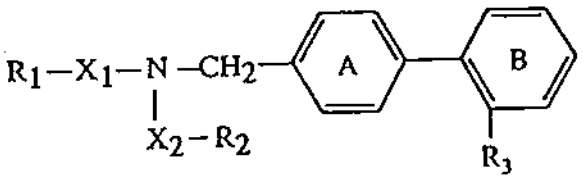
9. Procédé selon la revendication 1 ou 2 pour la préparation d'un composé de formule I dans lequel X_2 représente un radical alkylène en C_1-C_{10} ou alkylidène en C_1-C_7, qui sont éventuellement substitués par un groupe hydroxy, un radical cycloalkyle à 3-7 chaînons, cycloalcényle à 3-7 chaînons, phényle, pyrrolyle, pyrazolyle, imidazolyle, triazolyle, tétrazolyle, furyle, thiényle ou pyridyle, qui peuvent pour leur part être éventuellement substitués en outre par un groupe carboxy, (alcoxy inférieur)-carbonyle, phényl-(alcoxy inférieur)-carbonyle, carbamoyle dans lequel le fragment amino est éventuellement monosubstitué ou disubstitué, indépendamment l'un de l'autre, par un ou des groupes alkyle inférieur ou phényl-alkyle inférieur, ou peuvent être substitués par le groupe formyle, par un groupe di-(alcoxy inférieur)-méthyle, ou par un groupe oxy-(alkylène-oxy inférieur)-méthylène, un atome de carbone d'un radical alkylène en C_1-C_{10} ou alkylidène en C_1-C_7 pouvant être ponté par un groupe alkylène en C_2-C_8, ou X_2 représente un groupe cycloalkylène en C_3-C_7; X_3 représente un groupe alkylène inférieur ou alkylidène inférieur; les variables X_1, R_1, R_2, R_3 ont les significations indiquées dans la revendication 8, et les cycles (hétéro)aromatiques, y compris

les cycles A et B, peuvent être substitués comme indiqué dans la revendication 8, sous forme libre ou sous forme de sel.

10. Procédé selon la revendication 1 ou 2 pour la préparation d'un composé de formule I dans lequel les variables R_1, X_1, R_3 ont les significations indiquées respectivement dans les revendications 1 à 8; X_2 représente un radical alkylène inférieur ou alkylidène inférieur éventuellement substitué par un groupe hydroxy, cycloalkyle à 3-7 chaînons, phényle ou imidazolyle; et R_2 représente un radical carboxy, (alcoxy inférieur)-, phényl-(alcoxy inférieur)-, (alcoxy inférieur)-(alcoxy inférieur)-carbonyle, un radical carbamoyle qui est éventuellement monosubstitué ou disubstitué, indépendamment l'un de l'autre, par un ou des groupes alkyle inférieur ou phényl-alkyle inférieur, un radical amino, (alcanoyl inférieur)-, phényl-(alcanoyl inférieur)-, (alcane inférieur)-sulfonylamino, hydroxy, alcoxy inférieur, phényl-alcoxy inférieur ou phénoxy; X_3 représente $-CH_2-$; les radicaux (hétéro)aromatiques, y compris les cycles A et B, étant éventuellement substitués chacun par un ou plusieurs substituants choisis parmi des atomes d'halogène et des groupes trifluorométhyle, hydroxy, alcoxy inférieur, alkyle inférieur, hydroxyalkyle inférieur ou (alcoxy inférieur)-alkyle inférieur, sous forme libre ou sous forme de sel.

11. Procédé selon la revendication 1 ou 2 pour la préparation d'un composé de formule I dans lequel X_2 représente un radical alkylène inférieur ou alkylidène inférieur éventuellement substitué par un groupe hydroxy, cycloalkyle à 3-7 chaînons, cycloalcényle à 7 chaînons, phényle ou imidazolyle, un atome de carbone d'un radical alkylène inférieur ou alkylidène inférieur pouvant être ponté par un groupe alkylène en C_2-C_6, ou X_2 représente un groupe cycloalkylène en C_3-C_7; les variables X_1, X_3, R_1, R_2, R_3 ont les significations indiquées dans les revendications 8 à 10; et les cycles A et B, peuvent être substitués comme indiqué dans la revendication 10, sous forme libre ou sous forme de sel.

12. Procédé selon la revendication 1 ou 2 pour la préparation d'un composé de formule

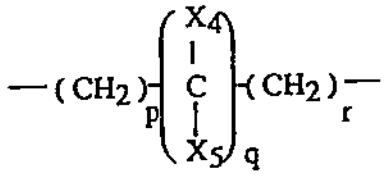


(Ia),

dans laquelle les variables R_1, X_1, X_2, R_2 et R_3 ont les significations données respectivement dans l'une des revendications 1 ou 3-11, et les cycles A et B, peuvent être substitués comme indiqué dans la revendication 11, sous forme libre ou sous forme de sel.

13. Procédé selon la revendication 1 ou 2 pour la préparation d'un composé de formule Ia dans lequel X_2 représente un radical alkylène inférieur ou alkylidène inférieur éventuellement substitué par un groupe hydroxy ou par un groupe cycloalkyle à 3-7 chaînons, un atome de carbone d'un radical alkylène inférieur ou alkylidène inférieur pouvant être ponté par un groupe alkylène en C_2-C_6, ou dans lequel X_2 représente un groupe cycloalkylène en C_3-C_7, et les variables R_1, X_1, R_2 et R_3 ont les significations indiquées respectivement dans l'une des revendications 1 ou 3-11; et les cycles A et B peuvent être substitués comme indiqué dans la revendication 11, sous forme libre ou sous forme de sel.

14. Procédé selon la revendication 1 ou 2 pour la préparation d'un composé de formule Ia, dans lequel X_2 représente le groupe de formule



(Ib)

dans laquelle p représente 0 ou 1, q représente 1 et r représente 0 ou 1, ou dans laquelle p représente 1 à 8 et q ainsi que r représentent chacun 0; X_4 représente un radical phényle ou alkyle inférieur éventuellement substitué par un groupe hydroxy, cycloalkyle à 3-7 chaînons, phényle ou imidazolyle; et X_5 représente un atome d'hydrogène

ou un groupe alkyle inférieur; R_2 représente un radical carboxy, (alcoxy inférieur)-carbonyle, phényl-(alcoxy inférieur)-carbonyle, (alcoxy inférieur)-(alcoxy inférieur)-carbonyle, hydroxy, alcoxy inférieur, phényl-alcoxy inférieur, phénoxy, amino, alcanoylamino inférieur, phénylalcanoylamino inférieur ou (alcane inférieur)-sulfonylamino; et les variables R_1, X_1 et X_3 ont les significations indiquées respectivement dans l'une des revendications 1 ou 3-8; les radicaux (hétéro)aromatiques, y compris les cycles A et B, étant éventuellement substitués chacun par un atome d'halogène ou par un groupe trifluorométhyle, hydroxy, alcoxy inférieur, alkyle inférieur ou hydroxyalkyle inférieur, sous forme libre ou sous forme de sel.

15. Procédé selon la revendication 1 ou 2 pour la préparation d'un composé de formule Ia, dans lequel X_2 représente le groupe de formule Ib, dans lequel p représente 0 ou 1, q représente 1 et r représente 0 ou 1, ou dans lequel p représente 1 à 8 et q ainsi que r représentent chacun 0; X_4 représente un radical phényle ou alkyle inférieur éventuellement substitué par un groupe hydroxy, cycloalkyle à 3-7 chaînons, phényle ou imidazolyle; et X_5 représente un atome d'hydrogène ou un groupe alkyle inférieur; ou X_4 et X_5 forment ensemble un radical alkylène en C_2-C_6, tel qu'alkylène en C_4-C_5, ou X_2 représente un radical cycloalkylène en C_3-C_7, tel que cycloalkylène en C_5-C_6; R_2 représente un radical carboxy, (alcoxy inférieur)-carbonyle, phényl-(alcoxy inférieur)-carbonyle, (alcoxy inférieur)-(alcoxy inférieur)-carbonyle, hydroxy, alcoxy inférieur, phényl-alcoxy inférieur, phénoxy, amino, alcanoylamino inférieur, phényl-alcanoylamino inférieur ou (alcane inférieur)-sulfonylamino; et les variables R_1, X_1 et R_3 ont les significations indiquées respectivement dans l'une des revendications 1 ou 3-8; les radicaux (hétéro)aromatiques, y compris les cycles A et B, étant éventuellement substitués chacun par un atome d'halogène ou par un groupe trifluorométhyle, hydroxy, alcoxy inférieur, alkyle inférieur ou hydroxyalkyle inférieur, sous forme libre ou sous forme de sel.

16. Procédé selon la revendication 1 ou 2 pour la préparation d'un composé de formule Ia, dans lequel R_1 représente un radical alkyle inférieur, tel qu'un radical alkyle en C_3-C_5, ou un radical alcényle inférieur, tel qu'un radical alcényle en C_3-C_5; X_1 représente CO ou SO_2; X_2 représente le groupe de formule Ib, dans lequel p et r représentent 0 ou 1, et q représente 1; X_4 représente un radical alkyle inférieur, tel qu'un radical alkyle en C_1-C_4, ou phényle, éventuellement substitué par un groupe hydroxy, cycloalkyle à 3-7 chaînons tel que cyclohexyle, par un groupe phényle ou imidazolyle, tel que 4-imidazolyle, éventuellement substitué par un atome d'halogène ou par le groupe hydroxy; et X_5 représente un atome d'hydrogène ou un groupe alkyle inférieur, tel qu'un groupe alkyle en C_1-C_4; ou X_4 et X_5 représentent ensemble un groupe alkylène en C_2-C_6, tel qu'un groupe alkylène en C_4-C_5; ou X_2 représente un radical cycloalkylène en C_3-C_7, tel qu'un radical cycloalkylène en C_5-C_6,; R_2 représente un radical carboxy, (alcoxy inférieur)-carbonyle tel qu'un groupe alcoxy(C_2-C_5)-carbonyle, phényl-(alcoxy inférieur)-carbonyle, tel que phényl-alcoxy-(C_1-C_4)-carbonyle, un radical (alcoxy inférieur)-(alcoxy inférieur)-carbonyle, tel qu'un radical alcoxy(C_1-C_4)-alcoxyC_2-C_5)-carbonyle, un groupe hydroxy ou alcoxy inférieur, tel qu'un groupe alcoxy en C_1-C_4; et R_3 représente le groupe carboxy ou 5-tétrazolyle; les radicaux (hétéro)aromatiques, y compris les cycles A et B, étant éventuellement substitués chacun par un atome d'halogène ou par un groupe trifluorométhyle, hydroxy, alcoxy inférieur, alkyle inférieur ou hydroxyalkyle inférieur, sous forme libre ou sous forme de sel.

17. Procédé selon la revendication 1 ou 2 pour la préparation d'un composé de formule Ia dans lequel R_1 représente un radical alkyle inférieur, tel qu'alkyle en C_3-C_5, ou alcényle inférieur, tel qu'alcényle en C_3-C_5; X_1 représente CO ou SO_2; X_2 représente le groupe de formule Ib, dans lequel p et r représentent 0 ou 1 et q représente 1; X_4 représente un radical alkyle inférieur, tel qu'un radical alkyle en C_1-C_4, ou phényle, éventuellement substitué par un groupe hydroxy, cycloalkyle à 3-7 chaînons, phényle ou imidazolyle, tel que 4-imidazolyle, éventuellement substitué par un atome d'halogène ou par le groupe hydroxy; et X_5 représente un atome d'hydrogène ou un groupe alkyle inférieur, tel qu'un groupe alkyle en C_1-C_4; R_2 représente un groupe carboxy, (alcoxy inférieur)-carbonyle, tel qu'un groupe alcoxy(C_2-C_5)-carbonyle, phényl-(alcoxy inférieur)-carbonyle, tel que phényl-alcoxy(C_1-C_4)-carbonyle, (alcoxy inférieur)-(alcoxy inférieur)-carbonyle tel qu'un groupe alcoxy(C_1-C_4)-alcoxy-(C_2-C_5)-carbonyle, un groupe hydroxy ou alcoxy inférieur tel qu'un groupe alcoxy en C_1-C_4; et R_3 représente le groupe carboxy ou 5-tétrazolyle; les radicaux (hétéro)aromatiques, y compris les cycles A et B, étant éventuellement substitués chacun par un atome d'halogène ou par un groupe trifluorométhyle, hydroxy, alcoxy inférieur, alkyle inférieur ou hydroxyalkyle inférieur, sous forme libre ou sous forme de sel.

18. Procédé selon la revendication 1 ou 2 pour la préparation d'un composé de formule Ia, dans lequel R_1 représente un radical alkyle inférieur, tel qu'un radical alkyle en C_3-C_5, ou bien un radical alcényle inférieur, tel qu'alcényle en C_3-C_5; X_1 représente CO ou SO_2; X_2 représente le groupe de formule Ib dans lequel p représente un nombre entier allant de 1 à 8 et q ainsi que r représentent 0; R_2 représente un groupe hydroxy, alcoxy inférieur tel qu'alcoxy en C_1-C_4, phényl-alcoxy inférieur tel que phényl-alcoxy-(C_1-C_4), phénoxy, un groupe alcanoylamino inférieur, tel qu'alcanoyl(C_1-C_4)-amino, un groupe phényl-(alcanoyl inférieur)-amino, tel que phényl-alcanoyl(C_1-C_4)-amino, un groupe (alcane inférieur)-sulfonylamino, tel qu'un groupe alcane(C_1-C_4)-sulfonylamino; et R_3 représente le groupe

carboxy ou, en premier lieu, 5-tétrazolyle; les radicaux (hétéro)aromatiques, y compris les cycles A et B, étant éventuellement substitués chacun par un atome d'halogène ou par un groupe trifluorométhyle, hydroxy, alcoxy inférieur, alkyle inférieur ou hydroxy-alkyle inférieur, sous forme libre ou sous forme de sel.

19. Procédé selon la revendication 1 ou 2 pour la préparation d'un composé de formule Ia, dans lequel R_1 représente un radical alkyle en C_3-C_5 ou, en second lieu, un radical alcényle en C_3-C_5; X_1 représente CO ou SO_2; X_2 représente un groupe de formule Ib dans lequel p et r représentent, indépendamment l'un de l'autre, 0 ou 1, et q représente 1; X_4 représente un groupe alkyle en C_1-C_4, hydroxyalkyle en C_1-C_4, cycloalkyl(C_3-C_7)-alkyle(C_1-C_4), phénylalkyle(C_1-C_4), ou imidazolyl-alkyle(C_1-C_4); et X_5 représente un atome d'hydrogène ou un groupe alkyle en C_1-C_4; ou X_4 et X_5 représentent ensemble le groupe tétraméthylène ou pentaméthylène; R_2 représente un groupe carboxy ou alcoxy(C_2-C_5)-carbonyle, ainsi qu'un groupe phényl-alcoxy(C_1-C_4)-carbonyle; et R_3 représente le groupe carboxy ou 5-tétrazolyle, sous forme libre ou sous forme de sel.

20. Procédé selon la revendication 1 ou 2 pour la préparation d'un composé de formule Ia, dans lequel R_1 représente un groupe alkyle en C_3-C_5 ou, en second lieu, un groupe alcényle en C_3-C_5; X_1 représente CO ou SO_2; X_2 représente un groupe de formule Ib dans lequel p et r représentent chacun 0 ou 1 et q représente 1; X_4 représente un groupe alkyle en C_1-C_4, hydroxyalkyle en C_1-C_4, cycloalkyl(C_3-C_7)-alkyle(C_1-C_4), phényl-alkyle(C_1-C_4), ou imidazolyl-alkyle(C_1-C_4); et X_5 représente un atome d'hydrogène; R_2 représente un groupe carboxy ou alcoxy(C_2-C_5)-carbonyle, ou un groupe phényl-alcoxy(C_1-C_4)-carbonyle; et R_3 représente le groupe carboxy ou 5-tétrazolyle, sous forme libre ou sous forme de sel.

21. Procédé selon la revendication 1 ou 2 pour la préparation d'un composé de formule Ia, dans lequel R_1 représente un groupe alkyle en C_3-C_5; X_1 représente CO; X_2 représente un groupe de formule Ib dans lequel q et r représentent 0 et p représente 1 à 3, ou dans lequel p et q représentent 1 et r représente 0; X_4 représente un groupe alkyle en C_1-C_4; X_5 représente un atome d'hydrogène ou un groupe alkyle en C_1-C_4; R_2 représente un groupe carboxy, alcoxy(C_2-C_5)-carbonyle; et R_3 représente le groupe carboxy ou 5-tétrazolyle, sous forme libre ou sous forme de sel.

22. Procédé selon la revendication 1 ou 2 pour la préparation d'un composé de formule Ia dans lequel R_3 représente le groupe 5-tétrazolyle, sous forme libre ou sous forme de sel.

23. Procédé selon la revendication 1 ou 2 pour la préparation d'un composé de formule Ia dans lequel R_1 représente un groupe alkyle en C_3-C_5; X_1 représente CO; X_2 représente un groupe de formule Ib dans lequel p représente 0 ou 1, r représente 0 et q représente 1; X_4 représente un groupe alkyle en C_1-C_4; et X_5 représente un atome d'hydrogène ou un groupe alkyle en C_1-C_4; ou X_4 et X_5 représentent ensemble le groupe tétraméthylène ou pentaméthylène; R_2 représente un groupe carboxy ou alcoxy(C_2-C_5)-carbonyle; et R_3 représente le groupe 5-tétrazolyle, sous forme libre ou sous forme de sel.

24. Procédé selon la revendication 1 ou 2 pour la préparation d'un composé de formule Ia, dans lequel R_1 représente un groupe alkyle en C_3-C_5; X_1 représente CO; X_2 représente un groupe de formule Ib dans lequel p représente 0 ou 1, r représente 0 et q représente 1; X_4 et X_5 représentent ensemble le groupe tétraméthylène ou pentaméthylène; R_2 représente un groupe carboxy ou alcoxy(C_2-C_5)-carbonyle; et R_3 représente le groupe tétrazolyle, sous forme libre ou sous forme de sel.

25. Procédé selon la revendication 1 ou 2 pour la préparation d'un composé de formule Ia dans lequel R_1 représente un groupe alkyle en C_3-C_5; X_1 représente CO; X_2 représente un groupe de formule Ib dans lequel p et r représentent 0 ou 1 et q représente 1; X_4 représente un groupe alkyle en C_1-C_4; et X_5 représente un atome d'hydrogène; R_2 représente un groupe carboxy ou alcoxy(C_2-C_5)-carbonyle; et R_3 représente le groupe 5-tétrazolyle, sous forme libre ou sous forme de sel.

26. Procédé selon la revendication 1 ou 2 pour la préparation d'un composé de formule Ia, selon l'une des revendications 14 à 25, dans lequel X_2 représente un groupe de formule Ib, q représente 1 et X_4 et X_5 ont des significations différentes, sous forme libre ou sous forme de sel, et dans lequel l'atome de carbone asymétrique concerné, portant les variables X_4 et X_5, a la configuration S.

27. Procédé selon la revendication 1 ou 2 pour la préparation de la (S)-N-(1-carboxy-2-méthylprop-1-yl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine, sous forme libre ou sous forme de sel, selon la revendication 1.

28. Procédé selon la revendication 1 ou 2 pour la préparation de la N-(2-carboxy-2,2-tétraméthylène-éthyl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine, sous forme libre ou sous forme de sel, selon la revendication 1.

29. Procédé selon la revendication 1 ou 2 pour la préparation de la N-(2-carboxy-2-éthylbut-1-yl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine, sous forme libre ou sous forme de sel, selon la revendication 1.

30. Procédé selon la revendication 1 ou 2 pour la préparation de la (S)-N-(1-carboxy-2-méthylprop-1-yl)-N-éthoxycarbonyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine, sous forme libre ou sous forme de sel, selon la revendication 1.

31. Procédé selon la revendication 1 ou 2 pour la préparation de la N-(1-carboxycyclohexyl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine, sous forme libre ou sous forme de sel, selon la revendication 1.

32. Procédé selon la revendication 1 ou 2 pour la préparation d'un composé selon la revendication 1, choisi parmi les suivants:

(S)-N-(1-carboxyéthyl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-(2-hydroxyéthyl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-(2-éthoxycarbonyl-2,2-tétraméthylène-éthyl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-(2-éthoxycarbonyl-2-éthylbut-1-yl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-(2-éthoxycarbonyl-2-méthylprop-1-yl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
(S)-N-(1-hydroxyméthyl-2-méthylprop-1-yl)-N-pentanoyl-N-[2'-1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-(2-éthoxycarbonyl-2,2-pentaméthylène-éthyl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
(S)-N-(1-carboxy-2-méthylprop-1-yl)-N-propyloxycarbonyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-(2-carboxy-2-méthylpropyl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-(2-carboxy-2,2-pentaméthylène-éthyl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
(S)-N-(1-aminocarbonyl-2-méthylprop-1-yl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine

et

(S)-N-(1-carboxy-2-méthylprop-1-yl)-N-5-oxopent-N-5-yl)-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,

chacun sous forme libre ou sous forme de sel.

