147144

FORM 7A

THE PATENTS ACT, 1970
& THE PATENT RULES, 2014

NOTICE OF OPPOSITION
Section 25(1) and rule 55

I, **DALBIR SINGH,** an Indian national of R.Z.F. 162, Nihal Vihar, Nangloi, New Delhi 110 041, hereby give representation by way of opposition to the grant of patent in respect of **Indian Patent Application 853/DELNP/2009 filed on February 5, 2009 and published under Section 11A on June 12, 20009** made by **BRISTOL MYERS SQUIBB COMPANY**, a US company of Route 206 & Province Line Road, Princeton, New Jersey 08543, USA, Israel on the following grounds:

1. That the complete specification does not sufficiently and clearly describe the invention and the method by which it is to be performed – Section 25(1)(g);
2. 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 – Section 25(1)(f);
3. 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 Section 25(1)(b) or having regard to what was used in India before the priority date of the applicant's claim – Section 25(1)(e);
4. That the patentee has failed to disclose to the Controller the information required by Section 8 or has furnished the information which in any material particular was false to this knowledge – Section 25(1)(h).

My address for service in India is:
LAW CHAMBERS OF G. NATARAJ
D-804, Aashiana Apartments
Mayur Vihar Phase I Ext.
Delhi 110 091
T: +91 11 22717645 / F: +91 11 45038460 / E: mail@gnataraj.com

I request that all communications be addressed to my attorneys at the address provided above.

Dated this the 8TH day of June 2015.

G.NATARAJ
Attorney for the Opponent

To
The Patent Office Branch
NEW DELHI

IPO DELHI 11-06-2015 15:42

FORM 7A

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& THE PATENT RULES, 2014

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G.NATARAJ
Attorney for the Opponent

To
The Patent Office Branch
NEW DELHI

INDIA NON JUDICIAL

Government of National Capital Territory of Delhi

e-Stamp

सत्यमेव जयते

Certificate No.	:	IN-DL28620959030716M
Certificate Issued Date	:	03-Nov-2014 12:27 PM
Account Reference	:	IMPACC (CR)/ dl796710/ DELHI/ DL-DLH
Unique Doc. Reference	:	SUBIN-DLDL79671054069902932124M
Purchased by	:	G NATARAJ
Description of Document	:	Article 48(c) Power of attorney - GPA
Property Description	:	Not Applicable
Consideration Price (Rs.)	:	0 (Zero)
First Party	:	G NATARAJ
Second Party	:	Not Applicable
Stamp Duty Paid By	:	G NATARAJ
Stamp Duty Amount(Rs.)	:	100 (One Hundred only)

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Towards Stamp Duty on Power of Authority from Dalbir Singh, an Indian citizen, of R.F.Z., 162, Nihal Vihar, Nangloi, New Delhi 110 041 in respect of pre-grant opposition to IN 853/DELNP/2009 .

IPO DELHI 11-06-2015 15:42

FORM 26

THE PATENTS ACT, 1970
& THE PATENT RULES, 2003

POWER OF AUTHORITY

I, **Dalbir Singh**, aged about 35 years, s/o Shri Gurmit Singh, resident of R.Z.F. 162, Nihal Vihar, Nangloi, New Delhi – 110 041, hereby authorize

Guruswamy Nataraj, Registered Patent Agent and Advocates, Jaishree Suryanarayanan, Manjula Gupta, and T. Srinivasa Murthy, all Advocates, all Indian citizens, and of **D 804, Aashiana Apartments, Mayur Vihar Phase I Extension, Delhi 110 091, India** jointly and severally on my behalf in filing and representing me in respect of any opposition, whether pre-grant or post-grant oppositions, under The Patents Act, 1970 from the Government of India in respect of **Indian Patent Application # 853/DELNP/2009** titled:

HEPATITIS C VIRUS INHIBITORS

and in all matters and proceedings before the Controller of Patents or the Government of India, in connection with said opposition(s) or incidental thereto, including filing of any document and payment of any fees, filing any request for amendment of any documents, filing of any interlocutory petitions, filing of any evidences, or any other document in connection with said opposition, attending any discussions or interviews, attending any and all official hearings in connection with said opposition(s) appointed by any authority empowered to do so, and in general to do all things as may be necessary or expedient, including appointment of any substitute or substitutes.

I hereby confirm and ratify any previous actions of the persons authorized hereinabove in relation to this/these opposition(s), and any matters and proceedings in connection therewith.

Dated this the 16th day of May 2015.