33. Procédé selon la revendication 1 ou 2 pour la préparation d'un composé selon la revendication 1, choisi parmi les suivants:

N-carboxyméthyl-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
(S)-N-(1-méthoxycarbonyléthyl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-[1-carboxy-2-(4-fluorophényl)éthyl]-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-[2-(4-fluorophényl)-1-méthoxycarbonyléthyl]-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-[2-(4-fluorophényl)-1-hydroxyméthyléthyl]-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-(2'-carboxybiphényl-4-ylméthyl)-N-[1-carboxy-2-(4-fluorophényl)éthyl]-N-pentanoylamine,
N-(2'-carboxybiphényl-4-ylméthyl)-N-[2-(4-fluorophényl)-1-méthoxycarbonyléthyl]-N-pentanoylamine,
(S)-N-(2'-carboxybiphényl-4-ylméthyl)-N-(1-hydroxyméthyl-2-phényléthyl)-N-pentanoylamine,
(S)-N-(2'-carboxybiphényl-4-ylméthyl)-N-(1-hydroxyméthyl-2-imidazol-4-yléthyl)-N-pentanoylamine,
(R)-N-(1-carboxyéthyl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
(1S),(2S)-N-(1-carboxy-2-méthylbut-1-yl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
(1S),(2S)-N-(1-méthoxycarbonyl-2-méthylbut-1-yl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
(S)-N-(1-carboxybut-1-yl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
(S)-N-(1-méthoxycarbonylbut-1-yl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
(S)-N-(1-carboxyéthyl)-N-hexanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
(S)-N-butanoyl-N-(1-carboxyéthyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
(S)-N-(1-carboxyprop-1-yl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)-biphényl-4-ylméthyl]amine,
(S)-N-(1-carboxy-2-cyclohexyléthyl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)-biphényl-4-ylméthyl]amine,
(S)-N-(2-cyclohexyl-1-méthoxycarbonyléthyl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)-biphényl-4-ylméthyl]amine,
(R)-N-(1-carboxy-2-méthylprop-1-yl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)-biphényl-4-ylméthyl]amine,
N-(2-méthoxyéthyl)-N-pentanoyl-N-[2'-1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-(2-benzyloxyéthyl)-N-pentanoyl-N-[2'-1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-(3-méthoxyprop-1-yl)-N-pentanoyl-N-[2'-1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-(3-benzyloxyprop-1-yl)-N-pentanoyl-N-[2'-1H-tétrazol-5-yl)-biphényl-4-ylméthyl]amine,

N-(3-hydroxyprop-1-yl)-N-pentanoyl-N-[2'-1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-(1-méthoxycarbonyl-1-méthyléthyl)-N-pentanoyl-N-[2'-1H-tétrazol-5-yl)-biphényl-4-ylméthyl]amine,
N-(2-carboxyéthyl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-(2-carboxyprop-1-yl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-(1-carboxy-1-méthyléthyl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-(5-hydroxypent-1-yl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-(1-carboxyprop-2-yl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-(2-éthoxycarbonyl-3-méthylbut-1-yl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-(2-carboxy-3-méthylbut-1-yl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-(3-phénoxyprop-1-yl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-[2-(4-hydroxyphényl)éthyl]-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-[3-(4-hydroxyphényl)prop-1-yl]-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-[8-hydroxyoct-1-yl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-[2-méthanesulfonylaminoéthyl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-(3-acétylaminoprop-1-yl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-(2-méthoxy-2-oxo-1-phényléthyl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-(4-hydroxybut-2-yl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-(2-hydroxy-1-phényléthyl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-[3-(4-hydroxybenzylcarbonylamino)prop-1-yl]-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-(3-éthoxycarbonylcyclohexyl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-(3-carboxycyclohexyl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
cis-N-(4-carboxycyclohexyl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
cis-N-(2-éthoxycarbonylcyclohexyl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
cis-N-(2-carboxycyclohexyl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-[2-[2-(4-hydroxyphényl)éthylaminocarbonyl]-2,2-tétraméthylène-éthyl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
(S)-N-(1-[2-(4-hydroxyphényl)éthylaminocarbonyl]-2-méthylprop-1-yl)]-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
(S)-N-(1-carboxy-2,2-diméthylprop-1-yl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
(S)-N-(1-méthoxycarbonyl-2-méthylprop-1-yl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-(4-phénoxybut-1-yl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-(2-hydroxy-1-phényl-2-oxoéthyl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
(S)-N-(1-benzyloxycarbonyl-2-méthylprop-1-yl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-butanoyl-N-(1-carboxy-1-méthyléthyl)-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-(4-hydroxybut-1-yl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
(S)-N-(1-benzyloxycarbonyl-2-méthylprop-1-yl)-N-[3-bromo-2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]-N-pentanoylamine,
(S)-N-[3-bromo-2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]-N-(1-carboxy-2-méthylprop-1-yl)-N-pentanoylamine,
N-(2-acétylaminoéthyl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-[2-(n-butoxycarbonyl)-2,2-tétraméthylène-éthyl]-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-(2-benzylaminocarbonyl-2,2-tétraméthylène-éthyl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
(S)-N-butyloxycarbonyl-N-(1-carboxy-2-méthylprop-1-yl)-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
(S)-N-(1-carboxy-2-méthylprop-1-yl)-N-méthoxycarbonyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-(2-diéthylaminocarbonyl-2,2-tétraméthylène-éthyl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-(2-méthyl-2-morpholine-4-ylcarbonylpropyl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-(1-carboxycyclopentyl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-(1-carboxy-1-éthylprop-1-yl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl-)biphényl-4-ylméthyl]amine,
(S)-N-(5-amino-1-carboxypent-1-yl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-butanesulfonyl-N-(2-éthoxycarbonyl-2,2-pentaméthylène-éthyl)-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-butanesulfonyl-N-(2-carboxy-2,2-pentaméthylène-éthyl)-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylmé-

thyl]amine,
N-butanesulfonyl-N-(2-éthoxycarbonyl-2-méthylprop-1-yl)-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-butanesulfonyl-N-(2-carboxy-2-méthylprop-1-yl)-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
(S)-N-butanesulfonyl-N-(1-tert-butoxycarbonyléthyl)-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
(S)-N-butanesulfonyl-N-(1-carboxyéthyl)-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
(S)-N-butanesulfonyl-N-(1-carboxy-2-méthylprop-1-yl)-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
(S)-N-(2-méthyl-1-méthylaminocarbonylprop-1-yl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
(S)-N-(1-diméthylaminocarbonyl-2-méthylprop-1-yl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
(S)-N-(2-méthyl-1-morpholine-4-ylcarbonylprop-1-yl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
(S)-N-(2'-carboxybiphényl-4-ylméthyl)-N-(1-carboxy-2-méthylprop-1-yl)-N-pentanoylamine,
(S)-N-(1,2-dicarboxyéthyl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
(S)-N-(1-carboxy-3-phénylprop-1-yl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
(S)-N-(2-cyclohexyl-1-hydroxyméthyl-éthyl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
(R)-N-(1-méthoxycarbonyl-2-méthylprop-1-yl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
(S)-N-(2-hydroxy-1-méthoxycarbonyl-éthyl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-pentanoyl-N-(1H-tétrazol-5-ylméthyl)-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-pentanoyl-N-pyrid-3-ylméthyl)-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
(S)-N-(1-carboxy-4-guanidinobut-1-yl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-(2-hydroxy-1-méthoxycarbonylprop-1-yl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-(1-benzyloxycarbonyl-1-méthyléthyl)-N-butanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
(S)-N-(1-carboxy-3-méthylbut-1-yl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-(1-carboxy-2-hydroxyéthyl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
(S)-N-(1-carboxy-2-hydroxyéthyl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
(S)-N-(2-méthyl-1-(2-phényléthylaminocarbonyl)prop-1-yl]-N-pentanoyl-N-[2'-(1H-tétrasol-5-yl)biphényl-4-ylméthyl]amine,
(S)-N-(2-benzyloxy-1-hydroxyméthyléthyl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
(S)-N-(1-carboxy-2-méthylprop-1-yl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-3-ylméthyl]amine,
(S)-N-(1-carboxy-2-méthylprop-1-yl)-N-pentanoyl-N-[3'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
(S)-N-[2-méthyl-1-(1,2,3,4-tétrahydroquinol-1-ylcarbonyl)prop-1-yl]-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
(S)-N-(2-méthyl-1-pipéridine-1-ylcarbonylprop-1-yl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
(S)-N-[2-méthyl-1-(1,2,3,4-tétrahydroisoquinol-2-ylcarbonyl)prop-1-yl]-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-(2-hydroxyméthyl-2-méthylprop-1-yl)-N-pentanoyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
N-éthoxycarbonyl-N-(2-éthoxycarbonyl-2-méthylprop-1-yl)-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine et
N-(2-carboxy-2-méthylprop-1-yl)-N-éthoxycarbonyl-N-[2'-(1H-tétrazol-5-yl)biphényl-4-ylméthyl]amine,
chacun sous forme libre ou sous forme de sel.

34. Procédé pour la préparation d'une composition pharmaceutique contenant, en tant que substance active, un composé selon l'une des revendications 1 ou 3 à 33, sous forme libre ou sous forme d'un sel pharmaceutiquement utilisable, éventuellement en plus d'adjuvants pharmaceutiques usuels, caractérisé en ce que l'on met la substance active, éventuellement avec addition d'adjuvants pharmaceutiques usuels, sous forme d'une composition pharmaceutique.

35. Utilisation d'un composé selon l'une des revendications 1 ou 3-33, sous forme libre ou sous forme d'un sel pharmaceutiquement utilisable, pour la préparation d'un agent antihypertenseur.

36. Utilisation d'un composé selon l'une des revendications 1 ou 3-33, sous forme libre ou sous forme d'un sel pharmaceutiquement utilisable, pour la préparation d'une composition pharmaceutique destinée au traitement thérapeutique ou prophylactique de l'insuffisance cardiaque.

37. Utilisation d'un composé selon l'une des revendications 1 ou 3-33, sous forme libre ou sous forme d'un sel pharmaceutiquement utilisable, pour la préparation d'une composition pharmaceutique destinée au traitement thérapeutique ou prophylactique de maladies qui sont provoquées par l'activité de l'angiotensine II.

US005217996A

United States Patent [19]

Ksander

[11] Patent Number: 5,217,996

[45] Date of Patent: Jun. 8, 1993

[54] **BIARYL SUBSTITUTED 4-AMINO-BUTYRIC ACID AMIDES**

[75] Inventor: **Gary Ksander**, Milford, N.J.

[73] Assignee: **Ciba-Geigy Corporation**, Ardsley, N.Y.

[21] Appl. No.: **824,132**

[22] Filed: **Jan. 22, 1992**

[51] **Int. Cl.**[5] **C07C 229/34**; A61K 31/235

[52] **U.S. Cl.** **514/533**; 514/563; 546/335; 549/452; 558/267; 558/275; 560/41; 562/450

[58] **Field of Search** 560/41, 39; 562/450; 549/77, 452, 496; 546/335; 558/267, 275; 514/533, 563

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,513,009	4/1985	Roques et al.	514/513
4,721,726	1/1988	Berger	514/464
4,939,261	7/1990	Ksander	562/444
5,021,430	6/1991	Ksander	514/332
5,096,925	3/1991	Ksander	514/522

FOREIGN PATENT DOCUMENTS

38758	10/1981	European Pat. Off. .
836934	1/1985	South Africa .
2207351	6/1989	United Kingdom .

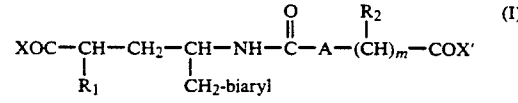
OTHER PUBLICATIONS

C. M. Ksander et al., J. Med. Chem. 32, 2519 (1989).

Primary Examiner—José G. Dees
Assistant Examiner—B. Frazier
Attorney, Agent, or Firm—Norbert Gruenfeld

[57] **ABSTRACT**

The invention relates to biaryl substituted 4-amino-butyric acid derivatives of formula I



(I)

wherein COX and COX′ independently represent carboxyl or carboxyl derivatized in form of a pharmaceutically acceptable ester or amide; R_1 represents hydrogen, lower alkyl, C_3–C_7-cycloalkyl-lower alkyl, aryl-lower alkyl, biaryl-lower alkyl, lower alkoxy, aryl-lower alkoxy, aryloxy, N-lower alkylamino, N,N-di-lower alkylamino, N-aryl-lower alkylamino, N,N-di-aryl-lower alkylamino, N-arylamino, N,N-diarylamino, lower alkanoylamino, aryl-lower alkanoylamino or aroylamino; R_2 represents hydrogen, hydroxy, lower alkoxy, lower alkyl, aryl-lower alkyl, C_3–C_7-cycloalkyl-lower alkyl, amino-lower alkyl, hydroxy-lower alkyl, lower alkylthio-lower alkyl, lower alkoxy-lower alkyl, aryl-lower alkylthio-lower alkyl or aryl-lower alkoxy-lower alkyl; biaryl represents phenyl substituted by carbocyclic or heterocyclic aryl; A represents a direct bond, lower alkylene, phenylene or cyclohexylene; m represents 1 or zero, provided that m represents 1 when A is a direct bond; or pharmaceutically acceptable salts thereof; pharmaceutical compositions comprising said compounds; methods for the preparation of said compounds and for the preparation of intermediates; and methods of treating disorders in mammals which are responsive to the inhibition of neutral endopeptidases by administration of said compounds to mammals in need of such treatment.

11 Claims, No Drawings

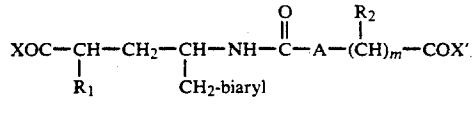
BIARYL SUBSTITUTED 4-AMINO-BUTYRIC ACID AMIDES

SUMMARY OF THE INVENTION

Endogenous atrial natriuretic peptides (ANP), also called atrial natriuretic factors (ANF) have diuretic, natriuretic and vasorelaxant functions in mammals. The natural ANF peptides are metabolically inactivated, in particular by a degrading enzyme which has been recognized to correspond to the enzyme neutral endopeptidase (NEP) EC 3.4. 24.11, also responsible for e.g. the metabolic inactivation of enkephalins.

The aim of the present invention is to provide novel biaryl substituted 4-amino-butyric acid amide derivatives described below which are useful as neutral endopeptidase (NEP) inhibitors, e.g. as inhibitors of the ANF-degrading enzyme in mammals, so as to prolong and potentiate the diuretic, natriuretic and vasodilator properties of ANF in mammals, by inhibiting the degradation thereof to less active metabolites. The compounds of the invention are thus particularly useful for the treatment of conditions and disorders responsive to the inhibition of neutral endopeptidase EC 3.4. 24.11, particularly cardiovascular disorders, such as hypertension, renal insufficiency including edema and salt retention, pulmonary edema and congestive heart failure. By virtue of their inhibition of neutral endopeptidase, the compounds of the invention may also be useful for the treatment of pain, depression and certain psychotic conditions. Other potential indications include the treatment of angina, premenstrual syndrome, Meniere's disease, hyperaldosteronism, hypercalciuria, ascites, glaucoma, asthma, inflammations and gastrointestinal disorders such as diarrhea, irritable bowel syndrome and gastric hyperacidity.

The present invention relates to biaryl substituted 4-amino-butyric acid derivatives of formula I



(I)

wherein COX and COX' independently represent carboxyl or carboxyl derivatized in form of a pharmaceutically acceptable ester or amide; R_1 represents hydrogen, lower alkyl, C_3–C_7-cycloalkyl-lower alkyl, aryl-lower alkyl, biaryl-lower alkyl, lower alkoxy, aryl-lower alkoxy, aryloxy, N-lower alkylamino, N,N-di-lower alkylamino, N-aryl-lower alkylamino, N,N-di-aryl-lower alkylamino, N-arylamino, N,N-diarylamino, lower alkanoylamino, aryl-lower alkanoylamino or aroylamino; R_2 represents hydrogen, hydroxy, lower alkoxy, lower alkyl, aryl-lower alkyl, C_3–C_7-cycloalkyl-lower alkyl, amino-lower alkyl, hydroxy-lower alkyl, lower alkylthio-lower alkyl, lower alkoxy-lower alkyl, aryl-lower alkylthio-lower alkyl or aryl-lower alkoxy-lower alkyl; biaryl represents phenyl substituted by carbocyclic or heterocyclic aryl; A represents a direct bond, lower alkylene, phenylene or cyclohexylene; m represents 1 or zero, provided that m represents 1 when A is a direct bond; or a pharmaceutically acceptable salt thereof.

Pharmaceutically acceptable ester and amide derivatives are preferably prodrug derivatives, such being convertible by solvolysis or under physiological conditions to the free carboxylic acids of formula I wherein COX and/or COX' represent carboxyl.

Compounds of formula I and derivatives thereof, depending on the nature of substituents, possess one or more asymmetric carbon atoms. The resulting diastereoisomers and optical antipodes are encompassed by the instant invention.

DETAILED DESCRIPTION OF THE INVENTION

The definitions used herein, unless denoted otherwise, have the following meanings within the scope of the present invention.

The term biaryl represents phenyl substituted by carbocyclic aryl or heterocyclic aryl as defined herein, ortho, meta or para to the point of attachment of the phenyl ring, advantageously para; biaryl is also represented as the $-C_6H_4-R_3$ substituent in formulae herein.

Carbocyclic aryl preferably represents preferably monocyclic carbocyclic aryl or optionally substituted naphthyl.

Monocyclic carbocyclic aryl represents optionally substituted phenyl, being preferably phenyl or phenyl substituted by one to three substituents, such being advantageously lower alkyl, hydroxy, lower alkoxy, lower alkanoyloxy, halogen, cyano, trifluoromethyl, lower alkanoylamino or lower alkoxycarbonyl. Monocyclic carbocyclic aryl particularly preferably represents phenyl or phenyl substituted by lower alkyl, lower alkoxy, hydroxy, halogen, cyano or trifluoromethyl.

Optionally substituted naphthyl represents 1- or 2-naphthyl or 1- or 2-naphthyl preferably substituted by lower alkyl, lower alkoxy or halogen.

Heterocyclic aryl represents preferably monocyclic heterocyclic aryl such as optionally substituted thienyl, indolyl, imidazolyl, furanyl, pyridyl, pyrrolyl or N-lower alkylpyrrolyl.

Optionally substituted furanyl represents 2- or 3-furanyl or 2- or 3-furanyl preferably substituted by lower alkyl.

Optionally substituted pyridyl represents 2-, 3- or 4-pyridyl or 2-, 3- or 4-pyridyl preferably substituted by lower alkyl, halogen or cyano.

Optionally substituted thienyl represents 2- or 3-thienyl or 2- or 3-thienyl preferably substituted by lower alkyl.

Optionally substituted indolyl represents preferably 2- or 3-indolyl or 2- or 3-indolyl preferably substituted by lower alkyl, lower alkoxy or halogen.

Optionally substituted imidazolyl is preferably 1- or 2-imidazolyl or 1- or 2-imidazolyl preferably substituted by lower alkyl.

Aryl as in aryl-lower alkyl, aryl-lower alkoxy, aryloxy, N-arylamino, N,N-diarylamino, aryl-lower alkoxycarbonyl or aryl-lower alkanoylamino is preferably phenyl or phenyl substituted by one or two of lower alkyl, lower alkoxy, hydroxy, lower alkanoyloxy, halogen, trifluoromethyl, cyano, lower alkanoylamino or lower alkoxycarbonyl.

The term "lower" referred to herein in connection with organic radicals or compounds respectively defines such with up to and including 7, preferably up and including 4 and advantageously one or two carbon atoms. Such may be straight chain or branched.

A lower alkyl group preferably contains 1–4 carbon atoms and represents e.g. ethyl, n- or iso-propyl, n-, iso-, sec.- or tert.-butyl or advantageously methyl.

A lower alkoxy group preferably contains 1–4 carbon atoms and represents for example methoxy, n-propoxy, isopropoxy, n-, iso-, sec.- or tert.-butoxy or advantageously ethoxy.

Aryl-lower alkyl is advantageously benzyl or phenethyl optionally substituted by one or two of lower alkyl, lower alkoxy, hydroxy, lower alkanoyloxy, halogen or trifluoromethyl.

Aryl-lower alkoxy represents advantageously e.g. benzyloxy, benzyloxy substituted by lower alkyl, lower alkoxy, lower alkanoyloxy, halogen or trifluoromethyl, or pyridylmethoxy.

Aryloxy preferably represents phenoxy or phenoxy substituted by lower alkyl, lower alkoxy, lower alkanoyloxy, halogen or trifluoromethyl.

N-arylamino and N,N-diarylamino represent advantageously N-phenylamino or N,N-diphenylamino optionally substituted in the phenyl moiety or phenyl moieties by lower alkyl, lower alkoxy, hydroxy, lower alkanoyloxy, halogen or trifluoromethyl.

The term C_3–C_7-cycloalkyl represents a saturated cyclic hydrocarbon radical which contains 3 to 7 and preferably 5 to 7 ring carbon and is, most preferably, cyclopentyl or cyclohexyl.

The term cycloalkyl-lower alkyl represents preferably 1- or 2-(cyclopentyl or cyclohexyl)ethyl, 1-, 2- or 3-(cyclopentyl or cyclohexyl)propyl, or 1-, 2-, 3- or 4-(cyclopentyl or cyclohexyl)-butyl.

Amino-lower alkyl represents preferably amino-(ethyl, propyl or butyl), particularly omega-amino-(ethyl, propyl or butyl).

A N-lower alkylamino group preferably contains 1–4 carbon atoms in the lower alkyl portion and represents, for example, N-n-propyl-amino, N-iso-propylamino, N-n-butylamino, N-tert.-butylamino and advantageously N-methylamino or N-ethylamino.

A N,N-di-lower alkylamino group preferably contains 1–4 carbon atoms in each lower alkyl portion and represents, for example, N,N-dimethylamino, N-methyl-N-ethylamino and advantageously N,N-diethylamino.

Hydroxy-lower alkyl is for example 2-hydroxyethyl and preferably hydroxymethyl.

Lower alkylthio as in lower alkylthio-lower alkyl represents advantageously C_1–C_4-alkylthio and preferably methylthio or ethylthio.

Lower alkylene represents branched or straight chain alkylene of 1 to 7 carbon atoms, advantageously straight chain (or linear) alkylene, such as methylene, ethylene, propylene, butylene, pentylene or hexylene and most preferably straight chain C_1–C_4-alkylene.

Phenylene represents preferably 1,3 or 1,4-phenylene, advantageously 1,4-phenylene.

Cyclohexylene represents preferably 1,4-cyclohexylene.

Halogen (halo) preferably represents fluoro or chloro, but may also be bromo or iodo.

Lower alkanoyloxy advantageously contains 2 to 5 carbon atoms and is preferably acetoxy, pivaloyloxy or propionyloxy.

Lower alkanoylamino advantageously contains 2 to 5 carbon atoms and is preferably acetylamino or propionylamino.

A lower alkoxycarbonyl group preferably contains 1 to 4 carbon atoms in the alkoxy portion and represents, for example, methoxycarbonyl, n-propoxycarbonyl, iso-propoxycarbonyl or advantageously ethoxycarbonyl.

Aroylamino is preferably benzoylamino or benzoylamino substituted on the benzene ring by lower alkyl, lower alkoxy, halogen or trifluoromethyl.

Carboxyl esterified in form of a pharmaceutically acceptable ester, represents advantageously a prodrug ester that may be convertible by solvolysis or under physiological conditions to the free carboxylic acid, such being preferably C_1–C_{20}-alkoxycarbonyl, advantageously lower alkoxycarbonyl; (amino, acylamino, mono-or di-lower alkylamino)-lower alkoxycarbonyl; carboxy-lower alkoxycarbonyl, e.g. alpha-carboxy-lower alkoxycarbonyl; lower alkoxycarbonyl-lower alkoxycarbonyl, e.g. alpha-lower alkoxycarbonyl-lower alkoxycarbonyl; α-(di-lower alkylamino, amino, mono-lower alkylamino, morpholino, piperidino, pyrrolidino, 1-lower alkylpiperazino)-carbonyl-lower alkoxycarbonyl; aryl-lower alkoxycarbonyl, preferably optionally (halo, lower alkyl or lower alkoxy)-substituted benzyloxycarbonyl, or pyridylmethoxycarbonyl; 1-(hydroxy, lower alkanoyloxy or lower alkoxy)-lower alkoxycarbonyl, e.g. pivaloyloxymethoxycarbonyl; (hydroxy, lower alkanoyloxy or lower alkoxy)-lower alkoxymethoxycarbonyl; bicycloalkoxycarbonyl-lower alkoxycarbonyl, e.g. bicyclo[2,2,1]-heptyloxycarbonyl-lower alkoxycarbonyl, especially bicyclo-[2,2,1]-heptyloxycarbonylmethoxycarbonyl such as bornyloxycarbonylmethoxycarbonyl; 1-(lower alkoxycarbonyloxy)-lower alkoxycarbonyl; 5-indanyloxycarbonyl; 3-phthalidoxycarbonyl and (lower alkyl, lower alkoxy or halo)-substituted 3-phthalidoxycarbonyl; polyhydroxy-lower alkoxycarbonyl or protected polyhydroxy-lower alkoxycarbonyl in which polyhydroxy-lower alkoxy and protected polyhydroxy-lower alkoxy represent preferably dihydroxypropyloxy or trihydroxybutyloxy wherein hydroxy groups are free or one or more, as appropriate, are protected in form of esters, e.g. a lower alkanoyl or a benzoyl ester, in form of ethers, e.g. a lower alkyl or benzyl ether, or, in case two vicinal hydroxy groups are involved, in the form of acetals or ketals, e.g. a lower alkylidene, a benzylidene or a 5- or 6-membered cycloalkylidene derivative.

Protected polyhydroxy-lower alkoxycarbonyl advantageously represents (2,2-dimethyl-1,3-dioxolan-4-yl)-methoxycarbonyl.

Acyl as in acyloxy or acylamino represents preferably lower alkanoyl, carbocyclic aryl-lower alkanoyl, aroyl, lower alkoxycarbonyl or aryl-lower alkoxycarbonyl, advantageously lower alkanoyl. Lower alkoxycarbonyl for acyl is preferably t-butoxycarbonyl (abbreviated t-BOC). Aryl-lower alkoxycarbonyl for acyl is preferably benzyloxycarbonyl (abbreviated CBZ).

Carboxy-lower alkoxycarbonyl represents advantageously e.g. 1-carboxyethoxycarbonyl.

Lower alkoxycarbonyl-lower alkoxycarbonyl represents advantageously e.g. 1-(ethoxycarbonyl)ethoxycarbonyl.

Amino-lower alkoxycarbonyl, mono-lower alkylamino-lower alkoxycarbonyl, di-(lower)alkylamino-lower alkoxycarbonyl advantageously represent e.g. aminoethoxycarbonyl, ethylaminoethoxycarbonyl, diethylaminoethoxycarbonyl.

Lower alkylidene is preferably isopropylidene.

Cycloalkylidene is preferably cyclohexylidene.

Carboxyl esterified in form of a pharmaceutically acceptable prodrug ester represents most advantageously C_1–C_4-alkoxycarbonyl, phenyloxycarbonyl, benzyloxycarbonyl optionally substituted on phenyl by lower alkyl, lower alkoxy, halo or trifluoromethyl,

pivaloyloxymethoxycarbonyl, 1-(C_2–C_4-alkanoyloxy)-ethoxycarbonyl, (2,2-dimethyl-1,3-dioxolan-4-yl)-methoxycarbonyl, 5-indanyloxycarbonyl, 3-phthalidoxycarbonyl, bornyloxycarbonylmethoxycarbonyl, 1-(C_1–C_4-alkoxycarbonyloxy)-ethoxycarbonyl or 3-pyridylmethoxycarbonyl.

Carboxyl derivatized in the form of a pharmaceutically acceptable amide represents preferably carbamoyl or N-substituted carbamoyl, advantageously [lower alkylamino, arylamino, di-lower alkylamino, morpholino, N-lower alkylpiperazino, pyrrolidino, piperidino, perhydroazepino, (amino or acylamino)-lower alkylamino or aryl-lower alkylamino]-carbonyl.

Pharmaceutically acceptable salts are either pharmaceutically acceptable acid addition salts for any basic compounds of the invention or salts derived from pharmaceutically acceptable bases for any acidic compounds of the invention.

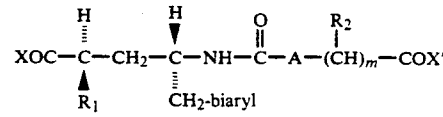
Pharmaceutically acceptable salts of basic compounds of the invention are acid addition salts, which are preferably such of therapeutically acceptable inorganic or organic acids, such as strong mineral acids, for example hydrohalic, e.g. hydrochloric or hydro-bromic acid, sulfuric, phosphoric or nitric acid; aliphatic or aromatic carboxylic or sulfonic acids, e.g. formic, acetic, propionic, succinic, glycollic, lactic, malic, tartaric, gluconic, citric, maleic, fumaric, pyruvic, phenylacetic, benzoic, 4-aminobenzoic, anthranilic, 4-hydroxybenzoic, salicylic, 4-aminosalicylic, pamoic, nicotinic, methanesulfonic, ethanesulfonic, hydroxyethanesulfonic, 1,2-ethanedisulfonic acid, benzenesulfonic, p-toluenesulfonic, naphthalenesulfonic, sulfanilic, cyclohexylsulfamic acid, or ascorbic acid.

Pharmaceutically acceptable salts of the acidic compounds of the invention, e.g. those having a free carboxyl group are salts formed with pharmaceutically acceptable bases, e.g. alkali metal salts (e.g. sodium, potassium salts), alkaline earth metal salts (e.g. magnesium, calcium salts), ammonium salts, mono-, di- or tri-lower (alkyl or hydroxyalkyl)-ammonium salts (e.g. ethanolammonium, diethanolammonium, triethanolammonium, tromethamine salts).

The compounds of the invention, of formula I and derivatives thereof may contain several asymmetric carbon atoms, depending on the nature of the substituents. Thus the compounds of the invention exist in the form of geometric isomers, racemates, diastereoisomers, pure enantiomers or mixtures thereof, all of which are within the scope of the invention.

For example, the compounds of formula I exist in isomeric forms, e.g. wherein the asymmetric carbon atom on the butyryl chain bearing the R_1 and/or biarylmethyl groups may either exist in the S or R configuration. The compounds of the invention, e.g. those of formula I having said two asymmetric centers exist as two different racemic diastereoisomeric forms which may be called erythro and threo depending on the relative orientation of the R_1 and biarylmethyl substituents of the chain. Each of the two racemates consists of the optically active enantiomers (or antipodes) having (S,S), (R,R), (R,S) or (S,R) configurations, respectively.

Preferred is the threo racemic form and particularly the enantiomeric form depicted in formula I'

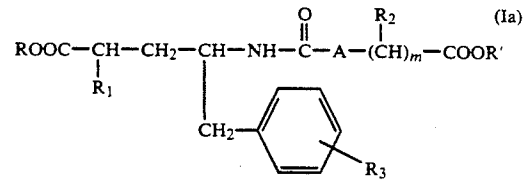


(I')

wherein COX, COX', R_1, R_2, A, biaryl and m have the meanings as defined herein above for compounds of formula I. The compounds of formulae Ia, Ib, Ic, Id, Ie and If given below are present as well, preferably in the enantiomeric form depicted in formula I'.

Illustrative thereof, in the above compounds of formula I wherein R_1 is lower alkyl, the carbon atom carrying said substituent is assigned the (R)-configuration; and the carbon atom carrying the biarylmethyl substituent is assigned the (S)-configuration.

More particularly, the present invention is concerned with and has for its object the compounds of formula Ia



(Ia)

wherein COOR and COOR' independently represent carboxyl or carboxyl derivatized in form of a pharmaceutically acceptable ester; R_1 represents hydrogen, lower alkyl, lower alkoxy, N-lower alkylamino, lower alkanoylamino, aryl-lower alkyl, aryl-lower alkoxy, aryloxy, N-arylamino or aroylamino wherein aryl in each case represents phenyl optionally substituted by lower alkyl, lower alkoxy, halogen, hydroxy, cyano, acyloxy or trifluoromethyl, or aryl represents thienyl or furanyl optionally substituted by lower alkyl; R_2 represents hydrogen, hydroxy, lower alkyl or aryl-lower alkyl wherein aryl independently has the meaning given above under R_1; R_3 represents phenyl, or phenyl substituted by lower alkyl, lower alkoxy, halogen, cyano, acyloxy or trifluoromethyl; or R_3 represents thienyl or furanyl optionally substituted by lower alkyl; A represents a direct bond, lower alkylene, 1,4-phenylene or 1,4-cyclohexylene; m represents 1 or zero provided that m represents 1 when A is a direct bond; or a pharmaceutically acceptable salt thereof.

Advantageously, R_3 is located in the para position.

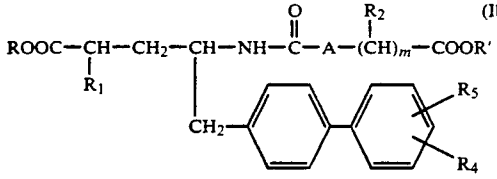
Particularly preferred embodiments of the invention as described above relate to:

a) compounds wherein R_3 is phenyl or phenyl substituted by lower alkyl, lower alkoxy, halogen, cyano, acyloxy or trifluoromethyl;

b) compounds wherein A is lower alkylene, m represents 1 or zero, and R_2 represents hydrogen, lower alkyl, hydroxy or lower alkoxy.

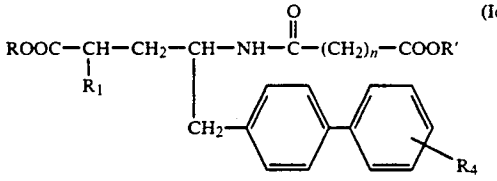
c) compounds wherein R_1 represents hydrogen, lower alkyl, lower alkoxy or aryl-lower alkyl wherein aryl represents phenyl optionally substituted by one or two of lower alkyl, lower alkoxy, halogen, hydroxy, cyano, acyloxy or trifluoromethyl; most preferably compounds wherein R_1 represents lower alkoxy or lower alkyl.

A particular embodiment of the invention relates to compounds of formula Ib



wherein COOR and COOR' independently represent carboxyl or carboxyl derivatized in form of a pharmaceutically acceptable ester; R_1 is hydrogen, lower alkyl, lower alkoxy or aryl-lower alkyl wherein aryl represents phenyl optionally substituted by lower alkyl, lower alkoxy, halogen, hydroxy, cyano, acyloxy or trifluoromethyl; R_2 represents hydrogen, hydroxy or lower alkoxy; R_4 and R_5 independently represent hydrogen, lower alkyl, hydroxy, lower alkoxy, halogen, cyano or trifluoromethyl; A represents lower alkylene; m represents 1 or zero; or a pharmaceutical acceptable salt thereof.

Particularly preferred are compounds of formula Ic

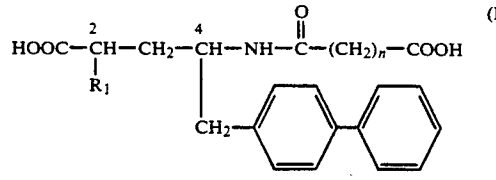


wherein COOR and COOR' independently represent carboxyl or carboxyl derivatized in form of a pharmaceutically acceptable ester; R_1 is lower alkyl or lower alkoxy; R_4 represents hydrogen, lower alkyl, lower alkoxy, halogen, or trifluoromethyl; n represents an integer 1 through 6; or a pharmaceutical acceptable salt thereof.

Preferred are compounds of formula Ic wherein COOR and COOR' independently represent carboxyl, C_1–C_{20}-alkoxycarbonyl, (carbocyclic or heterocyclic aryl)-lower alkoxycarbonyl, (di-lower alkylamino, N-lower alkylpiperazino, morpholino, pyrrolidino, piperidino or perhydrazepino)-C_2 to C_4-alkoxycarbonyl, dihydroxypropyloxycarbonyl protected in form of a ketal, 5-indanyloxycarbonyl, 3-phthalidoxycarbonyl, bicycloalkoxycarbonyl-lower alkoxycarbonyl, α-(lower alkoxycarbonyl or di-lower alkylaminocarbonyl)-lower alkoxycarbonyl, 1-(lower alkoxycarbonyloxy)-lower alkoxycarbonyl or 1-(lower alkanoyloxy)-lower alkoxycarbonyl; or a pharmaceutically acceptable salt thereof.

Particularly preferred are said compounds of formula Ic wherein COOR and COOR' independently represent carboxyl, C_1–C_4-alkoxycarbonyl, 3-pyridylmethoxycarbonyl, benzyloxycarbonyl optionally substituted on phenyl by lower alkyl, lower alkoxy, halo or trifluoromethyl, 5-indanyloxycarbonyl, 1-(C_2–C_5-alkanoyloxy)-ethoxycarbonyl, 3-phthalidoxycarbonyl, (2,2'-dimethyl-1,3-dioxolan-4-yl)-methoxycarbonyl, bornyloxycarbonylmethoxycarbonyl, 1-(C_1–C_4-alkoxycarbonyloxy)-ethoxycarbonyl; or a pharmaceutically acceptable salt thereof.

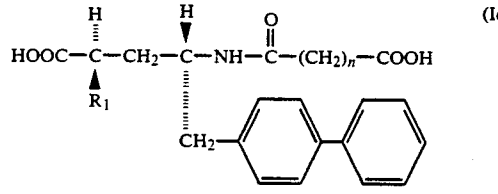
A preferred embodiment of the invention relates to compounds of formula Id



wherein R_1 is lower alkyl; n is an integer 1 through 4; or a pharmaceutically acceptable mono- or di-ester derivative thereof in which one or two of the acidic hydroxy groups of the carboxyl functional groups are esterified in form of a mono- or di-pharmaceutically acceptable ester; or a pharmaceutically acceptable salt thereof; or an optical antipode thereof.

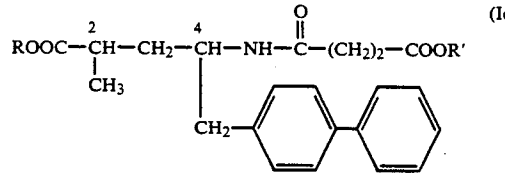
Preferred are said compounds of formula Id wherein R_1 is methyl and n is 2; and mono- or di-esters thereof.

As discussed before, the butyric acid compounds of e.g. formula Id exist in two distinct diastereomeric forms which may be called erythro and threo. Preferred are e.g. the compounds of formula Id as the threo diastereomer (racemate), more particularly as the enantiomeric form having the R-configuration at C-atom 2 and the S-configuration at C-atom 4 and wherein the butyryl portion is as depicted in formula Id'



wherein R_1 and n are as defined under formula Id; or a pharmaceutical acceptable mono-or diester derivative thereof; or a pharmaceutical acceptable salt thereof.

Particularly preferred are compounds of formula Ie



wherein COOR and COOR' independently represent carboxyl or carboxyl esterified in form of a pharmaceutical acceptable prodrug ester; or a pharmaceutically acceptable salt thereof.

Particularly preferred embodiments of the invention as described above relate to:

(a) compounds of the above formula Ie wherein R and R' independently represent hydrogen, C_1–C_4-alkyl, benzyl optionally substituted on phenyl by lower alkyl, lower alkoxy, halo or trifluoromethyl, pivaloyloxymethyl, 1-(C_2–C_4-alkanoyloxy)-ethyl, (2,2-dimethyl-1,3-dioxolan-4-yl)-methyl, 5-indanyl, 3-phthalidyl, bornyloxycarbonylmethyl, 1-(C_1–C_4-alkoxycarbonyloxy)-ethyl or 3-pyridylmethyl; or a pharmaceutically acceptable salt thereof;

(b) compounds of the above formula Ie wherein COOR' is carboxyl; and COOR represents carboxyl or carboxyl derivatized in form of a pharma-

ceutically acceptable ester; or a pharmaceutically acceptable salt thereof;

(c) compounds of the above formula Ie having the R-configuration at C-atom 2 and the S-configuration at C-atom 4;

(d) the compound according to the above formula Ie wherein COOR is ethoxycarbonyl and COOR' is carboxyl, namely being 4-[N-(3-carboxy-1-oxopropyl)amino]-4-(p-phenylphenylmethyl)-2-methylbutanoic acid ethyl ester, the (2R,4S)antipode thereof or a pharmaceutical acceptable salt thereof.

The novel compounds of the invention are pharmacologically potent neutral endopeptidase enzyme inhibitors which inhibit e.g. the degradation of atrial natriuretic factors (ANF) in mammals. They thus potentiate the diuretic and natriuretic effect of exogenous or endogenous ANF in mammals.

The compounds of the invention are thus particularly useful in mammals as diuretic, natriuretic (saluretic) and antihypertensive agents for the treatment of e.g. hypertension, congestive heart failure and edema.

As neutral endopeptidase inhibitors, the compounds are also e.g. enkephalinase inhibitors so as to inhibit the degradation of endogenous enkephalins and may thus also be useful for the treatment of pain in mammals.

The above-cited properties are demonstrable in vitro and in vivo tests, using advantageously mammals, e.g. mice, rats, dogs, monkeys or isolated organs, tissues and preparations thereof. Said compounds can be applied in vitro in the form of solutions, e.g. preferably aqueous solutions, and in vivo either enterally, parenterally, advantageously intravenously, e.g. as a suspension or in aqueous solution. The dosage in vitro may range between about 10^{-4} molar and 10^{-9} molar concentrations. The dosage in vivo may range depending on the route of administration, between about 0.01 and 50 mg/kg, advantageously between about 1.0 and 25 mg/kg.

The analgesic activity can be determined by measuring the potentiation of the analgesic effects of enkephalin and derivatives thereof, and by classical analgesic tests, such as the phenyl-p-benzoquinone induced writing test [J. Pharmacol. Exp. Therap. 125, 237 (1959)] and the hot plate test in the mouse [J. Pharmacol. Exp. Therap. 107, 385 (1953).

The antihypertensive activity can be determined in the spontaneously hypertensive rat, Goldblatt rat or Goldblatt dog by direct measurement of blood pressure. Advantageously, the effect is measured in the DOCA-salt hypertensive rat and/or renal hypertensive rat or dog model.

The diuretic (saluretic) activity can be determined in standard diuretic screens, e.g. as described in "New Antihypertensive Drugs", Spectrum Publications, 1976, pages 307–321, or by measuring the potentiation of atrial natriuretic factor-induced natriuresis and diuresis in the rat.

The potentiation of ANF can also be determined by measuring the increase in ANF plasma level achieved.

The in vitro inhibition of neutral endopeptidase (NEP) 3.4.24.11 can be determined as follows:

Neutral endopeptidase 3.4.24.11 activity is determined by the hydrolysis of the substrate glutaryl-Ala-Ala-Phe-2-naphthylamide (GAAP) using a modified procedure of Orlowski and Wilk (1981). The incubation mixture (total volume 125 μl) contains 4.2 μg of protein (rat kidney cortex membranes prepared by method of Maeda et al, 1983), 50 mM tris buffer, pH 7.4 at 25° C., 500 μM substrate (final concentration), and leucine aminopeptidase M (2.5 μg). The mixture is incubated for 10 minutes at 25° C. and 100 μl of fast garnet (250 μg fast garnet/ml of 10% Tween 20 in 1M sodium acetate, pH 4.2) is added. Enzyme activity is measured spectrophotometrically at 540 nm. One unit of NEP 24.11 activity is defined as 1 nmol of 2-naphthylamine released per minute at 25° C. at pH 7.4. IC_{50} values are determined, i.e. the concentration of test compound required for 50% inhibition of the release of 2-naphthylamine.

Neutral endopeptidase activity is also determined using ANF as a substrate. A trial natriuretic factor degrading activity is determined by measuring the disappearance of rat-ANF (r-ANF) using a 3 minute reverse phase-HPLC separation. An aliquot of the enzyme in 50 mM Tris HCl buffer, pH 7.4, is preincubated at 37° C. for 2 minutes and the reaction is initiated by the addition of 4 nmol of r-ANF in a total volume of 50 μl. The reaction is terminated after 4 minutes with the addition of 30 μl of 0.27% trifluoroacetic acid (TFA). Forty microliters of the mixture is injected into a reverse phase-HPLC and analyzed using a C4 cartridge in a 3 minute, isocratic separation. Twenty-three percent of buffer B (0.1% TFA in 80% acetonitrile) is used. Buffer A is 0.1% TFA in water. One unit of activity is defined as the hydrolysis of 1 nmol of r-ANF per minute at 37° C. at pH 7.4. IC_{50} values are determined, i.e. the concentration of test compound required for 50% inhibition of the hydrolysis of ANF.

The test compound is dissolved in dimethyl sulfoxide or 0.25M sodium bicarbonate solution, and the solution is diluted with pH 7.4 buffer to the desired concentration.

In vitro testing is most appropriate for the free carboxylic acids of the invention.

The effect of the compounds of the invention on rat plasma ANF concentration can be determined as follows:

Male Sprague-Dawley rats (275–390 g) are anesthetized with ketamine (150 mg/kg)/acepromazine (10%) and instrumented with catheters in the femoral artery and vein to obtain blood samples and infuse ANF, respectively. The rats are tethered with a swivel system and are allowed to recover for 24 hours before being studied in the conscious, unrestrained state.

In this assay, plasma ANF levels are determined in the presence and absence of NEP inhibition. On the day of study, all rats are infused continuously with ANF at 450 ng/kg/min. i.v. for the entire 5 hours of the experiment. Sixty minutes after beginning the infusion, blood samples for baseline ANF measurements are obtained (time 0) and the rats are then randomly divided into groups treated with the test compound or vehicle. Additional blood samples are taken 30, 60, 120, 180 and 240 minutes after administration of the test compound.

Plasma concentrations are determined by a specific radioimmunoassay. The plasma is diluted (×12.5, ×25 and ×50) in buffer containing: 50 mM Tris (pH 6.8), 154 mM NaCl, 0.3% bovine serum albumin, 0.01% EDTA. One hundred microliters of standards [rANF (99–126)] or samples are added to 100 μl of rabbit anti-rANF serum and incubated at 4° C. for 16 hours. Ten thousand cpm of [^{125}I]rANF are then added to the reaction mixture which is incubated at 4° C. for an additional 24 hours. Goat anti-rabbit IgG serum coupled to paramagnetic particles is added to the reaction mixture and bound [^{125}I]rANF is pelleted by exposing the mixture to

an attracting magnetic rack. The supernatant is decanted and the pellets counted in a gamma counter. All determinations are performed in duplicate. Plasma ANF levels are expressed as a percent of those measured in vehicle-treated animals which received ANF alone (450 ng/kg/min i.v.).

Illustrative of the invention, N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester at doses of about 1–30 mg/kg p.o., administered in 10% ethanol/polyethylene glycol (PEG) 400, produces significant increases in plasma ANF levels.