Dalbir Singh

(DALBIR SINGH)
OPPONENT

** Original document required*
** Notarization/Legalization not required*

To
The Patent Office Branch
at New Delhi

IN THE MATTER OF
Indian Patent Application 853/DELNP/2009
In the name of
BRISTOL-MYERS SQUIBB COMPANY

AND IN THE MATTER OF
A pre-grant representation by

DALVIR SINGH

TABLE OF CONTENTS

IN THE MATTER OF

Indian Patent Application 853/DELNP/2009

In the name of
BRISTOL-MYERS SQUIBB COMPANY
a US company
of Route 206 & Province Line Road, Princeton
New Jersey NJ 08543, USA

AND IN THE MATTER OF

A pre-grant representation by
DALVIR SINGH
An Indian national of
R.Z.F. 162, Nihal Vihar, Nangloi
New Delhi 110 041

WRITTEN STATEMENT OF OPPOSITION

1. On behalf of the above-named Opponent, we have the honour to provide herewith a written statement of opposition to Indian Patent Application 853/DELNP/2009 under Section 25(1) of The Patents Act, 1970.

I. DEFINITIONS

2. The following is a representative list of abbreviations/acronyms adopted in the present statement of opposition:

(a) IN 853/DELNP/2009 – as "IN '853"

(b) The Patents Act, 1970 –as "Act"

(c) The Patents Rules 2003 – as "Rules"

(d) Bristol-Myers Squibb Company – "BMS" or alternatively "Applicants"

(e) D1 – claims currently pending on IN '853

(f) D2 – WHO paper on Daclatasvir Patent Landscape, published April 2014

(g) D3 – print out from website of Applicants'

(h) D4 – IN 806/DELP/2010

(i) D5 – US Patent Publication 20040152073 (hereinafter US '073)

(j) D6 – US Patent 6,664,255 (hereinafter US '255)

(k) D7 – US Patent 6,900,207 (hereinafter US '207)

(l) D8 – US Patent 7,220,745 (hereinafter US '745)

(m) D9 - Thornber et al (1979, page 564)

(n) D10 – Copy of EMEA Approval

(o) D11 – Llinsa Brunet et al

(p) D12 – WO 2004/005264 (hereinafter WO '264)

(q) D13 – WO 2003/099274 (hereinafter WO '274)

3. The Opponent herein was a patient of Hepatitis C for a period of almost two years between the years 2013 and 2015. He has suffered tremendously due to the either non-availability, or the high cost of medication, with his weekly medical expenses exceeding Rs. 10000.00, apart from the financial assistance he was given by various well-wishers. In addition, due to the high cost of treatment, the Opponent has had to incur very high financial obligations, which are still being paid off.

4. The impugned application claims inter alia, that it relates to a substance capable of use in the treatment of Hepatitis C, which substance is apparently also called Daclatasvir. The Opponent believes that the substance in question is neither manufactured nor sold in India by Applicants herein and that Applicants in fact, have not probably even obtained the necessary approvals for marketing of such drug. The Applicants apparently also do not appear to have any intention of introducing the said drug Daclatasvir into India.

5. Opponent believes, in particular based on his own personal harrowing experience with Hepatitis C treatment regimens, that instruments such as patent applications should not become a tool for creation of a monopoly right which is then abused by the right holder by depriving the alleged benefits of such drug to patients. In the circumstances, Opponent believes that this impugned application is an example of an attempt to obtain a monopoly right, without any intention of

actually commercially or otherwise utilising such right for the benefit of the people of India.

6. It is respectfully submitted that a pre-grant representation under Section 25(1) can be filed by 'any person'. It is submitted that therefore, it is not necessary to establish a specific *locus standi* under the Act. In particular, there is no necessity to establish that a representor under Section 25(1) is a 'person interested' within the meaning of the Act. It is further submitted that a plethora of decisions of both various Hon'ble High Courts as well as of the Hon'ble IPAB have stipulated clearly that a pre-grant representation can be initiated by 'any person' and that a specific locus standi need not be established.

7. It is therefore submitted that the present pre-grant opposition is timely and correctly filed, and there cannot be any challenge or objection to the filing of this action by the above-named Opponent.

II. PRELIMINARY SUBMISSIONS

8. At the outset, it is respectfully stated that the following submissions are made without prejudice, and wherever appropriate, are to be read independent of each other. It is submitted that each ground taken in this representation is independent of the others, and does not constitute an admission or averment that the preceding or following grounds are either being surrendered or relinquished.

III. BIBLIOGRAPHIC BACKGROUND OF IN '853 AND EVENT HISTORY

9. IN '853 was filed on February 5, 2009 as a national phase entry from PCT International Application No. PCT/US2007/075544 (Publication No. WO 2008/021927 – hereinafter WO '927). WO '927 claims priority from US Provisional Patent Application 60/836,996 (hereinafter US '996) filed on August 11, 2006 as well as US Complete Patent Application No. 11/835,462 (hereinafter US '462) filed on August 8, 2007.

10. A request for examination was apparently filed on August 9, 2010.

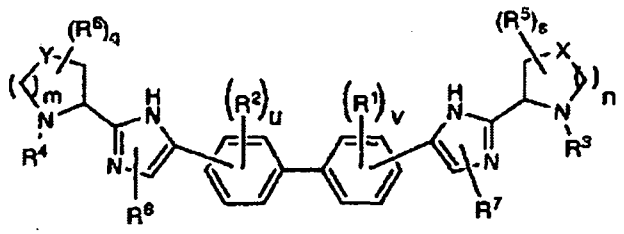
11. IN '853 was apparently examined by the Indian Patent Office on June 26, 2014. However, the Applicants have not as yet filed any response to the substantive objections raised therein.

12. The due date by which IN '853 has to be placed in condition for grant after complying with all requirements of the Act and the Rules, whether or not raised in the First Examination Report is June 26, 2015.

13. The PCT International application as published contained 40 claims. A copy of the claims currently pending on this application are annexed herewith marked as **D1**. The Opponent hereby reserves his right to initiate any further pre-grant opposition or file a further supplementary representation dependent on Applicants' response to this pre-grant representation and/or any response by Applicant to the First Examination Report inclusive of any amendments to any documents on this case.

14. IN '853 purports to relate to Hepatitis C virus inhibitors, and claims that the compounds disclosed therein are allegedly useful for treating HCV-infected patients by inhibition of HCV viral replication. The compounds in question are biphenyl imidazoles derivatives, which purportedly inhibit Hepatitis C virus replication by acting (inhibiting) the NS5A protein component thereof.

15. The broad general structure of the biphenyl imidazoles is given below (and also covered in Claim 1 of the application through a Markush structure).



(I),

16. The application asserts that compounds of the above structure are particularly useful for inhibition of Hepatitis C virus, particularly by inhibition of NS5A protein (see description – pages 2 – 11). Surprisingly, however, applicants on page 627 of the description (sole disclosure on what could be termed as an attempt to

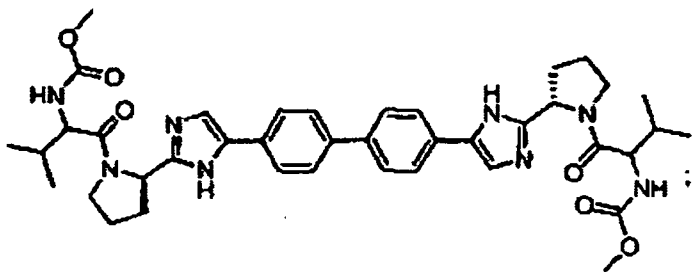
demonstrate utility) admit that compounds falling within the broad structure of Claim 1 actually demonstrate a 10-fold less inhibitory activity against drug resistant cells, when compared with wild-type cells.

17. Comparative data on any alleged improvement in efficacy is missing. This data has still not been supplied even now (a year after the application has been examined, and six years after it was filed) – clearly demonstrating that the alleged inhibitory activity was speculative at the time of filing of the application, and continues to be uncertain.

18. The written description of IN '853 extends over 630 pages, but is remarkably silent in respect of compliance with the requirement of Indian law and procedure relating to patent applications. From pages 1 through 25, applicants attempt to describe various embodiments of the alleged invention. Of these 25 pages, only a page and a half is devoted to actually discussing the alleged need for the alleged invention. Another 20 pages comprise more or less a reproduction of claim 1 and a listing of what purport to be embodiments of the alleged invention (all of which lack support in the remaining 600 pages of the complete specification). The remaining two pages comprise a listing of known drugs with which the claimed compounds can allegedly be 'co-administered'.