The antihypertensive effect can be determined in desoxycorticosterone acetate (DOCA)-salt hypertensive rats.

DOCA-salt hypertensive rats (280–380 g) are prepared by the standard method. Rats underwent a unilateral nephrectomy and one week later are implanted with silastic pellets containing 100 mg/kg of DOCA. The rats are maintained on 1% NaCl/0.2% KCl drinking water for three to five weeks until sustained hypertension is established. The antihypertensive activity is evaluated at this time.

Two days before an experiment, the rats are anesthetized with methoxyflurane and instrumented with catheters in the femoral artery to measure arterial blood pressure. Forty-eight hours later, baseline arterial pressure and heart rate are recorded during a 1 hour period. The test compound (30 mg/kg p.o.) or vehicle is then administered and the same cardiovascular parameters are monitored for an additional 5 hours.

Illustrative of the invention, N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester at a dose of 30 mg/kg p.o., administered in PEG 400, produces a significant reduction in blood pressure in the DOCA-salt hypertensive rat model.

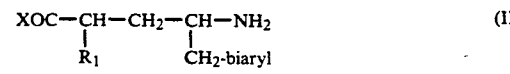
The potentiation of the natriuretic effect of ANF can be determined as follows:

Male Sprague-Dawley rats (280–360 g) are anesthetized with Inactin (100 mg/kg i.p.) and instrumented with catheters in the femoral artery, femoral vein and urinary bladder to measure arterial pressure, administer ANF and collect urine, respectively. A continuous infusion of normal saline (33 μl/min) is maintained throughout the experiment to promote diuresis and sodium excretion. The experimental protocol consists of an initial 15 minute collection period (designated as pre-control) followed by three additional collection periods. Immediately after completion of the pre-control period, test compound or vehicle is administered; nothing is done for the next 45 minutes. Then, blood pressure and renal measurements are obtained during a second collection period (designated control; 15 min). At the conclusion of this period, ANF is administered (1 μg/kg i.v. bolus) to all animals and arterial pressure and renal parameters are determined during two consecutive 15 minutes collection periods.

Mean arterial pressure, urine flow and urinary sodium excretion are determined for all collection periods. Blood pressure is measured with a Gould p50 pressure transducer, urine flow is determined gravimetrically, sodium concentration is measured by flame photometry, and urinary sodium excretion is calculated as the product of urine flow and urine sodium concentration.

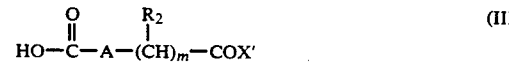
The compounds of the invention are thus particularly useful as inhibitors of neutral endopeptidase, enhancing the potency and duration of action of artrial natriuretic peptide(s). The compounds are therefore particularly useful for the treatment of cardiovascular disorders such as hypertension, edema and salt retention, and cardiac conditions such as congestive heart failure.

The compounds of the invention of formula I may be prepared using the following process which comprises: condensing a compound of formula II



(II)

wherein COX, R_1 and biaryl have the meaning as defined above, in temporarily protected form if required; with a compound of formula III



(III)

or a reactive functional derivative thereof, wherein A, R_2, m and COX' have the meaning as defined above, in temporarily protected form if required; and, if temporarily protecting any interfering reactive group(s), removing said protecting group(s), and then isolating the resulting inventive compound; and, if desired, converting any resulting compound into another compound of the invention, and/or, if desired, converting a resulting free compound into a salt or a resulting salt into the free compound or into another salt, and/or, if desired, separating a mixture of isomers or racemates obtained into the single isomers or racemates, and/or, id desired, resolving a racemate obtained into the optical antipodes.

In starting compounds and intermediates which are converted to the compounds of the invention in a manner described herein, functional groups present, such as carboxyl, amino and hydroxy groups, are optionally protected by conventional protecting groups that are common in preparative organic chemistry. Protected carboxyl, amino and hydroxy groups are those that can be converted under mild conditions into free carboxyl, amino and hydroxy groups without other undesired side reactions taking place.

The purpose of introducing protecting groups is to protect the functional groups from undesired reactions with reaction components and under the conditions used for carrying out a desired chemical transformation. The need and choice of protecting groups for a particular reaction is known to those skilled in the art and depends on the nature of the functional group to be protected (carboxyl group, amino group etc.), the structure and stability of the molecule of which the substituent is a part, and the reaction conditions.

Well-known protecting groups that meet these conditions and their introduction and removal are described, for example, in J. F. W. McOmie, "Protective Groups in Organic Chemistry", Plenum Press, London, New York 1973, T. W. Greene, "Protective Groups in Organic Synthesis", Wiley, New York 1984, and also in "The Peptides", Vol. I, Schroeder and Luebke, Academic Press, London, New York, 1965.

The preparation of compounds of the invention according to the above process, i.e. the condensation of an amine of formula II with the acid of formula III, or a functional reactive derivative thereof, is carried out by methodology well-known for peptide synthesis.

Reactive functional derivatives of compounds of formula III are preferably halides, anhydrides such as succinic anhydride, glutaric anhydride, or mixed anhydrides such as the pivaloyl, alkoxycarbonyl or cyanoacetyl anhydride.

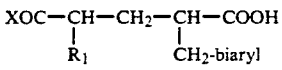
The condensation of an amine of formula II with a free carboxylic acid of formula III is carried out advantageously in the presence of a condensing agent such as dicyclohexylcarbodiimide or N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide and hydroxybenzotriazole in an inert polar solvent such as dimethylformamide or methylene chloride, preferably at room temperature.

The condensation of an amine of formula II with a reactive functional derivative of an acid of formula III in the form of an acid halide, advantageously an acid chloride, anhydride or mixed anhydride, is carried out in an inert solvent such as toluene or methylene chloride, advantageously in the presence of a base, e.g. an inorganic base such as potassium carbonate or an organic base such as triethylamine or pyridine, preferably at room temperature.

The starting materials of formula III are acids or functional derivatives thereof known in the art or which may be prepared by conventional methods known in the art.

The starting materials of formula II are known or, if new, may be prepared according to conventional methods, e.g., those illustrated by the examples herein.

For example, the compounds of formula II may be prepared by converting a compound of formula IV

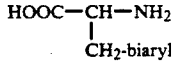


(IV)

wherein COX, R_1 and biaryl have the meaning mentioned above, in temporarily protected form if required, into a suitable carboxylic acid amide or carboxylic acid azide and then subjecting this compound to a Hofmann reaction or to a Curtius rearrangement in a manner well known in the art. The compounds of formula IV are known, for example, from U.S. Pat. No. 5,021,430 or may be prepared analogous to the methods described therein.

In a preferred alternative route, the starting materials of formula II may be prepared by

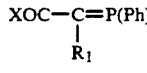
(a) reducing the carboxylic group of a biarylalanine of formula V



(V)

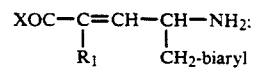
in temporarily protected form if required, to yield the respective aldehyde;

(b) subsequently reacting said aldehyde with a triphenylphosphonium compound of formula VI



(VI)

(c) hydrogenating the resulting compound of formula VII



(VII)

and, if temporarily protecting any interfering reactive group(s), removing said protective group(s) and then isolating the resulting product. In the above formulae V, VI and VII, the variables COX, R_1 and biaryl have the meaning as defined under formula I. The above reaction steps (a), (b) and (c) are carried out by methodology well-known in the art.

For example, in step (a) the compound of formula V, advantageously an amino protected compound of formula V, is reacted first of all with a hydroxylamine or a salt thereof, e.g. with N,O-dimethylhydroxylamine hydrochloride; the resulting hydroxylamine amide is then reduced to the aldehyde in a conventionel manner, e.g. with lithium aluminum hydride.

Reaction step (b) represents a conventional Wittig reaction which may be performed in a manner known in the art.

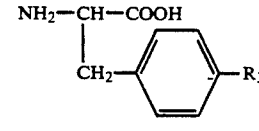
Reaction step (c) as well represents a commonly known hydrogenation reaction which may be performed e.g. with molecular hydrogen in the presence of a suitable catalyst such as palladium/charcoal.

Biarylalanines of formula V are either known in the art or can be prepared according to methods reported in the art.

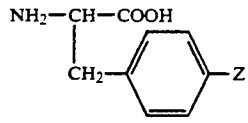
As to the preparation of the biarylalanines of formula V as starting materials in optically active form, such can be prepared e.g. by resolution or by one of the following methods:

(a) Adapting a method described in Tetrahedron Letters 1988, 6075, a biarylmethanol, e.g. 4-biphenylylmethanol, is converted to a reactive derivative, e.g. the bromide, which is then condensed with an N-acyl derivative of 2,3-diphenyl-6-oxomorpholine, e.g. the N-carbobenzyloxy-(2R,3S)-isomer, in the presence of a strong base such as sodium bis-trimethylsilylamide, to yield e.g. N-carbobenzyloxy-2(R),3(S),5(S)-6-oxo-2,3-diphenyl-5-(4-biphenylylmethyl)-morpholine. Catalytic hydrogenolysis, e.g. using hydrogen and palladium on charcoal as catalyst, yields the optically active (S)-(+)-4-biphenylalanine.

(b) Alternatively, using the Pd (0)-catalyzed cross-coupling reaction described in Tetrahedron Letters 31, 1665 (1990), J. Organic Chemistry 55, 906 (1990) and Tetrahedron 45, 6670 (1989) as developed by W. Shieh et al, the substantially optically pure chiral biarylalanines, of the formula



or the N-acyl and/or carboxy ester derivatives thereof wherein R_3 has meaning as defined hereinabove, can be prepared by: condensing a reactive esterified optically active tyrosine derivative of the formula



wherein the amino and carboxy groups are in protected form (as N-acyl and esterified carboxy ester derivatives), and Z represents reactive esterified hydroxy (advantageously trifluoromethylsulfonyloxy) with an aryl boronic acid in which aryl corresponds to R_3 as defined above, in the presence of a palladium (0) catalyst, in particular tetrakis(triphenylphosphine)palladium (0), and in the presence of an anhydrous base (such as an alkali metal carbonate), in an inert solvent (such as xylene or toluene) at an elevated temperature ranging from about 50° to 150° C., and removing any protecting groups as required.

For example, N-t-butoxycarbonyl-tyrosine methyl ester is first converted to N-t-butoxycarbonyl-4-trifluoromethylsulfonyloxy-phenylalanine methyl ester (N-t-butoxycarbonyltyrosine triflate methyl ester). This compound is then condensed with an arylboronic acid (e.g. phenylboronic acid) in the presence of anhydrous potassium carbonate, and tetrakis (triphenylphosphine) palladium (0) complex as catalyst, in toluene preferably at an elevated temperature, advantageously at about 100° to obtain N-t-butoxycarbonyl-4-biphenylalanine methyl ester. After N-deacylation, substantially optically pure 4-biphenylalanine methyl ester is obtained with a configuration corresponding to that of the tyrosine derivative used as starting material.

The arylboronic acids are either commercial or can be prepared as described in the literature, e.g. J. Org. Chem. 49,5237 (1984).

The triphenylphosphonium compounds of formula VI are either known in the art or can be prepared according to methods reported in the art.

Compounds of the invention wherein COX or COX' represent carboxyl derivatized in form of a pharmaceutically acceptable amide can also be prepared according to the above methods using corresponding starting materials wherein COX or COX' represent carbamoyl or N-substituted carbamoyl.

The compounds of the invention so obtained, can be converted into each other according to conventional methods. Thus, for example, resulting amides or esters may be hydrolyzed with aqueous alkalies, such as alkali metal carbonates or hydroxides. Resulting free acids may be esterified with e.g. said unsubstituted or substituted alkanols or reactive esterified derivatives thereof such as alkyl halides, or diazoalkanes. Free acids are also converted into said metal, ammonium or acid addition salts in conventional manner.

Thus, any resulting free acid or base can be converted into a corresponding metal, ammonium or acid addition salt respectively, by reacting it with an equivalent amount of the corresponding base, basic salt, acid or ion exchange preparation, e.g. said free acids with alkali or ammonium hydroxides or carbonates, or e.g. free amines with said inorganic or organic acids respectively. Any resulting salt may also be converted into the free compound, by liberating the latter with stronger acids or bases, respectively. In view of the close relationship between the free compounds and the salts thereof, whenever a compound of the invention, or intermediate, is referred to in this context, a corresponding salt is also intended, provided such is possible or appropriate under the circumstances.

The compounds, including their salts, may also be obtained in the form of their hydrates, or include other solvent used for the crystallization. Furthermore, the functional derivatives of the free acids of formula I, wherein the carboxy groups are esterified by identical or different radicals may be prepared by condensing a free acid of formula I or a mono- or di-ester derivative thereof with an esterifying agent of the formula VIII

$$R_6—Z \qquad \text{(VIII)}$$

wherein Z represents hydroxy or a reactive esterified hydroxyl group; and R_6 represents an esterifying radical as defined herein for the carboxylic esters (encompassed e.g. by COX or COX' representing esterified carboxy), in particular said non-aromatic radicals.

A reactive esterified hydroxyl group, such as Z in a compound of the formula VIII, is a hydroxyl group esterified by a strong inorganic or organic acid. Corresponding Z groups are in particular halo, for example chloro, bromo or preferably iodo, also sulfonyloxy groups, such as lower alkyl- or arylsulfonyloxy groups, for example (methane-, ethane-, benzene- or toluene-) sulfonyloxy groups, also the trifluoromethylsulfonyloxy group.

The esterification of the carboxyl groups, optionally in salt form, with a compound of formula VIII wherein Z represents a reactive esterified hydroxyl group, is performed in a manner known per se, in the presence of for example an organic base, such as an organic amine, for example a tertiary amine, such as tri-lower alkylamine, for example trimethylamine, triethylamine or ethyl-di-isopropylamine, an N,N-di-lower-alkyl-aniline, for example N,N-di-methylaniline, a cyclic tertiary amine, such as an N-lower-alkylated morpholine, for example N-methyl-morpholine, a base of the pyridine type, for example pyridine, an inorganic base, for example hydroxides, carbonates, or hydrogen carbonates of alkali metals or alkaline-earth metals, for example sodium, potassium or calcium hydroxide, carbonate or hydrogen carbonate, or a quaternary ammonium base, such as a tetraalkylammonium hydroxide, carbonate or hydrogen carbonate, for example in which alkyl is e.g. methyl, ethyl, propyl, isopropyl, butyl, or the like, or an alkali metal salt of bis-trialkylsilylamide (e.g. trimethyl) optionally in the presence of a crown ether such as 18-crown-6 in a suitable inert solvent or solvent mixture, e.g. acetonitrile, toluene, and the like.

A trifunctional free acid, e.g. of the formula I, or a monoester or diester thereof, is preferably first converted into a salt of one of the stated organic or inorganic bases, especially into the sodium or potassium salt, and is then reacted with a compound of the formula VIII. The compounds of formula VIII are known or can be prepared by methods well-known to the art.

A compound of the formula or VIII wherein Z is a reactive esterified hydroxyl group can be prepared in situ. For example, a compound of the formula VIII wherein Z is chloro can be converted by treatment with sodium iodide in a solvent, for example in acetone or acetonitrile, into a compound of the formula VIII wherein Z is iodo; or esterification can be carried out with a chloro compound of the formula VIII in the presence of sodium iodide.

Esterification of a compound with a free carboxyl group using in excess an alcohol of formula VIII

(wherein Z represents hydroxy) is carried out in a manner known per se, e.g. in the presence of an acid catalyst e.g. sulfuric acid or boron trifluoride etherate, preferably at an elevated temperature, advantageously ranging from about 40° C. to 100° C. Alternately, the esterification of a compound with a free carboxyl group can be carried out with at least an equimolar amount of the alcohol in the presence of a condensing agent such as dicyclohexylcarbodiimide or N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide in a polar solvent such as methylene chloride, in the presence of a base if required, e.g. such as 4-(dimethylamino)pyridine.

Conversely, carboxylic acid esters can be converted to compounds of the invention with a free carboxy group using methods and conditions generally known in the art and illustrated herein. Depending on type of ester involved, useful reagents include aqueous acids or bases; also anhydrous reagents such as trialkylsilyl halides, hydrobromic acid in glacial acetic acid; also hydrogen and a hydrogenolysis catalyst. For instance, trialkyl esters can be converted to the free trifunctional acids by treatment with hydrobromic acid in glacial acetic acid, e.g. at room temperature or elevated temperature. Also trialkyl esters can be converted to the mono esters wherein carboxy only remains esterified, by treatment with e.g. trimethylsilyl bromide at room temperature.

Any benzyl esters can be selectively hydrogenolyzed with e.g. hydrogen in the presence of a catalyst such as palladium on charcoal.

In the case mixtures of stereoisomers or optical isomers of the above compounds are obtained, these can be separated into the single isomers by methods in themselves known, e.g., by fractional distillation, crystallization and/or chromatography. Racemic products can be resolved into the optical antipodes, for example, by separation of diastereomeric salts thereof, e.g., for basic compounds by the fractional crystallization of d- or l-(tartrate, mandelate or camphorsulfonate) salts, or for acidic compounds by fractional crystallization of d- or l-(alpha-methylbenzylamine, cinchonidine, cinchonine, quinine, quinidine, ephedrine, dehydroabietylamine, brucine or strychnine)-salts.

The above-mentioned reactions are carried out according to standard methods, in the presence or absence of diluents, preferably such as are inert to the reagents and are solvents thereof, of catalysts, alkaline or acidic condensing or said other agents respectively and/or inert atmospheres, at low temperatures, room temperature or elevated temperatures, preferably near the boiling point of the solvents used, at atmospheric or superatmospheric pressure.

The invention further includes any variant of said processes, in which an intermediate product obtainable at any stage of the process is used as a starting material and any remaining steps are carried out, or the process is discontinued at any stage thereof, or in which the starting materials are formed under the reaction conditions, or in which the reaction components are used in the form of their salts or optically pure antipodes. Mainly those starting materials should be used in said reactions, that lead to the formation of those compounds indicated above as being preferred.

The present invention additionally relates to the use in mammals of the compounds of the invention and their pharmaceutically acceptable, non-toxic acid addition salts, or pharmaceutical compositions thereof, as medicaments, e.g. as neutral endopeptidase inhibitors, e.g. for the treatment of cardiovascular disorders such as hypertension, edema, salt retention and congestive heart failure.

The present invention also relates to the use of the compounds of the invention for the preparation of pharmaceutical compositions especially pharmaceutical compositions having neutral endopeptidase inhibiting activity, and e.g. antihypertensive or saluretic activity.

The pharmaceutical compositions according to the invention are those suitable for enteral, such as oral or rectal, transdermal and parenteral administration to mammals, including man, for the treatment of cardiovascular disorders, such as hypertension, comprising an effective amount of a pharmacologically active compound of the invention or a pharmaceutically acceptable salt thereof, alone or in combination with one or more pharmaceutically acceptable carriers.

The pharmacologically active compounds of the invention are useful in the manufacture of pharmaceutical compositions comprising an effective amount thereof in conjunction or admixture with excipients or carriers suitable for either enteral or parenteral application. Preferred are tablets and gelatin capsules comprising the active ingredient together with a) diluents, e.g. lactose, dextrose, sucrose, mannitol, sorbitol, cellulose and/or glycine; b) lubricants, e.g. silica, talcum, stearic acid, its magnesium or calcium salts and/or polyethyleneglycol; for tablets also c) binders, e.g. magnesium aluminum silicate, starch paste, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose and/or polyvinylpyrrolidone; if desired, d) disintegrants, e.g. starches, agar, alginic acid or its sodium salt, or effervescent mixtures; and/or e) absorbents, colorants, flavors and sweeteners. Injectable compositions are preferably aqueous isotonic solutions or suspensions, and suppositories are advantageously prepared from fatty emulsions or suspensions. Said compositions may be sterilized and/or contain adjuvants, such as preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure and/or buffers. In addition, the compositions may also contain other therapeutically valuable substances. Said compositions are prepared according to conventional mixing, granulating or coating methods, respectively, and contain about 0.1 to 75%, preferably about 1 to 50%, of the active ingredient.

Suitable formulations for transdermal application include an effective amount of a compound of the invention with carrier. Advantageous carriers include absorbable pharmacologically acceptable solvents to assist passage through the skin of the host. Characteristically, transdermal devices are in the form of a bandage comprising a backing member, a reservoir containing the compound, optionally with carriers, optionally a rate controlling barrier to deliver the compound to the skin of the host at a controlled and predetermined rate over a prolonged period of time, and means to secure the device to the skin.

A unit dosage for a mammal of about 50 to 70 kg may contain between about 10 and 100 mg of the active ingredient. The dosage of active compound is dependent on the species of warm-blooded animal (mammal), the body weight, age and individual condition, and on the form of administration.

The following examples are intended to illustrate the invention and are not to be construed as being limitations thereon. Temperatures are given in degrees Centigrade. If not mentioned otherwise, all evaporations are

performed under reduced pressure, preferably between about 15 and 100 mm Hg. Optical rotations are measured at room temperature at 589 nm (D line of sodium), 365 nm or other wavelengths as specified in the examples.

The prefixes R and S are used to indicate the absolute configuration at each asymmetric center.

EXAMPLE 1

To a solution of N-(3-carbo(t)butoxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester (0.80 g) in 15 ml of CH_2Cl_2 at room temperature are added 3 ml of trifluoroacetic acid. The mixture is stirred overnight and concentrated. The residue is dissolved in tetrahydrofuran (THF), and 6.5 ml of 1N NaOH is added. The mixture is concentrated and triturated with ether. The solid can be recrystallized from methylene chloride-hexane to give sodium N-(3-carboxyl-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methyl butanoic acid ethyl ester melting at 159°-160° C.; $[\alpha]_D^{20} = -11.4°$ (methanol).

The starting material is prepared as follows:

A solution of α-t-BOC-(R)-tyrosine methyl ester (5.9 g, 20 mmol) and pyridine (8 mL, 100 mmol) in methylene chloride (30 mL) is cooled to 0°-5° C. Trifluoromethanesulfonic anhydride (4 mL, 23 mmol) is added at 0°-5° C., and the resulting mixture is held for another 30 minutes. The reaction mixture is diluted with water (60 mL) and methylene chloride (100 mL), and washed sequentially with 0.5N sodium hydroxide solution (1×50 mL), water (1×60 mL), 10% citric acid solution (2×75 mL) and water (1×60 mL). The organic phase is dried over $MgSO_4$ and concentrated to an oil. The oil is purified by column chromatography (silica gel, hexane/ethyl acetate, 2:1 to give methyl(R)-2-(t-butoxycarbonylamino)-3-[4-(trifluoromethylsulfonyloxy)phenyl]-propionate which crystallizes on standing; m.p. 46°-48° C.; $[\alpha]^{20}_D - 36.01°$ (c=1, $CHCl_3$).

Nitrogen is passed through a suspension of (R)-2-(t-butoxycarbonylamino)-3-[4-(trifluoromethylsulfonyloxy)-phenyl]-propionate (1.75 mmol), phenylboronic acid (3.5 mmol), anhydrous potassium carbonate (2.63 mmol) and toluene (17 mL) for 15 minutes. Tetrakis(triphenylphosphine)palladium(0) is added, and the mixture is heated at 85°-90° for 3 hours. The reaction mixture is cooled to 25° C., diluted with ethyl acetate (17 mL) and washed sequentially with saturated sodium bicarbonate (1×20 mL), water (1×20 mL), 10% citric acid (1×20 mL), water (1×20 mL) and saturated sodium chloride solution (1×20 mL). The organic phase is concentrated, and the residue is purified by column chromatography (silica gel, hexane/ethyl acetate 2:1) to yield methyl (R)-2-(t-butoxycarbonylamino)-3-(p-phenylphenyl)-propionate which can also be called N-(R)-t-butoxycarbonyl-(p-phenylphenyl)-alanine methyl ester.

To a solution of N-(R)-t-butoxycarbonyl-(p-phenylphenyl)-alanine methyl ester (6.8 g) in 60 ml of THF and 20 ml of methanol are added 20 ml of aqueous 1N sodium hydroxide solution. The mixture is stirred for 1 h at room temperature and then acidified with 21 ml of 1N hydrochloric acid. The aqueous solution is extracted 3× with ethyl acetate. The combined organic extracts are dried ($MgSO_4$), filtered and concentrated to give N-(R)-t-butoxycarbonyl-(p-phenylphenyl)-alanine, m.p. 98°-99° C.; $[\alpha]^{20}_D - 18.59°$ (c=1, methanol).

To a solution of N-(R)-t-butoxycarbonyl-(p-phenylphenyl)-alanine (4.8 g) in 70 ml of methylene chloride (CH_2Cl_2) at 0° C. with 1.65 g of N,O-dimethylhydroxylamine HCl, 1.7 g of triethylamine and 2.85 g of hydroxybenzotriazole are added 5.37 g of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride. The mixture is stirred 17 h at room temperature. The mixture is concentrated taken up in ethyl acetate (EtOAc) and washed with saturated sodium bicarbonate, 1N HCl and brine, then dried ($MgSO_4$), filtered and concentrated to give N-(R)-t-butoxycarbonyl-(p-phenylphenyl)-alanine N,O-dimethyl hydroxylamine amide.

To a 0° C. solution of N-(R)-t-butoxycarbonyl-(p-phenylphenyl)-alanine N,O-dimethyl hydroxylamine amide (5.2 g) in 250 ml of diethyl ether are added 0.64 g of lithium aluminum hydride. The reaction is stirred for 30 min. and quenched with aqueous potassium hydrogen sulfate. The mixture is stirred for additional 5 min., poured onto 1N HCl, extracted (3×) with EtOAc, dried ($MgSO_4$), filtered, and concentrated to give N-(R)-4-t-butoxycarbonyl-(p-phenylphenyl)-alanine carboxaldehyde as a colorless oil.

To a 0° C. solution of N-(R)-t-butoxycarbonyl-(p-phenylphenyl)-alanine carboxaldehyde (4.4 g) in 200 ml of CH_2Cl_2 are added 10 g of carboethoxyethylidene phenyl phosphorane. The mixture is warmed to room temperature, stirred for 1 h, washed with brine, dried ($MgSO_4$), filtered and concentrated. The residue is chromatographed on silica gel eluting with (1:2) ether:-hexane to give N-t-butoxycarbonyl-(4R)-(p-phenylphenylmethyl)-4-amino-2-methyl-2-butenoic acid ethyl ester.

A solution of N-t-butoxycarbonyl-(4R)-(p-phenylphenylmethyl)-4-amino-2-methyl-2-butenoic acid ethyl ester (4.2 g) in 400 ml of ethanol is suspended with 2.0 g of 5% palladium on charcoal and then is hydrogenated at 50 psi for 6 h. The catalyst is removed by filtration and the filtrate is concentrated to give N-t-butoxycarbonyl(4S)-(p-phenylphenylmethyl)-4-amino-2-methylbutanoic acid ethyl ester as a 80:20 mixture of diastereomers.

To the N-t-butoxycarbonyl(4S)-(p-phenylphenylmethyl)-4-amino-2-methylbutanoic acid ethyl ester (4.2 g) in 40 ml of CH_2Cl_2 at 0° C. is bubbled dry hydrogen chloride gas for 15 min. The mixture is stirred 2 h and concentrated to give (4S)-(p-phenylphenylmethyl)-4-amino-2-methylbutanoic acid ethyl ester hydrochloride as a 80:20 mixture of diastereomers.

To a room temperature solution of the above amine salt (3.12 g) in 15 ml of CH_2Cl_2 and 15 ml of pyridine are added 13.5 g of succinic anhydride. The mixture is stirred for 17 h, concentrated, dissolved in ethyl acetate, washed with 1N HCl and brine, and dried ($MgSO_4$) to give N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2-methylbutanoic acid ethyl ester as a 80:20 mixture of diastereomers.

The above N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2-methylbutanoic acid ethyl ester diastereomeric mixture (3.9 g) and N,N-dimethylformamide-di-t-butyl acetal (8.8 ml) are heated at 80° C. in 40 ml of toluene for 2 h. The mixture is poured onto ice-1N HCl, extracted with ether, chromatographed on silica gel eluting with (2:1) toluene-:ethyl acetate to give N-(3-carbo(t)butoxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester as the more polar mate-

rial and the corresponding (S,S) diastereomer as the less polar material.

EXAMPLE 2

To a solution of N-(3-carboxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl-4-amino-(2R)-methylbutanoic acid ethyl ester (0.33 g) in 20 ml of (1:1) ethanol:tetrahydrofuran (THF) at room temperature are added 5 ml of 1N sodium hydroxide solution (NaOH) and stirred for 17 h. The mixture is concentrated, dissolved in water and washed with ether. The aqueous layer is acidified with 1N hydrochloric acid (HCl), extracted 3× with ethyl acetate (EtOAc), dried over magnesium sulfate ($MgSO_4$), filtered and concentrated. The residue is triturated with ether to yield N-(3-carboxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl-4-amino-(2R)-methylbutanoic acid melting at 158°–164° C., $[\alpha]_D^{20} = -23.5°$ (methanol).

EXAMPLE 3

Following the procedures described in Examples 1 or 2, the following compounds are prepared:

N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2S-methylbutanoic acid melting at 165°–167° C.;

N-(3-carboxy-1-oxopropyl)-(4S)-[p-(4-methylphenyl)-phenylmethyl]-4-amino-2R-methyl butanoic acid melting at 165°–170° C., $[\alpha]_D^{20} = -18.4°$ (c=1, methanol);

N-(3-carboxy-1-oxopropyl)-(4R)-p-phenylphenylmethyl-4-amino-2S-methylbutanoic acid, melting at 145°–149° C.;

N-(3-carboxyl-1-oxopropyl)-(4R)-p-phenylphenylmethyl-4-amino-(2R)-methylbutanoic acid, melting at 162°–165° C.;

N-(3-carboxy-1-oxopropyl)-4(S,R)-p-phenylphenylmethyl-4-amino-2(S,R)-methyl butanoic acid, melting at 165°–167° C.;

Sodium N-(3-carboxy-1-oxopropyl)-4(S,R)-p-phenylphenylmethyl-4-amino-2(S,R)-methylbutanoic acid ethyl ester, melting at 165°–167° C.;

Sodium N-(3-carboxy-1-oxopropyl)-(4R)-p-phenylphenylmethyl-4-amino-2S-methylbutanoic acid ethyl ester, melting at 117°–120° C.;

N-(3-ethoxycarbonyl-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid, melting at 178°–190° C.;

N-(2-carboxy-1-oxoethyl)-(4S)-p-phenylphenylmethyl-4-amino-2(S,R)-methylbutanoic acid, melting at 160°–161° C.;

N-(5-carboxy-1-oxopentyl)-(4S)-p-phenylphenylmethyl-4-amino-2R-methylbutanoic acid, melting at 124°–127° C.;

Sodium N-(3-carboxy-1-oxopropyl)-4(S,R)-p-phenylphenylmethyl-4-amino-2(S,R)-methoxybutanoic acid, melting at 180°–185° C.;

Sodium N-(3-carboxy-1-oxopropyl)-4(S,R)-p-phenylphenylmethyl-4-amino-2(S,R)-methoxybutanoic acid indanyl ester, melting at 134°–136° C.;

N-(3-carboxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl-4-amino-butanoic acid, melting at 163°–166° C.;

N-(3-carboxy-3-hydroxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl-4-amino-2R-methylbutanoic acid, melting at 156°–170° C.

EXAMPLE 4

Following the procedures described in example 1 except substituting glutaric anhydride for succinic anhydride, the following compounds are prepared:

N-(4-carboxy-1-oxobutyl)-(4S)-p-phenylphenylmethyl-4-amino-2R-methylbutanoic acid, melting at 152°–155° C.

Sodium N-(4-carboxy-1-oxobutyl)-(4S)-p-phenylphenylmethyl-4-amino-2R-methylbutanoic acid ethyl ester, melting at 68°–72° C.

EXAMPLE 5

Following the procedures described in example 1 except substituting carbobutoxyethylidene phenyl phosphorane for carboethoxyethylidene phenyl phosphorane, the following compound is prepared:

Sodium N-(3-carboxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl-4-amino-2R-methylbutanoic acid n-butyl ester, melting at 155°–165° C.

EXAMPLE 6

To a room temperature solution of N-t-butoxycarbonyl-(4R)-p-phenylphenylmethyl-4-amino-2-methyl-2-butenoic acid ethyl ester (0.50 g) in 2 ml ethanol and 4 ml THF are added 2.0 ml of 1N NaOH. The reaction is stirred until the disappearance of starting material monitored by thin layer chromatography. The mixture is concentrated, dissolved in sodium bicarbonate and washed with ether. The aqueous layer is acidified with 3N HCl and extracted (3×) with ethyl acetate. The organic extracts are washed with brine, dried ($MgSO_4$), filtered and concentrated to give N-t-butoxycarbonyl-(4R)-p-phenylphenylmethyl-4-amino-2-methyl-2-butenoic acid.

To a room temperature solution of N-t-butoxycarbonyl-(4R)-p-phenylphenylmethyl-4-amino-2-methyl-2-butenoic acid (0.30 g) in 10 ml of CH_2Cl_2 are added 0.123 g of dimethyl aminopyridine, 0.203 g of 5-indanol and 0.387 g of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride. The mixture is stirred overnight, and then is concentrated and taken up in ethyl acetate. The organics are washed with saturated sodium bicarbonate (2×), 1N HCl (2×) and brine (2×), dried ($MgSO_4$), filtered, concemtrated and chromatographed on silica gel eluting with (1:4) ethyl acetate:hexane to give N-t-butoxycarbonyl-(4R)-p-phenylphenylmethyl-4-amino-2-methyl-2-butenoic acid indanyl ester. This material is converted to sodium N-(3-carboxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl-4-amino-2R-methylbutanoic acid indanyl ester melting at 60°–65° C. according to the procedures described in example 1.

EXAMPLE 7

To a solution of (4S)-p-phenylphenylmethyl-4-amino-2-methylbutanoic acid ethyl ester hydrochloride (0.84 g) in 10 ml of methylene chloride are added 0.58 g of adipic acid mono methyl ester, 0.293 g of triethylamine, 0.49 g of hydroxybenzotriazole and 0.928 g of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride. The reaction is stirred at room temperature overnight. The mixture is concentrated and the residue is taken up in ethyl acetate. The organics are washed with sodium bicarbonate, 1N HCl, brine, dried ($MgSO_4$), filtered and evaporated. The residue is chromatographed on silica gel eluting with (1:2) ethyl acetate:hexane to give the more polar diastereomer N-(5-carbomethoxy-1-oxopentyl)-(4S)-p-phenylphenylmethyl-

4-amino-2R-methylbutanoic acid ethyl ester. The less polar (S,S) diastereomer is also isolated.

To a solution of N-(5-carbomethoxy-1-oxopentyl)-(4S)-p-phenylphenylmethyl-4-amino-2R-methylbutanoic acid ethyl ester (0.58 g) in 10 ml of THF and 10 ml of ethanol are added 4.0 ml of 1N NaOH. The reaction is stirred overnight. The mixture is concentrated taken up in water and washed with ether (2×). The aqueous layer is acidified with 2N HCl and extracted with ethyl acetate (2×). The organics are dried ($MgSO_4$), filtered, concentrated and recrystallized from methylene chloride-ether to give N-(5-carboxy-1-oxopentyl)-(4S)-p-phenylphenylmethyl-4-amino-2R-methylbutanoic acid, melting at 124°–127° C.

EXAMPLE 8

Preparation of 1,000 capsules each containing 50 mg of the active ingredient, as follows:

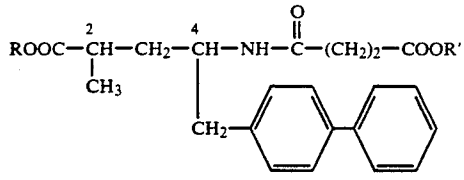
N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester sodium salt	50.00 g
Lactose	187.00 g
Modified starch	80.00 g
Magnesium stearate	3.00 g

Procedure: All the powders are passed through a screen with openings of 0.6 mm. The drug substance is placed in a suitable mixer and mixed first with the magnesium stearate, then with the lactose and starch until homogenous. No. 2 hard gelatin capsules are filled with 300 mg of said mixture each, using a capsule filling machine.

Analogously capsules are prepared, containing about 10–100 mg of the other compounds disclosed and exemplified herein, e.g. the compounds of examples 1–5.

What is claimed is:

1. A compound of formula Ie



(Ie)

wherein COOR and COOR′ independently represent carboxyl or carboxyl esterified in form of a pharmaceutical acceptable prodrug ester, or a pharmaceutically acceptable salt thereof.

2. A compound according to claim **1** wherein R and R′ independently represent hydrogen, C_1–C_4-alkyl, benzyl optionally substituted on phenyl by lower alkyl, lower alkoxy, halo or trifluoromethyl, pivaloyloxymethyl, 1-(C_2–C_4-alkanoyloxy)-ethyl, (2,2-dimethyl-1,3-dioxolan-4-yl)-methyl, 5-indanyl, 3-phthalidyl, bornyloxycarbonylmethyl, 1-(C_1–C_4-alkoxycarbonyloxy)-ethyl or 3-pyridylmethyl; or a pharmaceutically acceptable salt thereof.

3. A compound according to claim **1** wherein COOR′ is carboxyl; and COOR represents carboxyl or carboxyl derivatized in form of a pharmaceutically acceptable ester; or a pharmaceutically acceptable salt thereof.

4. A compound according to claim **1** having the R-configuration at C-atom 2 and the S-configuration at C-atom 4.

5. A compound according to claim **1**, being N-(3-carboxy-1-oxopropyl)-4-(p-phenylphenylmethyl)-4-amino-2-methylbutanoic acid ethyl ester, the (2R,4S)-antipode thereof, or a pharmaceutical acceptable salt thereof.

6. A compound according to claim **4** being N-(3-carboxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl-4-amino-(2R) -methylbutanoic acid or a pharmaceutically acceptable salt thereof.

7. A compound according to claim **4** being N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R) -methylbutanoic acid ethyl ester or a pharmaceutically acceptable salt thereof.

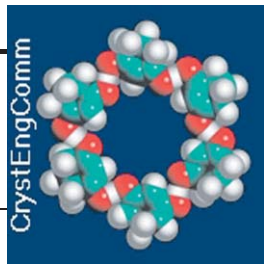
8. A neutral endopeptidase inhibiting pharmaceutical composition comprising an effective neutral endopeptidase inhibiting amount of a compound of claim **1**, in combination with one or more pharmaceutically acceptable carriers.

9. A neutral endopeptidase inhibiting pharmaceutical composition according to claim **8** comprising an effective neutral endopeptidase inhibiting amount of N-(3-carboxy-1-oxopropyl)-4-(p-phenylphenylmethyl)-4-amino-2-methylbutanoic acid ethyl ester, the (2R,4S)-antipode thereof, or a pharmaceutical acceptable salt thereof.

10. A method of treating cardiovascular disorders which comprises administering to a mammal in need of such treatment an effective neutral endopeptidase inhibiting amount of a compound of claim **1** in combination with one or more pharmaceutically acceptable carriers.

11. A method of treating cardiovascular disorders according to claim **10** which comprises administering to a mammal in need of such treatment an effective neutral endopeptidase inhibiting amount of 4-[N-(3-carboxy-1-oxopropyl)-amino]4-(p-phenylphenylmethyl)-2-methylbutanoic acid ethyl ester, the (2R,4S)-antipode thereof or a pharmaceutical acceptable salt thereof.

* * * * *



Highlight

Building co-crystals with molecular sense and supramolecular sensibility

Christer B. Aakeröy and Debra J. Salmon

Department of Chemistry, Kansas State University, Manhattan, Kansas 66506, USA. E-mail: aakeroy@ksu.edu

Received 27th April 2005, Accepted 22nd June 2005
First published as an Advance Article on the web 4th July 2005

Molecular recognition is typically associated with molecules in solution, but such events are also responsible for organizing molecules in the solid state. Translating principles of molecular recognition to solid-state assembly of heteromeric molecular solids is of key importance to the development of versatile, reliable and practical supramolecular synthesis. In this article we provide an overview of some modular and transferable strategies for the synthesis of binary and ternary supermolecules and co-crystals based upon a hierarchy of intermolecular interactions, notably hydrogen bonds.

Introduction

What is the most likely outcome when a homogeneous solution containing two different molecular solutes is allowed to evaporate to dryness? Unless a chemical reaction driven by the formation of covalent bonds takes place between the two solutes, one would, as a rule, expect the appearance of two separate molecular solids. This is a manifestation of the inherent structural selfishness of molecules,[1] and it is relied upon every time recrystallization is employed as a method of purification. Recrystallization processes represent essential steps during covalent synthetic procedures and are performed on a daily basis in every synthetic laboratory around the world. In the supramolecular laboratory, however, the very same process provides the supramolecular chemist with an opportunity to move in a completely different direction—a co-crystallization is a deliberate attempt at bringing together different molecular species within one periodic crystalline lattice without making or breaking covalent bonds. Recrystallization and co-crystallization processes are, in essence, only distinguishable by their intents. The goal of the former is a homomeric product, whereas the latter procedure strives for a heteromeric product: success for the former means failure for the latter. In general, the odds are stacked firmly in favor of a homomeric product, Scheme 1, so how do we go about developing reliable, effective, and versatile synthetic methods for the directed assembly of heteromeric co-crystals? This article will attempt to provide some practical suggestions by outlining supramolecular synthetic strategies based upon modular hydrogen-bond driven approaches to the design and synthesis of binary and ternary supermolecules and co-crystals.

Christer B. Aakeröy

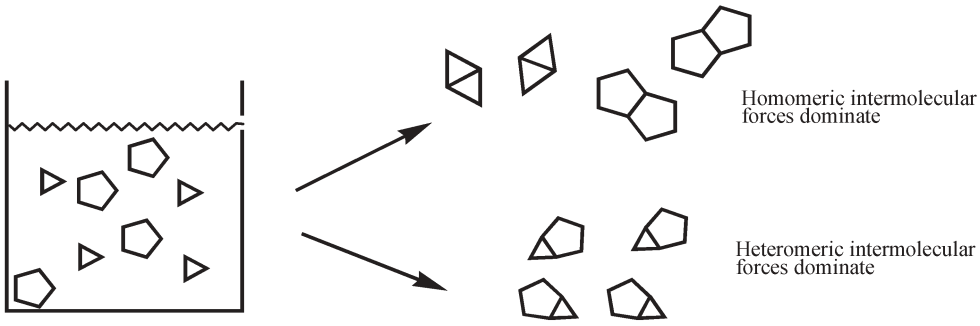
Christer Aakeröy was born in Sweden but thanks to immigrant parents he was lucky enough to acquire a Norwegian citizenship. After a few unglamorous yet invaluable years working in meat-packing factories, as a substitute teacher, and travelling around Europe, he eventually went to University and obtained an M.Sc. in Chemistry (minors in Mathematics, Biology, and Pedagogy) from Uppsala University. After participating in a student exchange program he was unexpectedly offered a Scholarship from BP to carry out research with the ultimate goal of making artificial bones and teeth. Despite the fact that not a single molar was ever made, he gained a Ph.D. in Inorganic Chemistry from the University of Sussex with Ken Seddon. In 1992, Aakeröy received a Fellowship from the Swedish National Academy of Science that allowed him to spend some time at the University of Minnesota in the laboratories of Peggy Etter and Jan Almlöf. He subsequently landed a position as a Lecturer in Inorganic Chemistry at the Queen's University of Belfast. In 1996 he accepted a position as an Assistant Professor at Kansas State University where he was promoted to Associate Professor in 2001.

Covalent *vs.* non-covalent synthesis

Covalent synthesis has become an enormously powerful discipline[2] because organic chemists have been able to establish reproducible links between molecular structure, reactivity, and reaction pathways through systematic studies of innumerable organic reactions. The explicit correspondence between chemical functional groups and their reactivity has provided a foundation for highly efficient construction of new molecules of enormous variety and complexity. The arrival and on-going development of synthetic organic chemistry arguably represent one of the most important scientific stories of the 20th century.

Debra J. Salmon

Debra J. Salmon earned a B.S. degree in Chemistry from Kansas State University in 2005. She has worked with Dr Christer Aakeröy since October 2002, in which time she has gained a deep appreciation for the art of growing co-crystals. She will enter graduate school at the University of Arizona in Fall 2005 to pursue a Ph.D. degree in Chemistry.



Scheme 1 Recrystallization (homomeric) or co-crystallization (heteromeric)?

The history of organic synthetic chemistry has produced reliable methods for chemical transformations, and names like Grignard, Wittig and Suzuki are prominent members of the collective that the experienced synthetic chemist has labeled "Named reactions". Each individual reaction can often be described in a concise yet comprehensive manner—"…this is the transformation of A into B, by treatment with X and Y". These recipes, which often involve specific catalysts and reagents that facilitate covalent coupling reactions between two different molecular fragments, play a crucial role in every aspect of synthetic chemistry.

In contrast, supramolecular synthesis[3] has not reached anywhere near the same level of sophistication, and despite much progress[4,5] we do not yet have access to a 'dictionary' that allows us to translate from molecular structure to supramolecular assembly. We have so far only converted a fraction of our considerable understanding of solution-based molecular recognition phenomena into practical solid-state targeted crystal engineering. Specifically, there is much to be done when it comes to the preparation of molecular co-crystals, a synthesis that requires the assembly and spatial organization of different molecular building blocks within the same periodic crystalline lattice. However, there is no doubt that if we could employ our extensive knowledge of molecular structure/function and apply it to the directed assembly of supramolecular species, then we will have taken a crucial step towards new materials that are faster, cheaper, smarter, or more efficient than current alternatives. In addition, we would gain new insight that is directly applicable to molecular-recognition driven biological catalysis and reactivity.