19. Pages 26 through 626 comprise what purport to be working examples allegedly providing support for the claimed compounds. Pages 626-634 comprise two paragraphs of the alleged biological activity, and a lengthy table setting out what purport to be the alleged inhibitory action of the claimed compounds. What is significant is that the entire written description – exactly 634 pages till the claims section – contains numerous assertions as to the alleged utility of the compounds of the invention – all of which are liberally prefaced by the speculative 'can be' or 'may be'. The entire written description is silent as to any positive statement that the compounds have been tested and have been found more efficacious over prior art biphenyl benzimidazole compounds in terms of Hepatitis C inhibition, let alone specific NS5A protein inhibition.

20. Admittedly, Hepatitis C virus is a pandemic – affecting millions of people all over the world. The applicant herein claims that the compounds of the invention are useful for treatment of Hepatitis C virus, particularly by inhibition of the NS5A protein. It is also significant to note that Applicants' claim that IN '853 covers a specific compound Daclatasvir (INN name), otherwise known by its IUPAC name: "Methyl[(2*S*)-1-{(2*S*)-2-[4-(4'-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-2-pyrrolidinyl]-1*H*-imidazol-4-yl}-4-biphenylyl)-1*H*-imidazol-2-yl]-1-pyrrolidinyl}-3methyl-1-oxo-2-butanyl] carbamate, and having the structure given below:



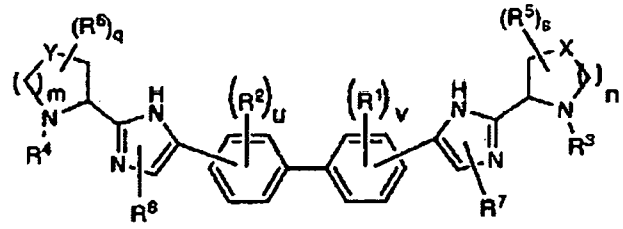
(see **D2** – WHO paper on Daclatasvir Patent Landscape, publ. April 2014, after circulation to Applicants; see also **D3**: print out from website of Applicants).

21. Surprisingly, there is not a single working example in the entire written description which relates to Methyl[(2*S*)-1-{(2*S*)-2-[4-(4'-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl) amino]-3-methylbutanoyl}-2-pyrrolidinyl]-1*H*-imidazol-4-yl}-4-biphenylyl)-1*H*-imidazol-2-yl]-1-pyrrolidinyl}-3methyl-1-oxo-2-butanyl] carbamate. The closest compound is possibly that described in Example 24-23 viz. methyl ((1S)-1-(((2S)2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate hydrochloride salt. On applicants' own showing, this compound of Example 24-23 is a N2 polymorph (see **D4** – IN 806/DELP/2010).

22. As stated above, there are 40 claims currently pending on this application, considering that Applicants have not as yet filed any response to the First Examination Report addressing any of the objections contained therein. We

reiterate that the Opponent reserves his right to file any further opposition/statement of objections in case applicants amend the claims as part of the examination process. A short summary of the claims is set out below.

23. There are three independent product claims on this application. Claim 1, 17 and 18. Claim 1 covers a Markush structure (given below) and lists several optional substitutions, and effectively covers a multitude of compounds.

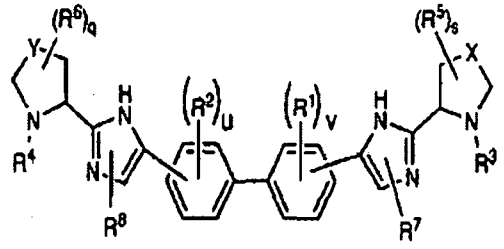


(I),

24. The compound of claim 1 is essentially a biphenyl imidazole with five member N containing rings.

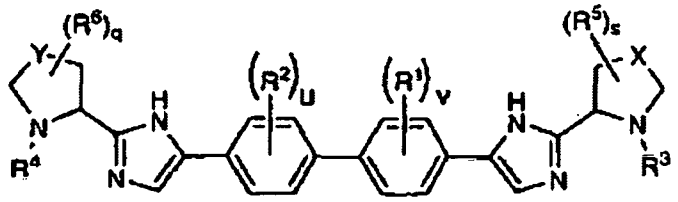
25. Claims 2 through 16 cover various purported embodiments of the compound of formula I given in claim 1.

26. Claim 17 is an independent Markush claim called compound of formula II, and is represented below:



(II),

27. Independent Claim 18 again covers a separate Markush structure which again covers a multitude of possible compounds (with no evidence that such compounds have actually been prepared). The compound is reproduced below for reference.