What is a co-crystal?

Crystal engineering is, by definition, a highly interdisciplinary area, which goes some ways towards explaining why unambiguous definitions and systematic nomenclatures have yet to be developed, let alone fully embraced, within this field. The term co-crystal is certainly not well-defined, and in the current literature we encounter terms like molecular complexes, co-crystals, molecular adducts, molecular salts, clathrates, inclusion compounds, *etc.*, that often are meant to describe one and the same family of chemical compounds. The purpose of this article is not to propose new definitions or to weigh in on the current semantic/semiotic debate,[6] but it will be necessary to delineate the scientific realm of this Highlight. This article will then adhere (reasonably strictly) to the following rules/definitions:

1. Only compounds constructed from discrete *neutral* molecular species will be considered as co-crystals. Consequently, all solids containing ions, including complex transition-metal ions, are excluded.[7]

2. Only co-crystals made from reactants that are solids at ambient conditions will be included.[8] Therefore all hydrates and other solvates are excluded which, in principle, eliminates compounds that are typically classified as clathrates or inclusion compounds (where the guest is a solvent or a gas molecule).

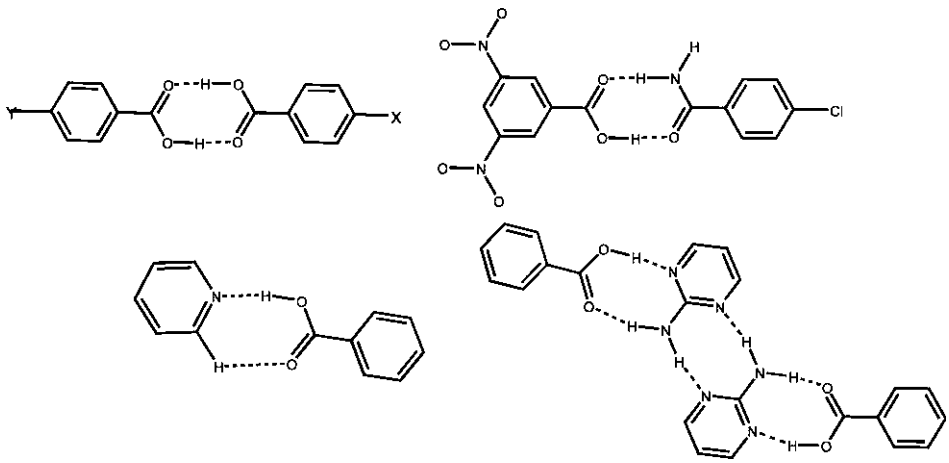
3. A co-crystal is a structurally homogeneous crystalline material that contains two or more neutral building blocks that are present in definite stoichiometric amounts.

At this point we are essentially left with two families of compounds: binary donor–acceptor complexes and hydrogen-bonded co-crystals. This article will focus heavily upon representatives from the latter category.[9]

Examples of binary co-crystals

There are, strictly speaking, no "discrete" aggregates within a solid-state framework but it is nevertheless possible to classify an assembly as being 0-D, 1-D, 2-D or 3-D depending upon the type of intermolecular interactions that are present within and between collections of certain molecules.

Some examples of 0-D assemblies, Scheme 2, in co-crystals include heteromeric carboxylic acid : carboxylic acid dimers



Scheme 2 Four 0-D motifs found in co-crystals created by heteromeric hydrogen-bond interactions.

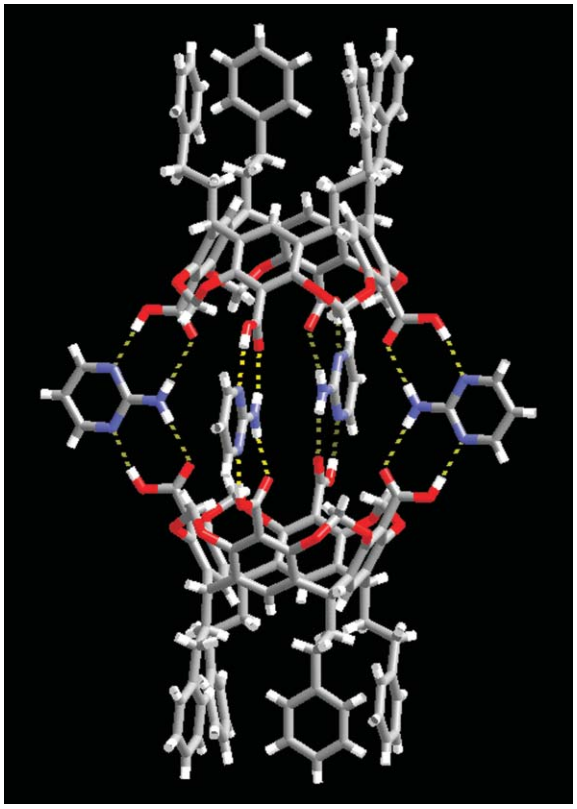


Fig. 1 Binary co-crystal containing a capsule held together by multiple carboxylic acid–aminopyrimidine interactions.[25]

(1 : 1),[10] pyridine : carboxylic acid dimers (1 : 1),[11] 2-aminopyrimidine : carboxylic acid trimers (1 : 2),[12] pyridine : bis(hydroxymethyl)biphenyl trimers (2 : 1),[13] bipyridine : carboxylic acid trimers (1 : 2),[14] 2-aminopyrimidine : carboxylic acid tetramers (2 : 2),[12,15] bipyridine : resorcinol tetramers (2 : 2),[16] 3,5-dinitrobenzoic acid : nicotinic acid tetramers (2 : 2),[17] isonicotinamide : carboxylic acid tetramers (2 : 2),[18] 2-pyridone : carboxylic acid pentamers (4 : 1),[19] melamine : thymine tetramers (1 : 3),[20] melamine : barbital hexamers (3 : 3),[21] and

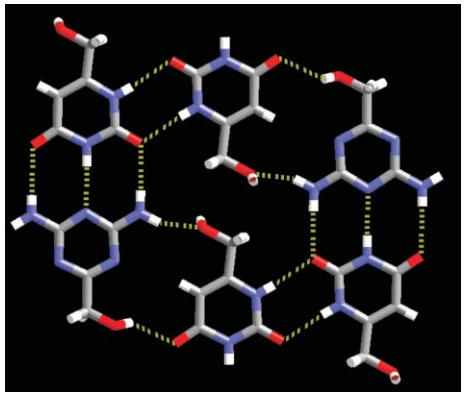


Fig. 2 A central hexameric motif in the hydrogen-bonded 2-D network in a diaminotriazine : uracil co-crystal.[41]

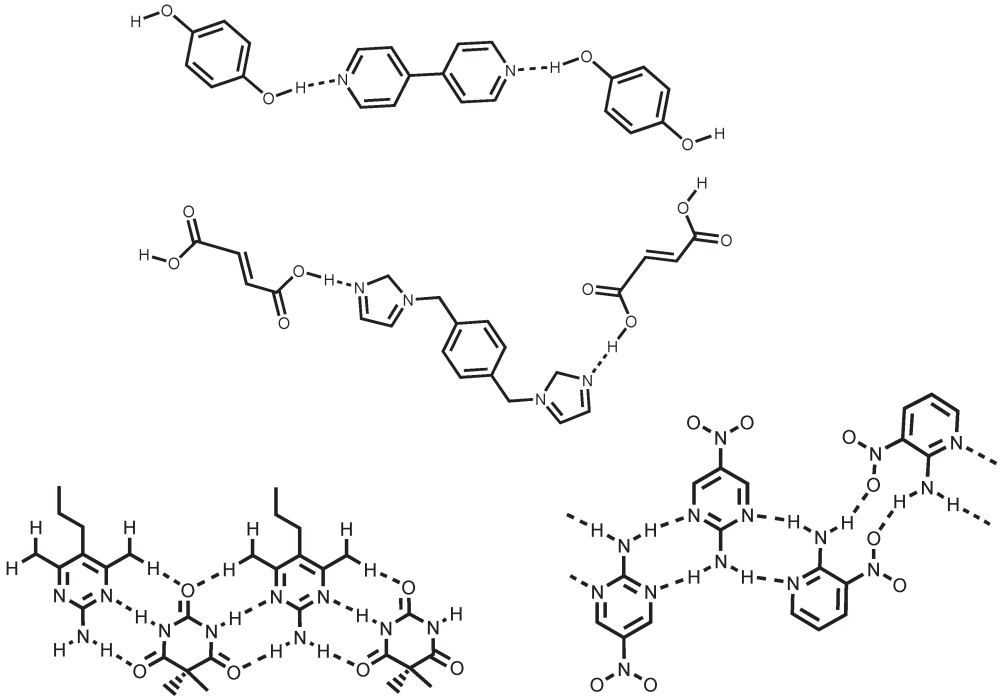
tripenylphosphine oxide with a variety of hydrogen-bond donors (1 : 1).[22,23]

More complex, multicomponent, co-crystals containing 0-dimensional motifs also include several elegant examples of capsules held together by hydrogen bonds,[24] Fig. 1.

Examples of co-crystals containing chains, ribbons, and other infinite 1-D motifs, Scheme 3, include: bipyridine : dihydroxybenzene,[26] melamine : cyanuric acid,[27] bipyridine : (fluorinated)dibromobenzene,[28] bipyridine : (diiodobenzene, tetraiodoethylene or diiodine),[29] 2-aminopyridine : dicarboxylic acid,[30] triaminopyrimidine : barbituric acid,[31] 2-aminopyrimidine : dicarboxylic acid,[32] 1,2,3-trihydroxybenzene : hexamethylenetetramine,[33] diols : diamines[34], bis-benzimidazole : dicarboxylic acid,[35] and 2-amino-5-nitropyrimidine : 2-amino-3-nitropyridine.[36]

Many infinite 2-D assemblies have also been constructed including (but not limited to): piperazine : carboxylic acid,[37] trithiocyanuric : bipyridine,[38] pyridyloxamide : dicarboxylic acid,[39] picolylaminocyclohexenone : dicarboxylic acid,[40] triazine : uracil,[41] tris-(4-pyridyl)triazine : trimesic acid,[42] bipyridine : ureylene dicarboxylic acid,[43] and isonicotinamide : dicarboxylic acid,[18,44] Fig. 2.

Finally, some examples of 3-D motifs in binary co-crystals include tetrabromoadamantane : hexamethylenetetramine,[45]



Scheme 3 Four 1-D motifs generated by heteromeric hydrogen-bond interactions.

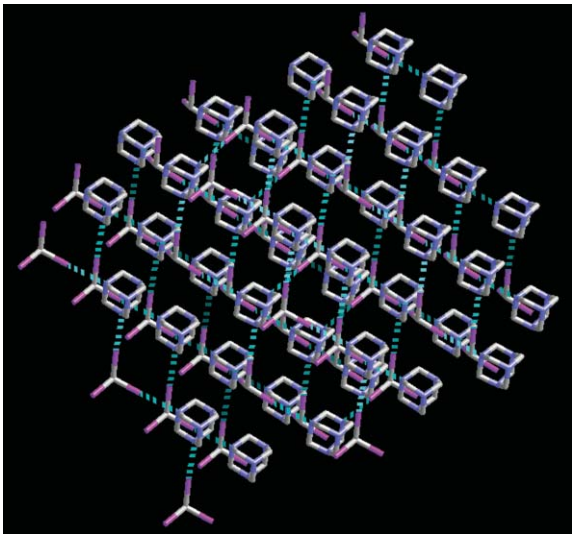


Fig. 3 The 3-D network in an iodoform : hexamethylenetetramine co-crystal.[47]

carbamazepine : tetracarboxylic acid-adamantane[46] 1,4-diiodotetrafluorobenzene : hexamethylenetetramine,[29] and iodoform : hexamethylenetetramine,[47] Fig. 3.

From pattern recognition to synthons and practical crystal engineering

The whole notion of structural motifs and patterns within a solid framework is closely linked to the idea that some intermolecular interactions are more important than others.[48] The challenge of recognizing and classifying motifs generated by multiple intermolecular interactions was addressed by Etter *et al*,[49] using a system based upon graph-set notation that allow structural motifs to be described in a consistent and 'user-friendly' way. The graph-set approach uses four principal *motifs*: chains (*C*), dimers (*D*), rings (*R*), and intramolecular hydrogen bonds (*S*), as descriptors of hydrogen-bonded molecular solids. Although this notation may not provide an unambiguous assignment of every structural arrangement, it is flexible enough to facilitate a systematic description of a wide range of structures. An indication of the impact that this nomenclature has had is provided by the fact that two of the early graph-set publications[49,50] have together received more than 1,100 citations (SciFinder Scholar, American Chemical Society 2005). An explanation for this success can undoubtedly be found in the appealing simplicity of this approach, and descriptors such as $R_4^2(8)$ (an eight-membered ring with four hydrogen-bond donors and two hydrogen-bond acceptors) and $R_2^2(8)$ (*e.g.* the carboxylic head-to-head dimer), have become widely recognizable.

In the context of structural motifs and pattern preferences, an intriguing and very helpful analogy between covalent and supramolecular synthesis has been captured with the term 'supramolecular synthon',[51] a robust, transferable connector that can be used for linking molecules together using non-covalent interactions. Synthons describe recognition events that take place when molecules assemble into supermolecules and offer an important illustration of the conceptual similarities between retrosynthetic organic synthesis and supramolecular assembly.[52]

One of the attractions of supramolecular chemistry is the extraordinary potential for synthesis of new materials that can be achieved much more rapidly and more effectively than with conventional covalent means. For supramolecular synthesis to advance, it is obviously important to characterize, classify, and analyze structural patterns, space group frequencies, and symmetry operators.[53] However, at the same time we also need to bring together this information with the explicit aim of improving and developing supramolecular synthesis—the deliberate combination of *different* discrete molecular building blocks within periodic crystalline materials. Why be concerned with the assembly of different molecular components within a solid? Broadly speaking, the interplay and communication between molecules within a solid framework provide many of the properties that are uniquely characteristic of a pure compound. The ability to change key physical properties *e.g.* solubility, crystal morphology, mechanical stability, *etc.*, of a specialty chemical while retaining its essential bio-physical or molecular activity is of enormous commercial and fundamental interest. Examples of how this can be achieved are regularly demonstrated through the conversion of a pharmacologically active molecule into its chloride or acetate salt.[54] Access to reliable and versatile synthetic strategies for co-crystals can furnish alternative approaches to materials design and preparation that may offer better control (and tunability) of fundamental physical properties of a wide range of specialty chemicals.

Synthesis of co-crystals and the supramolecular yield

The fact that 4-bromo-4′-cyanobiphenyl[55] and 4-bromobenzonitrile[56] form crystal structures where the molecular components are aligned in a head-to-tail fashion with relatively short Br···N contacts indicates that there are stabilizing intermolecular interactions between cyano and bromo moieties,[57] Fig. 4. However, there are no known examples of successful synthesis of binary co-crystals driven by CN···Br interactions.[58] Such interactions can organize molecules within a lattice but have yet to bring about the assembly of heteromeric co-crystals.[59] There is clearly a difference between observing a large number of short-contacts in molecular crystal structures composed of only one type of building block and translating such interactions into useful synthetic tools for constructing *heteromeric* architectures.

Much current work in organic crystal engineering is now geared towards synthesizing co-crystals using supramolecular reactions based upon reliable synthons and, so far, the majority of organic molecular co-crystals have been assembled *via* conventional (stronger) hydrogen bonds. Weaker hydrogen bonds and many other intermolecular interactions such as, nitro···iodo, cyano···nitro, halogen···halogen, *etc.*, have not yet been found to be broadly useful tools for construction of co-crystals. The success and efficiency for any set of supramolecular reactions can be judged by the frequency of occurrence of desired intermolecular interactions and connectivities in the resulting solid. The probability that a certain motif will appear in a crystalline lattice is, in many ways, a measure of the *yield of a supramolecular reaction*. Just as a covalent synthetic chemist searches for ways in which a specific reaction can be promoted or prevented, a supramolecular chemist tries to identify the experimental regime where a synthon prevails despite competition from other non-covalent forces.

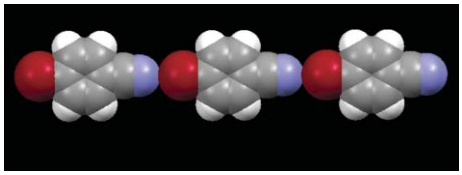
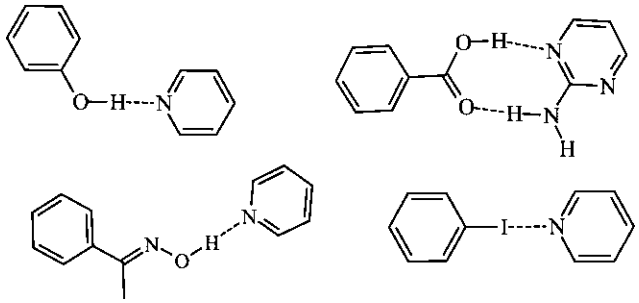


Fig. 4 A chain of molecules organized in a head-to-tail manner in 4-bromobenzonitrile.



Scheme 4 Four dimeric motifs constructed *via* heteromeric intermolecular interactions.

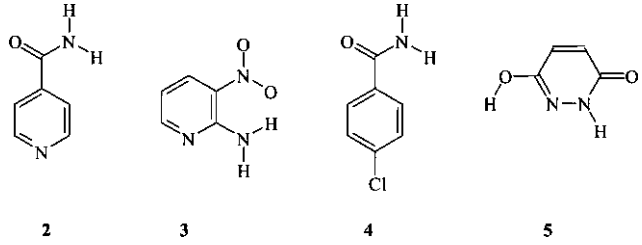
Heteromeric interactions are better than homomeric interactions

A survey of hydrogen-bonded co-crystals in the CSD[60] reveals that most of them have been prepared using strategies that utilize suitable combinations of chemical entities (or functional groups) located on different molecules such that they would prefer to interact and bind heteromerically, Scheme 4, rather than with themselves (homomerically).[61]

The most widely used synthons for the directed assembly of binary co-crystals have contained a carboxylic acid in combination with a suitable N-containing heterocycle. For example, there are three co-crystals in the CSD with pyrazine,[62] seven with phenazine,[63] sixteen with 4,4′-bipyridine,[64] one with pyrimidine,[65] and nine co-crystals with either azapyrine, quinoline, phenanthroline,[66] and a benzoic acid–based counterpart. In every case, the expected/intended carboxylic acid···N(heterocycle), O–H···N, hydrogen bond is present. For slightly more complex heterocycles (*i.e.* with added substituents capable of hydrogen bonding) the results are still very consistent; 11 of 12 carboxylic acid : isonicotinamide co-crystals contain an acid···pyridine interaction[67]—a good example of a high-yielding supramolecular reaction.

There are, in fact, very few occurrences of binary hydrogen-bond based co-crystals that do not contain a primary intermolecular interaction that heteromerically link discrete building blocks. Two such examples include 4-nitrobenzamide : pyrazinecarboxamide (1 : 1) **1**,[68] and 3,5-dintrobenzoic acid : 4-(*N*,*N*-dimethylamino)benzoic acid (1 : 1).[69] The latter was the only example, in a series of ten acid···acid co-crystals, where two homomeric dimers were formed in preference to one heteromeric dimer.[70]

The overriding conclusion from the extensive data available in the CSD is clear. In order to convince two different discrete chemical species to coexist in a molecular co-crystal there needs to be some specific molecular-recognition based reason for their solid-state union.[68] Although individual structures that defy rationalization will appear from time to time, there is no doubt that the important 'big picture' reveals structural trends, patterns of behavior, and reproducible motifs that, when combined, can be developed into a library of high-yielding supramolecular reactions.



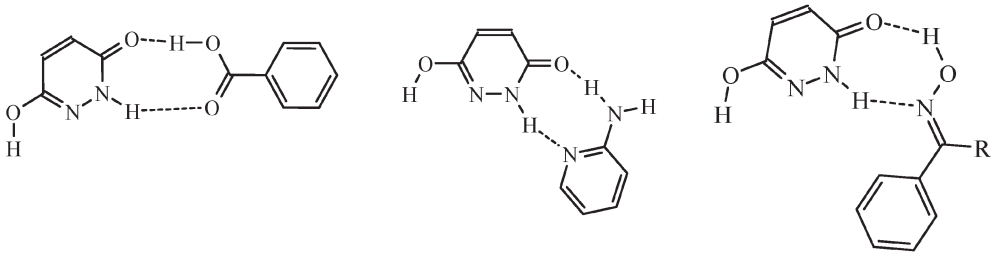
Scheme 5 Molecules capable of forming a variety of hydrogen-bonded synthons: isonicotinamide, **2**, 2-amino-3-nitropyridine, **3**, ?4-chlorobenzamide, **4**, and maleic hydrazide, **5**.

Do polymorphic compounds make good co-crystallizing agents?[36]

A good co-crystallizing agent (CA) should be able to form heteromeric intermolecular interactions with the target molecule that are more favorable than the homomeric interactions that may exist.[18] The CA must also have the ability to 'tolerate' the presence of a different molecular building block within the same crystalline lattice, which makes it reasonable to search for co-crystallizing agents amongst polymorphic compounds.[71] Polymorphism means that a compound is found in more than one crystalline manifestation which,[72] in turn, indicates that such compounds display a degree of structural flexibility. In other words, the multidimensional potential-energy surface that describes the thermodynamics governing the molecular recognition processes that eventually leads to crystal growth is likely to contain many accessible local energy minima.

The suggestion that polymorphic compounds are more likely to form co-crystals than compounds that never display polymorphism is somewhat difficult to quantify. However, from a practical perspective it would be extremely useful to have access to reliable guidelines for how we might focus and target a search for reliable co-crystallizing agents for a specific family of compounds. This challenge prompted us to examine four polymorphic compounds:[36] isonicotinamide **2**, 2-amino-5-nitropyrimidine[73] **3**, 4-chlorobenzamide **4**,[74] and maleic hydrazide **5**,[75,76] and several co-crystals thereof. The reason for selecting **2–5** (apart from the fact that they are all polymorphic) was that they are all potentially capable of engaging in several well-defined and robust intermolecular hydrogen-bond interactions, Scheme 5.

Three of the four polymorphic compounds examined in this study[36] readily form co-crystals, *e.g.* 2-hexeneoic acid : isonicotinamide, 2-amino-5-nitropyrimidine : 2-amino-3-nitropyridine, and 3-dimethylaminobenzoic acid : 4-chlorobenzamide. The structural behavior of **2–4** supports the suggestion that polymorphs make good co-crystallizing agents (provided that solubility differences are not too large). However, we were unsuccessful in preparing any co-crystals with maleic hydrazide, despite the fact that it exists in three different polymorphs. We tried a range of crystallization techniques as well as an extensive series of molecular compounds that, in principle, could form complementary hydrogen-bond interactions with a 2-pyridone moiety, Scheme 6.



Scheme 6 Three examples of known synthons that could facilitate the formation of co-crystals involving maleic hydrazide.

Synthon flexibility

The failure to produce any co-crystals with **5** may cast doubts on the notion that polymorphic compounds make good co-crystallizing agents, unless there is a significant structural difference in the polymorphic behavior between **2–5**. We decided to take a closer look at all the polymorphs **2ab**, **3a–c**, **4a–c**, and **5a–c** using graph-set notation in order to uncover possible reasons for the unwillingness of **5** to participate in molecular co-crystals. The two polymorphs of isonicotinamide, **2a** and **2b**, display very different intermolecular connectivities. In **2a** there is an amide···amide head-to-head interaction as well as the commonly occurring N–H···O link between adjacent dimers resulting in a $C(4)R_2^2(8)$ motif. However, the primary intermolecular forces in **2b** are significantly different as there is a catemeric amide···amide hydrogen bond, C(4), as well as an amide···pyridine interaction, C(7). A classification of the three polymorphs of **3** reveals that the expected intramolecular amine···nitro hydrogen bond is present in all three forms. **3b** and **3c** have identical intermolecular connectivities and the primary hydrogen-bond motifs are thus best described with the same graph-set notion, $R_2^2(12)R_2^2(8)S(6)$. In **3a**, however, there are infinite hydrogen-bonded ribbons, yielding the graph-set notation $R_2^2(10)R_2^2(8)S(6)$. In the structures of **4a** and **4c** the amide moieties form amide–amide catemers, $C(4)R_2^2(8)R_4^2(8)$. The difference between the two structures lies in the arrangement of aromatic rings with respect to one another. While the graph set notation for **4b** is similar to **4a** and **4c**, the larger hydrogen-bonded ring creates a two-dimensional network, $C(4)R_2^2(8)R_6^4(16)$. In contrast, all three polymorphs of **5**, the one compound that would not readily produce co-crystals, contain identical hydrogen-bonded ladders: $R_4^2(14)R_2^2(8)$, Fig. 5.

The fact that these three polymorphs all contain the same extended networks was also noted in the original paper: "*Three forms of MH* (maleic hydrazide) *provide a unique example of polymorphic structures built of similar hydrogen-bonded aggregates. The same hydrogen-bonded supramolecular aggregates organize into different lattices of different symmetries*···".[76b]

A detailed structural examination of **2–5** has enabled the identification of significant differences, in terms of molecular recognition patterns, between the different polymorphs that, in turn, may provide practical guidelines for ranking candidates that are potentially suitable as co-crystallizing agents.

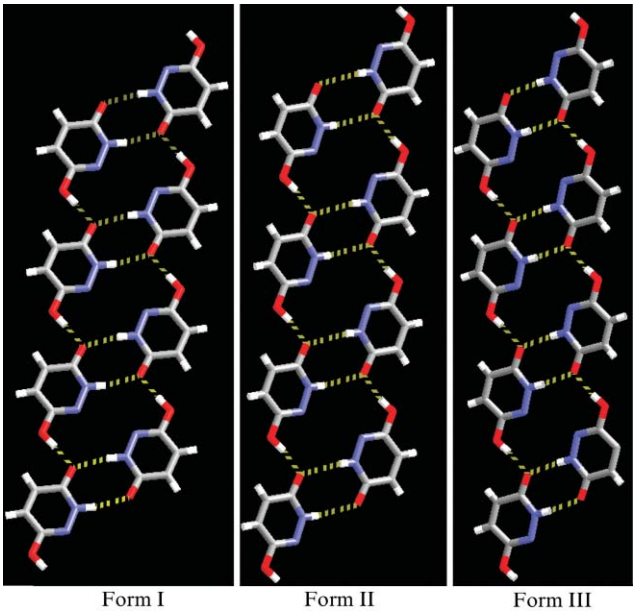


Fig. 5 The primary hydrogen-bond motifs in the three known polymorphs of maleic hydrazide display the same connectivity.

Co-crystals are not necessarily easy to prepare since such heteromeric systems are only likely to appear if the non-covalent forces between different molecules are more favorable than those that exist between molecules in the corresponding homomeric crystals. An important consideration when attempting to prepare co-crystals is to choose a co-crystallizing agent that is already known to be polymorphic. However, structural flexibility alone is not always enough. It may be equally important to select molecules that can adopt alternative packing patterns as well as display *synthon flexibility*—an ability to participate in several different robust and well-defined intermolecular interactions that can satisfy the demands of multiple hydrogen-bond donors/acceptors on a variety of molecules.

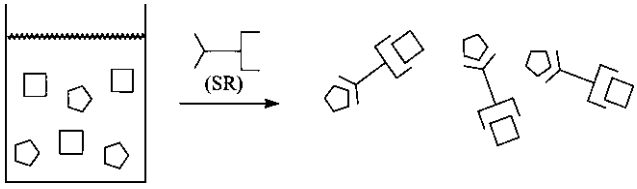
Beyond binary co-crystals: The need for supramolecular reagents

Through systematic structural studies of families of molecular solids we and many others have sought to examine the competition and balance between different intermolecular interactions.[77–79] It is becoming clear that under certain conditions it is possible to carefully manipulate the way in which molecules recognize and bind by 'tuning' the strengths of site-specific complementary hydrogen-bond functionalities. We have tried to forge some of this knowledge about intermolecular forces into a practical tool for making ternary and higher-order co-crystals. Central to this approach is the availability of molecular building blocks that can provide supramolecular directionality, selectivity and reliability. Such building blocks, *supramolecular reagents* (SR's), contain two or more different binding sites, attachment points, that can be used to selectively attract, bind and organize two or more different molecules into a supermolecule with predictable connectivity and shape. The supramolecular reagent is the hub for the assembly process and will become part of the supermolecule—this heteromeric aggregate will also appear in the resulting crystalline solid enabling the synthesis of co-crystals of increasing complexity.

In order to establish how far this relatively simple modular supramolecular concept can be extended, we have attempted to design *ternary* supermolecules with predictable connectivity and stoichiometry,[80] Scheme 7.

Since hydrogen bonds frequently form in a hierarchical fashion (best-donor to best-acceptor, second best-donor to second best-acceptor, *etc.*),[81,82] the chances of producing a new binary co-crystal are greatly improved by positioning the best hydrogen-bond donor and the best hydrogen-bond acceptor on different molecular building blocks.[68] The physical validity of a best-donor/best-acceptor classification or interpretation of hydrogen-bond interactions can be rationalized in terms of a desire of the system to maximize multiple electrostatic interactions. The centerpiece of our first deliberate attempt at making ternary co-crystals using a best-donor : best-acceptor approach was isonicotinamide.[80] This molecule readily recognizes and binds to carboxylic acids to form 1 : 1 binary co-crystals that contain a robust and reproducible heteromeric hydrogen-bonded motif, Fig. 6.

The best donor (carboxylic acid) and the best acceptor (pyridine nitrogen) form an intermolecular O–H···N hydrogen



Scheme 7 General description of a coupling reaction of two different molecules and a supramolecular reagent (SR) resulting in 1 : 1 : 1 ternary supermolecules.

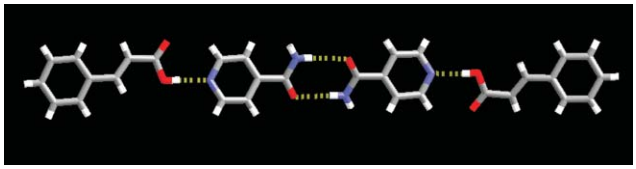


Fig. 6 Primary motif typical of the majority of 1 : 1 isonicotinamide : carboxylic acid co-crystals.[18]

bond, and the tetrameric supermolecule is completed through a self-complementary amide–amide interaction. Isonicotinamide is a good example of a supramolecular reagent suitable for constructing ternary co-crystals: it has two distinctly different, yet relatively strong, hydrogen-bond moieties, it shows good 'structural flexibility' since it is polymorphic, and it also displays 'synthon flexibility' as the two known polymorphs display different hydrogen-bond interactions. The primary hydrogen bond in this system is the acid–pyridine interaction and, since hydrogen bonds have large electrostatic components, the strength of this interaction is governed by the acidity of the carboxylic acid donor.[83]

The 'weaker' link in the tetrameric motif shown in Fig. 6 is the amide···amide interaction. Since many reported structures contain heteromeric amide···acid hydrogen bonds (in preference to the corresponding homomeric options),[84] our plan was to replace it with a more favorable heteromeric acid···amide interaction, allowing us to bring in a third component in a specific manner. By offering two different carboxylic acids to isonicotinamide, we expected the stronger acid to interact preferentially with the best acceptor (the pyridine nitrogen atom) and the weaker acid to form a heteromeric motif with the remaining amide moiety. This supramolecular design strategy was put to the test by allowing equimolar amounts of a weaker acid, a stronger acid, and isonicotinamide to react in an aqueous solution.

Compound **6**, 3,5-dinitrobenzoic acid : isonicotinamide : 3-methylbenzoic acid (1 : 1 : 1), contains the desired three-component supermolecule with the expected connectivity. The stronger acid ($pK_a = 2.8$)[85] interacts with the pyridine nitrogen atom, and the weaker acid ($pK_a = 4.3$) competes successfully for the amide moiety and forms a heteromeric hydrogen-bonded motif, Fig. 7.

Compound **7**, 3,5-dinitrobenzoic acid : isonicotinamide : 4-(*N*,*N*-dimethyl)aminobenzoic acid (1 : 1 : 1), is also a ternary co-crystal with the intended three-component supermolecule. The acid–pyridine nitrogen interaction persists, and the weaker acid ($pK_a = 6.5$) forms a heteromeric motif with the amide moiety, Fig. 8.

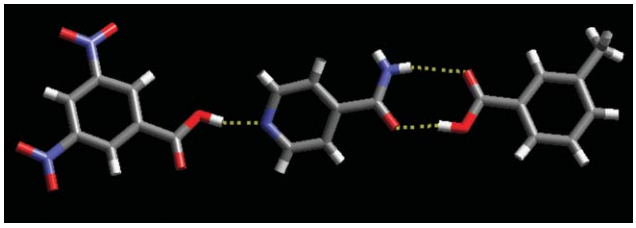


Fig. 7 The ternary supermolecule in **6**.

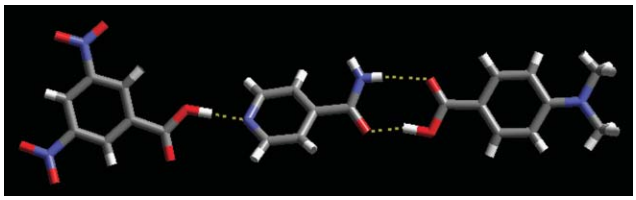


Fig. 8 The ternary supermolecule in **7**.

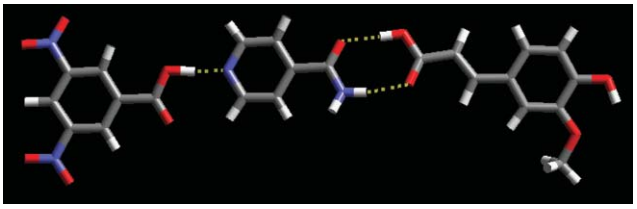


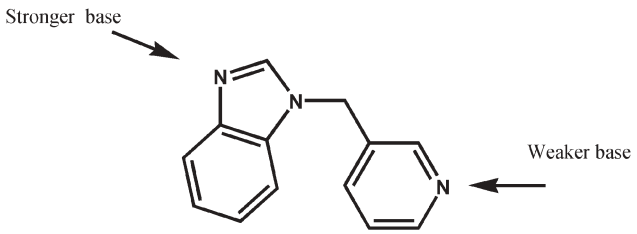
Fig. 9 The ternary supermolecule in **8**.

Finally, 3,5-dinitrobenzoic acid : isonicotinamide : 4-hydroxy-3-methoxycinnamic acid **8**, is also a 1 : 1 : 1 ternary co-crystal with the same primary supramolecular connectivity as in **6** and **7**, Fig. 9. The desired trimer persists even in the presence of the potentially disrupting OH-moiety on the weaker acid ($pK_a = 4.4$).

All three structures, **6–8**, contain ternary supermolecules synthesized with the aid of a suitable supramolecular reagent that employs a hierarchy of hydrogen-bond interactions for the desired intermolecular organization and assembly. Although these forces are weaker than covalent interactions, it is clearly possible to assemble more than two different building blocks in a preconceived manner. To date we have been able to crystallographically characterize about a dozen ternary co-crystals based upon the acid : isonicotinamide : acid combination. In each and every case, the connectivity of the observed supermolecule is consistent with the underlying supramolecular synthetic strategy and is readily rationalized through differences in pK_a values—this reaction, with isonicotinamide as the supramolecular reagent seems to proceed with a very high supramolecular yield.

Despite its success, however, isonicotinamide is not sufficiently versatile to make it an ideal supramolecular reagent. First, it is capable of forming self-complementary amide···amide and amide···pyridine hydrogen bonds, which makes it inherently difficult to combine isonicotinamide with molecules that lack moieties that can compete successfully with the hydrogen-bonding capabilities of the amide functionality. Second, since the two binding sites on isonicotinamide are attached to the same backbone, it is impossible to tune the electronics of the two sites independently, which reduces the versatility. Consequently, there is a need for second-generation SR's that can be refined in such a way that they offer more opportunities for modular supramolecular synthesis of ternary co-crystals through enhanced structural selectivity and specificity.

In this context, we recently presented[86] a series of asymmetric bis-heterocycles where two different binding sites (hydrogen-bond acceptor sites) are linked by a methylene bridge in order to provide increased solubility in a range of solvents. The two binding sites have significantly different basicities,[87] which means that their ability to accept hydrogen bonds vary. They also lack strong hydrogen-bond donors and, consequently, homomeric intermolecular interactions will be weak and less likely to prevent the desired heteromeric interactions, Scheme 8.



Scheme 8 An asymmetric ditopic supramolecular reagent with two different binding sites (hydrogen-bond acceptors) that can be electronically modified independently through suitable covalent substituents.

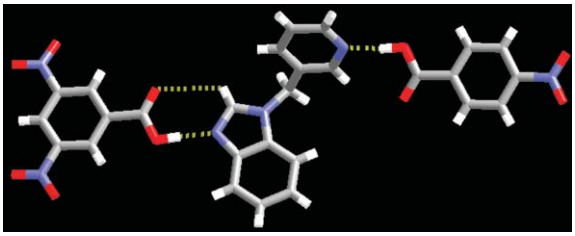


Fig. 10 One of the two ternary supermolecules in the crystal structure of **9**. The stronger acid binds to the stronger base (left-hand side), and the second-best acid binds to the second-best base (right-hand side).

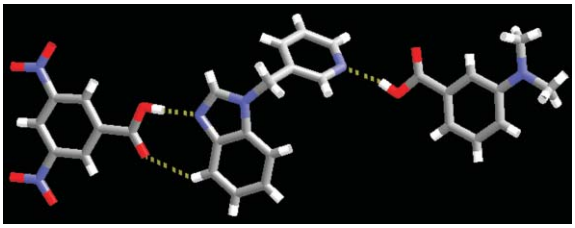


Fig. 11 The ternary supermolecule in the crystal structure of **10**. The stronger acid binds to the stronger base (left-hand side), and the weaker acid binds to the weaker base (right-hand side).

Even though pK_a/pK_b values do not provide direct measures of hydrogen-bond strength, hydrogen-bond abilities and free energies of complexation have been correlated with pK_a values and, within closely related classes of compounds, such comparisons frequently yield correct qualitative results.[88,89] The basicity of each heterocycle can also be independently altered through suitable covalent substitution, which provides a practical handle for fine-tuning differences in intermolecular reactivity. Tunability is particularly important as it creates a versatile supramolecular reagent with the potential for a high degree of transferability. The ability of these SR's to form ternary supermolecules with predictable connectivity was put to the test by allowing each SR to react with pairs of different carboxylic acids in a 1 : 1 : 1 ratio.[90] The target in each case is a crystal structure containing a 1 : 1 : 1 ternary supermolecule where the primary intermolecular interactions can be rationalized according to the best donor/best acceptor protocol.

The crystal structure of **9** contains two crystallographically unique ternary supermolecules with identical connectivity, Fig. 10.

The primary intermolecular interactions in this structure are the O–H···N hydrogen bonds between the stronger acid (3,5-dinitrobenzoic acid) and the more basic nitrogen atom of the benzimidazol-1-yl ring, and the O–H···N hydrogen bonds from the weaker acid (4-nitrobenzoic acid) to the less basic nitrogen atom of the pyridyl moiety.

The crystal structure of **10** shows the presence of a ternary 1 : 1 : 1 supermolecule with the same connectivity as that found in **9**, Fig. 11.

The primary synthons comprise an O–H···N hydrogen bond between the stronger acid, 3,5-dinitrobenzoic acid, and the most basic heterocyclic moiety, and a second O–H···N

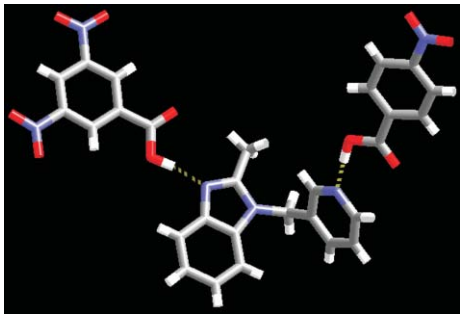


Fig. 12 The ternary supermolecule in the crystal structure of **11**. The stronger acid binds to the stronger base (left-hand side), and the second-best acid binds to the second-best base (right-hand side).

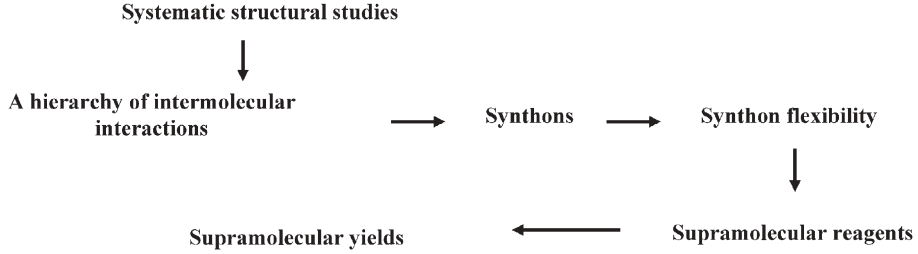
interaction between the weaker acid, 3-*N*,*N*-dimethylaminobenzoic acid, and the less basic acceptor, the pyridyl moiety.

The crystal structure of **11** contains a 1 : 1 : 1 supermolecule with the desired connectivity, Fig. 12. The best acceptor, the benzimidazol-1-yl moiety, forms an O–H···N hydrogen bond with the best donor, the stronger acid. The second-best acceptor, the pyridyl moiety, binds to the weaker acid *via* an O–H···N hydrogen bond.

All three structures, **9–11**, contain ternary supermolecules constructed through the deliberate use of directional intermolecular synthetic operations. The supramolecular reagents each have two binding sites that differ primarily in their basicity, but neither site is otherwise biased or predisposed towards interacting preferentially with either of the two competing carboxylic acids. The differences in basicity are translated into supramolecular reactivity and selectivity that subsequently carry over into the solid state, which demonstrates that supramolecular assembly can be controlled by fine-tuning individual binding sites. This raises the possibility that a solution to the problem of making non-covalent one-pot synthesis "sequential" may be to devise modular assembly processes based upon a hierarchy of intermolecular interactions derived from molecular properties and structural trends.

Codicil

Even though molecular recognition is typically associated with molecules in solution, such interactions are also responsible for organizing molecules in the solid state. Translating principles of molecular recognition to solid-state assembly of heteromeric molecular solids is of key importance to the development of versatile and reliable strategies for practical supramolecular synthesis. In this article we have attempted to outline some modular and transferable supramolecular design strategies based upon a hierarchy of intermolecular interactions. The starting point for these efforts is provided by a body of readily available structural information that subsequently allows for the identification of suitable supramolecular reagents. The effectiveness of these compounds as active and reliable builders of heteromeric supramolecular aggregates can eventually be evaluated and quantified using the supramolecular yield, Scheme 9.



Scheme 9 Design, implementation, and evaluation of supramolecular synthesis of co-crystals.

The supramolecular synthetic strategies presented herein will, without a doubt, generate several unexpected results; however, through covalent synthesis we have unlimited opportunities for modulating the electronic and geometric details of each binding site on a supramolecular reagent such that a variety of chemical functionalities can be targeted for binding. In this way we can build a team of SR's where each member is capable of affecting the assembly of new supermolecules with a high degree of specificity and reliability, thereby clearing a path towards practical and transferable guidelines for versatile supramolecular synthesis. We are currently probing the limits and limitations of this hierarchical approach to non-covalent synthesis by examining the structural reactivity of libraries of supramolecular reagents containing multiple binding sites with easily adjustable differences in hydrogen-bond donating/accepting capabilities. Given the dramatic developments in supramolecular chemistry over the recent decades it is inevitable that much more complex supermolecules and higher-order co-crystals will be synthesized through an improved awareness of the balance and competition between intermolecular interactions. Such progress will undoubtedly also deepen our understanding of a range of fundamental events such as biomolecular activity, crystallization processes, and physico-chemical signaling mechanisms. In addition, supramolecular reactions of this type may have important ramifications for the pharmaceutical industry[91] (circumventing patents, modifying crystal habit and bioavailability, and facilitating processing), and may also lead to new strategies for chiral separation.

Acknowledgements

We are grateful for financial support from NSF (CHE-0316479) and Kansas State University.

References and notes

1 J. D. Dunitz, in *Perspectives in Supramolecular Chemistry: The Crystal as a Supramolecular Entity*, ed. G.R. Desiraju, Wiley, Amsterdam, 1995.
2 E. J. Corey, *Chem. Soc. Rev.*, 1988, **17**, 111; K. C. Nicolaou and E. J. Sorensen, *Classics in total synthesis*, Wiley-VCH, Weinheim, 1996.
3 J.-M. Lehn, *Supramolecular Chemistry*, VCH, Weinheim, 1995.
4 C. B. Aakeröy, *Acta Crystallogr., Sect. B*, 1997, **53**, 569; B. Moulton and M. J. Zaworotko, *Chem. Rev.*, 2001, **101**, 1629; G. R. Desiraju, *Acc. Chem. Res.*, 2002, **35**, 565; M. W. Hosseini, *CrystEngComm*, 2004, **6**, 318; L. R. MacGillivray, *CrystEngComm*, 2004, **6**, 77; D. Braga, *Chem. Commun.*, 2003, 2751; L. Brammer, *Chem. Soc. Rev.*, 2004, **33**, 476; C. B. Aakeröy and A. M. Beatty, *Aust. J. Chem.*, 2001, **54**, 409.
5 D. L. Caulder and K. N. Raymond, *Acc. Chem. Res.*, 1999, **32**, 975; D. N. Reinhoudt and M. Crego-Calama, *Science*, 2002, **295**, 2403; J.-M. Lehn, *Science*, 2002, **295**, 2400; M. W. Hosseini, *Acc. Chem. Res.*, 2005, **38**, 312; CrystEngComm Discussion 1; Innovation in Crystal Engineering (http://www.rsc.org/publishing/journals/ce/cecd1.asp).
6 G. R. Desiraju, *CrystEngComm*, 2003, **5**, 466; J. D. Dunitz, *CrystEngComm*, **5**, 506.
7 A solid containing building blocks with formal charges is a salt, and there is no need to describe it as an adduct, molecular adduct, proton-transfer solid, molecular salt, or variations hereof.
8 One could also make a case for including materials such as those prepared through co-condensation at reduced temperatures or elevated pressure in very elegant ways by Boese and co-workers: R. Boese, M. T. Kirchner, W. E. Billups and L. R. Norman, *Angew. Chem. Int. Ed.*, 2003, **42**, 1961.
9 Other intermolecular forces such as py···iodo will also be included.
10 J. A. R. P. Sarma and G. R. Desiraju, *J. Chem. Soc., Perkin Trans. 2*, 1985, 1905.
11 T. Sugiyama, J. Meng and T. Matsuura, *J. Mol. Struct.*, 2002, **611**, 53.
12 D. E. Lynch, G. Smith, D. Freney, K. A. Byriel and C. H. L. Kennard, *Aust. J. Chem.*, 1994, **47**, 1097.
13 L. R. Nassimbeni, H. Su, E. Weber and K. Skobridis, *Cryst. Growth Des.*, 2004, **4**, 85.
14 R. D. B. Walsh, M. W. Bradner, S. Fleischman, L. A. Morales, B. Moulton, N. Rodrigues-Hornedo and M. J. Zaworotko, *Chem. Commun.*, 2003, 186.
15 D. E. Lynch, T. Latif, G. Smith, K. A. Byriel, C. H. L. Kennard and S. Parsons, *Aust. J. Chem.*, 1998, **51**, 403.
16 L. R. MacGillivray, J. L. Reid and J. A. Ripmeester, *J. Am. Chem. Soc.*, 2000, **122**, 7817.
17 J. Zhu and J.-M. Zheng, *Chin. J. Struct. Chem.*, 2004, **23**, 417.
18 C. B. Aakeröy, A. M. Beatty and B. A. Helfrich, *J. Am. Chem. Soc.*, 2002, **124**, 14425.
19 C. B. Aakeröy, A. M. Beatty and M. Zou, *Cryst. Eng.*, 1998, **1**, 225.
20 R. F. M. Lange, F. H. Beijer, R. P. Sijbesma, R. W. W. Hooft, H. Kooijman, A. L. Spek, J. Kroon and E. W. Meijer, *Angew. Chem. Int. Ed.*, 1997, **36**, 969.
21 J. A. Zerkowski, C. T. Seto and G. M. Whitesides, *J. Am. Chem. Soc.*, 1992, **114**, 5473.
22 M. Y. Antipin, A. I. Akhmedov, Y. T. Struchkov, E. I. Matrosov and M. I. Kabachnik, *Zh. Strukt. Khim.*, 1983, **24**, 86; D. E. Lynch, G. Smith, K. A. Byriel and C. H. L. Kennard, *Acta Crystallogr., Sect. C*, 1993, **49**, 718.
23 M. C. Etter and T. W. Panunto, *J. Am. Chem. Soc.*, 1988, **110**, 5896; M. C. Etter and P. W. Baures, *J. Am. Chem. Soc.*, 1988, **110**, 639.
24 (*a*) L. R. MacGillivray, P. R. Diamente, J. L. Reid and J. A. Ripmeester, *Chem. Commun.*, 2000, 359; (*b*) G. W. V. Cave, M. J. Hardie, B. A. Roberts and C. L. Raston, *Eur. J. Org. Chem.*, 2001, 3227; (*c*) For a good overview see: D. R. Turner, A. Pastor, M. Alajarin and J. W. Steed, *Struct. Bond.*, 2004, **108**, 97–168.
25 K. Kobayashi, T. Shirasaka, K. Yamaguchi, S. Sakamoto, E. Horn and N. Furukawa, *Chem. Commun.*, 2000, 41.
26 C. Glidewell, G. Ferguson, R. M. Gregson and A. J. Lough, *Acta Crystallogr., Sect. C*, 1999, **55**, 2133.
27 A. Ranganathan, V. R. Pedireddi and C. N. R. Rao, *J. Am. Chem. Soc.*, 1999, **121**, 1752.
28 A. De Santis, A. Forni, R. Liantonio, P. Metrangolo, T. Pilati and G. Resnati, *Chem. Eur. J.*, 2003, **9**, 3974.
29 R. B. Walsh, C. W. Padgett, P. Metrangolo, G. Resnati, T. W. Hanks and W. T. Pennington, *Cryst. Growth Des.*, 2001, **1**, 165.
30 F. Garcia-Tellado, S. J. Geib, S. Goswami and A. D. Hamilton, *J. Am. Chem. Soc.*, 1991, **113**, 9265.
31 J.-M. Lehn, M. Mascal, A. DeCian and J. Fischer, *Chem. Commun.*, 1990, 479.
32 M. C. Etter and D. A. Adsmond, *Chem. Commun.*, 1990, 589.
33 M. Tremayne and C. Glidewell, *Chem. Commun.*, 2000, 2425.
34 O. Ermer and A. Eling, *J. Chem. Soc., Perkin Trans. 2*, 1994, 925.
35 C. B. Aakeröy, J. Desper, B. Leonard and J. F. Urbina, *Cryst. Growth Des.*, 2005, **5**, 865.
36 C. B. Aakeröy, A. M. Beatty, B. A. Helfrich and M. Nieuwenhuyzen, *Cryst. Growth Des.*, 2003, **3**, 159.
37 T.-J. M. Luo and G. T. R. Palmore, *Cryst. Growth Des.*, 2002, **2**, 337.
38 V. R. Pedireddi, S. Chatterjee, A. Ranganathan and C. N. R. Rao, *J. Am. Chem. Soc.*, 1997, **119**, 10867.
39 T. L. Nguyen, F. W. Fowler and J. W. Lauher, *J. Am. Chem. Soc.*, 2001, **123**, 11057.
40 J. Xiao, M. Yang, J. W. Lauher and F. W. Fowler, *Angew. Chem. Int. Ed.*, 2000, **39**, 2132.
41 F. H. Beijer, R. P. Sijbesma, J. A. J. M. Vekemans, E. W. Meijer, H. Kooijman and A. L. Spek, *J. Org. Chem.*, 1996, **61**, 6371.
42 B.-Q. Ma and P. Coppens, *Chem. Commun.*, 2003, 2290.
43 J. J. Kane, R.-F. Liao, J. W. Lauher and F. W. Fowler, *J. Am. Chem. Soc.*, 1995, **117**, 12003.
44 P. Vishweshwar, A. Nangia and V. M. Lynch, *Cryst. Growth Des.*, 2003, **3**, 783.
45 D. S. Reddy, D. C. Craig and G. R. Desiraju, *Chem. Commun.*, 1994, 1457.
46 S. G. Fleischman, S. S. Kuduva, J. A. McMahon, B. Moulton, R. D. B. Walsh, N. Rodriguez-Hornedo and M. J. Zaworotko, *Cryst. Growth Des.*, 2003, **3**, 909.
47 T. Dahl and O. Hassel, *Acta Chem. Scand.*, 1970, **24**, 377.
48 C. B. Aakeröy, J. Desper, E. Elisabeth, B. Helfrich, B. Levin and J. Urbina, *Z. Kristallogr.*, 2005, **220**, 325.
49 M. C. Etter, J. C. MacDonald and J. Bernstein, *Acta Crystallogr., Sect. B*, 1990, **46**, 256.
50 J. Bernstein, R. E. Davis, L. Shimoni and N.-L. Chang, *Angew. Chem., Int. Ed., Engl.*, 1995, **34**, 1555.
51 G. R. Desiraju, *Angew. Chem., Int. Ed., Engl.*, 1995, **34**, 2311.

52 A. Nangia and G. R. Desiraju, *Acta Crystallogr., Sect. A*, 1998, **54**, 934.
53 C. P. Brock and J. D. Dunitz, *Acta Crystallogr., Sect. A*, 1991, **47**, 854.
54 S. E. Byrn, R. R. Pfeiffer and J. G. Stowell, *Solid State Chemistry of Drugs*, SSCI, Inc., West Lafayette, 1999.
55 P. Kronenbusch, W. B. Gleson and D. Britton, *Cryst. Struct. Commun.*, 1976, **5**, 17.
56 D. Britton, J. Konnert and S. Lam, *Cryst. Struct. Commun.*, 1977, **6**, 45.
57 H. Quast, Y. Gorlach, E.-M. Peters, K. Peters, H. G. von Schnering, L. M. Jackman, G. Ibar and A. J. Freyer, *Chem. Ber.*, 1986, **119**, 1801.
58 The crystal structure of tetrafluoro-1,4-diiodobenzene tetramethyl-1,4-dicyanobenzene represents a rare example of a co-crystal assembled *via* CN···I interactions: D. Britton and W. B. Gleason, *Acta Crystallogr., Sect. E*, 2002, **58**, o1375.
59 There are, however, examples of co-crystals formed between 1,2-dibromotetrafluoroethane and N-heterocycles such a 1,4-dimethylpiperazine: Q. Chu, Z. Wang, Q. Huang, C. Yan and S. Zhu, *New. J. Chem.*, 2003, **27**, 1522.
60 F. A. Allen, *Acta Crystallogr., Sect. B*, 2002, **58**, 380.
61 C. Huang, L. Leiserowitz and G. M. Schmidt, *J. Chem. Soc., Perkin Trans. 2*, 1973, 503; F. Pan, W. S. Wong, V. Gramlich, C. Bosshard and P. Gunter, *Chem. Commun.*, 1996, 2; J. A. Zerkowski, J. C. MacDonald and G. M. Whitesides, *Chem. Mater.*, 1997, **9**, 9; R.-F. Liao, J. W. Lauher and F. W. Fowler, *Tetrahedron*, 1996, **52**, 3153; N. Shan, A. D. Bond and W. Jones, *Cryst. Eng.*, 2002, **5**, 9; V. R. Pedireddi, W. Jones, A. P. Chorlton and R. Docherty, *Chem. Commun.*, 1996, 997; P. Vishweshwar, A. Nangia and V. M. Lynch, *J. Org. Chem.*, 2002, **67**, 556; C. B. Aakeröy, A. M. Beatty, M. Nieuwenhuyzen and M. Zou, *Tetrahedron*, 2000, **56**, 6693.
62 CSD codes: OCAYUM, OCASAT, and POFPAB.
63 CSD codes: GURVOE, GURVUK, LUDFUL, UNECAR, ZUPKUQ, and ZUPLAX.
64 CSD codes: BEQWAV, FIHYEA, FIJCIK, FIJCUW, HUPPOX, MUFNIK, NOPXIZ, OJENIA, PULWUO, RAPHAR, SUXVOW, UDUZIC, UDOZOI, UHELUO, XUNGIW, and XUNGOC.
65 CSD code: POFPEF.
66 CSD codes: CUFSET, LUSWEB, PANYIM, PANZEJ, PAPDIT, PAPFOB, UNEBOE, WUKREZ, and WUKROJ.
67 CSD codes: AJAKEB, AJAKIF, ASAXOH, ASAXUN, BUDWEC, BUDZUV, BUFBIP, BUFQAU, LUNMEM, LUNMIC, LUNMOW, and VAKTOR.
68 C. B. Aakeröy, J. Desper and B. A. Helfrich, *CrystEngComm*, 2004, **6**, 19.
69 C. V. K. Sharma, K. Panneerselvam, T. Pilati and G. R. Desiraju, *J. Chem. Soc., Perkin Trans. 2*, 1993, 2209.
70 V. R. Pedireddi and J. PrakashReddy, *Tetrahedron Lett.*, 2002, **43**, 4927.
71 There are, of course, other aspects that need to be considered *e.g.*, solubility differences between drug and CA (if the co-crystals are to be prepared *via* solution-based methods) before embarking upon a series of co-crystallizations.
72 J. Bernstein, *Polymorphism in Molecular Crystals*, Oxford University Press, New York, 2002.
73 C. B. Aakeröy, M. Nieuwenhuyzen and S. L. Price, *J. Am. Chem. Soc.*, 1988, **120**, 8986.
74 Forms I and III of 4-chlorobenzamide: T. Taniguch, K. Nakata, Y. Takaki and K. Sakurai, *Acta Crystallogr., Sect. B*, 1978, **34**, 2574 . Form II: T. Hayashi, K. Nakata, Y. Takaki and K. Sakurai, *Bull. Chem. Soc. Jpn.*, 1980, **53**, 801.
75 P. D. Cradwick, *Nature*, 1975, **258**, 774.
76 (*a*) A. Katrusiak, *Acta Crystallogr., Sect. C*, 1993, **49**, 36; (*b*) A. Katrusiak, *Acta Crystallogr., Sect. B*, 2001, **57**, 697.
77 C. B. Aakeröy, A. M. Beatty and D. S. Leinen, *CrystEngComm*, 2002, **4**, 310; J. Valdés-Martínez, M. Del Rio-Ramirez, S. Hernández-Ortega, C. B. Aakeröy and B. A. Helfrich, *Cryst. Growth Des.*, 2001, **2**, 485; C. B. Aakeröy, A. M. Beatty, M. Tremayne, D. M. Rowe and C. C. Seaton, *Cryst. Growth Des.*, 2001, **2**, 377.
78 C. B. Aakeröy, A. M. Beatty and D. S. Leinen, *Cryst. Growth Des.*, 2000, **1**, 47; C. B. Aakeröy, A. M. Beatty, M. Nieuwenhuyzen and M. Zou, *J. Mater. Chem.*, 1998, **8**, 1385; C. B. Aakeröy, J. Desper and J. F. Urbina, *Cryst. Growth Des.*, 2005, **5**, 1283.
79 A. D. Burrows, *Struct. Bond.*, 2004, **111**, 55–96.
80 C. B. Aakeröy, A. M. Beatty and B. A. Helfrich, *Angew. Chem. Int. Ed.*, 2001, **40**, 3240.
81 M. C. Etter, *J. Phys. Chem.*, 1991, **95**, 4601.
82 M. C. Etter, *Acc. Chem. Res.*, 1990, **23**, 120.
83 If the acid is too strong, the proton will be transferred to the nitrogen atom resulting in an ionic compound and not a co-crystal. Some examples of crystal engineering of ionic systems include *e.g.*: J. A. Swift, A. M. Pivovar, A. M. Reynolds and M. D. Ward, *J. Am. Chem. Soc.*, 1998, **120**, 5887; F. Xue and T. C. W. Mak, *J. Phys. Org. Chem.*, 2000, **13**, 405; P. Cudic, J.-P. Vigneron, J.-M. Lehn, M. Cesario and T. Prangé, *Eur. J. Org. Chem.*, 1999, 2479; C. V. K. Sharma and A. Clearfield, *J. Am. Chem. Soc.*, 2000, **122**, 4394; S. Ferlay, R. Holakovsky, M. W. Hosseini, J.-M. Planeix and N. Kyritsakas, *Chem. Commun.*, 2003, 1224; C. B. Aakeröy, P. B. Hitchcock and K. R. Seddon, *J. Chem. Soc., Chem. Commun.*, 1992, 553; C. B. Aakeröy, D. P. Hughes and M. Nieuwenhuyzen, *J. Am. Chem. Soc.*, 1996, **118**, 10134; A. M. Beatty, K. E. Granger and A. E. Simpson, *Chem. Eur. J.*, 2002, **8**, 3254; A. M. Beatty, C. L. Schneider, A. E. Simpson and J. L. Zaher, *CrystEngComm*, 2002, **4**, 282; D. Braga, L. Maini, M. Polito and F. Grepioni, *Struct. Bond.*, 2004, **111**, 1–32.
84 L. Leiserowitz and F. Nader, *Acta Crystallogr., Sect. B*, 1977, **33**, 2719.
85 All pK_a/pK_b values from: G. Kartum, W. Vogel and K. Andrussov, *Dissociation constants of organic acids in aqueous solution*, Butterworth & Co. Publishers, London, 1961.
86 C. B. Aakeröy, J. Desper and J. F. Urbina, *Chem. Commun.*, 2005, 2820.
87 An estimate for the differences in basicity between the pyridyl and the benzimidazol-1-yl moieties were obtained by calculating pK_a values for the conjugated acids of the two hydrogen-bond acceptors in each SR: 3-(benzimidazol-1-yl)methylpyridine: $pK_a = 4.71 \pm 0.10$ and 5.72 ± 0.30 for pyridyl and benzimidazol-1-yl moieties, respectively; 3-(2-methylbenzimidazol-1-yl)methylpyridine: $pK_a = 4.72 \pm 0.10$ and 5.85 ± 0.18 for pyridyl and benzimidazol-1-yl moieties, respectively. The calculations were performed using Advanced Chemistry Development (ACD/Labs) Software Solaris V4.76 (© 1994–2005 ACD/Labs).
88 M. H. Abraham, *Chem. Soc. Rev.*, 1993, **22**, 73.
89 S. Shan, S. Loh and D. Herschlag, *Science*, 1996, **272**, 97.
90 3,5-Dinitrobenzoic acid ($pK_a = 2.8$); 4-nitrobenzoic acid ($pK_a = 3.44$); 3-*N*,*N*-(dimethylamino)benzoic acid ($pK_a = 4.30$): G. Kartum, W. Vogel and K. Andrussov, *Dissociation constants of organic acids in aqueous solution*, Butterworth & Co. Publishers, London, 1961.
91 Ö. Almarsson and M. J. Zaworotko, *Chem. Commun*, 2004, 1889.

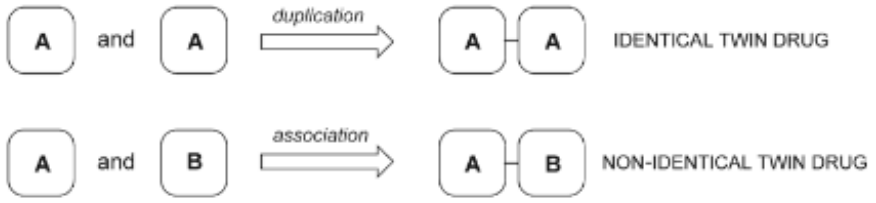


Fig. 16.1 Identical and non-identical twin drugs.

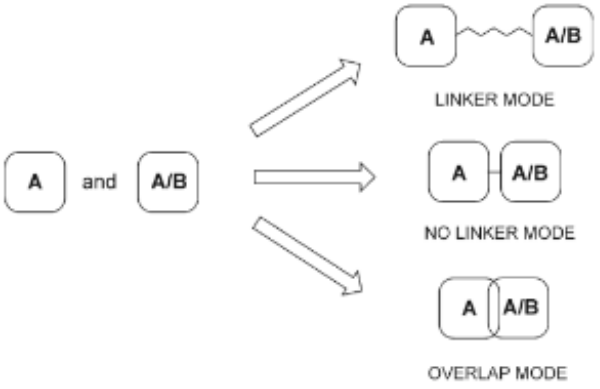


Fig. 16.2 Modes of combining two moities in twin drugs.

The administration of twin drugs can be favourable compared with the two separated drugs. The new entity will have its own pharmacokinetic property (absorption, distribution and metabolism) and thus possible improved efficacy *in vivo*. This aspect represents the main advantage of designing dual acting drugs in addition to the beneficial therapeutic combination of the two active principles. The twin drug must express both activities in an appropriate balance: a stochiometric association of diazepam (2–20 mg per day) with aspirin (200–2000 mg per day) would be nonsense.

It has also to be considered that the twin drug may produce its constituents after its administration (metabolism). In this case, the twin drug is actually a prodrug of the pharmacophoric entities. If the twin drug is not split *in vivo*, then the mechanism of action can be as followed: (1) for identical twin drugs, the interaction of the pharmacophoric moities with a symmetric macromolecule is conceivable especially when the targeted protein exists as a dimer; an additional interaction with another binding site (an allosteric site for example) on the targeted macromolecule is also possible (Fig. 16.6) and will trigger the biological response; (2) in the case of non-identical twin drugs or dual acting drugs, the simultaneous interaction with both targeted macromolecules is of course excluded; the main advantage resides in the new pharmacological profile of the hybrid derivative.

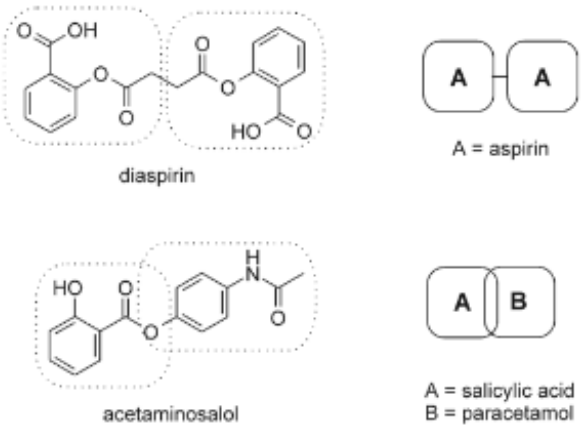


Fig. 16.3 Examples of identical and non-identical twin drugs.

II IDENTICAL TWIN DRUGS

A Symmetry in nature

Nature is efficient in producing compounds with a high degree of symmetry which allows reduction of information and complexity levels.[4] Natural symmetry is observed for the assembly of macromolecules (oligomers)[5] as for HIV protease, hemoglobin and insulin. The aggregation of insulin monomers to hexamers in presence of zinc affords a macromolecular complex with a high degree of symmetry[6] (C_3 symmetry). DNA, by means of its symmetrical double-stranded structure, determines the cell's morphology and function. These well-organized macromolecular systems constitute binding sites for smaller molecules, including water and ions.

Symmetrical natural compounds generally present a C_2 symmetry axis (Fig. 16.7), like the alkaloids lobelanine (treatment for drug addicts), sparteine (Grave's disease treatment) or isochondrodendrine, and the anticoagulant dicumarol and antispermatogenic gossypol.[7,8]