(III),

28. Claim 19 comprises a list of over 800 compounds with their IUPAC names. None of the compounds listed is Methyl[(2*S*)-1-{(2*S*)-2-[4-(4'-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl) amino]-3-methylbutanoyl}-2-pyrrolidinyl]-1*H*-imidazol-4-yl}-4-biphenylyl)-1*H*-imidazol-2-yl]-1-pyrrolidinyl}-3methyl-1-oxo-2-butanyl] carbamate.

29. Claim 20 is an independent claim providing structures of several compounds, including, purportedly, methyl [(2*S*)-1-{(2*S*)-2-[4-(4'-{2-[(2*S*)-1-{(2*S*)-2-[(methoxy carbonyl)amino]-3-methylbutanoyl}-2-pyrrolidinyl]-1*H*-imidazol-4-yl}-4-biphenylyl)-1*H*-imidazol-2-yl]-1-pyrrolidinyl}-3-methyl-1-oxo-2-butanyl] carbamate. However, as explained hereinabove, there is no working example which actually supports the formation or existence of this compound.

30. Claim 21 is another independent claim which again lists various compounds by their IUPAC names. Claim 22 is dependent on claim 21 and covers specifically various di-HCL salt forms of these compounds.

31. Claims 23-34 claim different compounds and their pharmaceutically acceptable salt forms.

32. Claim 35 relates to a composition covering a combination of the compound of claim 1 and a pharmaceutically acceptable carrier.

33. Claim 36 (and claim 37-40) which depend on claim 35, covers the alleged combination of the composition of claim 35 with one or more additional compounds with Hepatitis C inhibitory activity. The entire written description is silent on any such interaction between the compounds of claim 1 and such additional actives, and in particular, as to any example of any synergistic interaction in such combinations.

GROUNDS OF OPPOSITION

IV. Section 25(1)(h) – non-compliance with Section 8

34. It is respectfully submitted that the instant application is liable to be refused on the ground of non-compliance with the statutory mandate of Sec. 8. It is further submitted that this is an absolute ground for rejection, and the statute does not provide any discretion whatsoever, moreover, when the non-compliance has been deliberate and mala fide. It is submitted that Applicants' failure to comply with the requirement of Section 8 extends to both Section 8(1) and 8(2).

35. The applicants have apparently filed a Form 3 and submitted certain prosecution histories on or around April 29, 2015. It must be noted that this has been done towards the very end of the prosecution term, and in direct contravention of the spirit and legislative intent underlying Section 8.

36. The Applicant will no doubt in due course file a petition stating that "it took time to compile information from multiple jurisdictions:. It is submitted that any such petition must be rejected in limine and the deliberate non-compliance of Section 8 viewed with seriousness. In particular, for example, any assertion by Applicant that 'it took them time' to compile such report has no meaning in this era of technology – where details of patent families are retrievable in a matter of few minutes. In addition, particular reference is drawn to **D2** where an external agency, the WHO provided applicants with details of their patent applications. Given this, it would be stretching the limits of credibility to accept applicants' assertion that it took 11 months from issuance of the First Examination Report to compile the necessary information and furnish it to the IPO.

37. It is submitted that IN '853 should be rejected due to the deliberate non-compliance with Section 8 of the Act. The attention of the Learned Controller is drawn to the fact that, even subsequent to issuance of the First Examination Report on June 26, 2014 specifically requiring compliance with Section 8(2) read with Rule 12(3) within a period of 6 months, Applicants' took a full 11 months, and then supplied incomplete information.

38. It is submitted that delay by Applicants should not be condoned considering Applicants have been negligent or acted in a mala fide manner. In view of the above IN '853 should be rejected under Sec. 25(1)(h) of the Act.

V. Section 25(1)(g) – IN 806 is liable to be refused since it does not sufficiently and clearly describe the invention or the method by which it is to be performed.

39. There is a statutory requirement in Sec. 10(4) that every complete specification shall particularly and fully describe the invention, its operation or use, and the method by which it is to be performed. Similarly, Sec 10(4)(b) expressly requires that an applicant for patent disclose in the complete specification the best method of performing the invention which is known to the applicant.

40. It is submitted out that the statutory requirement is that the written description must **both** sufficiently and clearly describe the invention and the method by which it is to be performed. The requirement for sufficient and clear disclosure of the alleged 'invention' encompasses the requirement to identify material and relevant prior art that may exist, the problems associated with such prior art, and the utility of the alleged 'invention' in terms of overcoming or avoiding such problems. It is respectfully submitted that none of the alleged inventions are clearly or sufficiently described in the written description.

41. The claims on IN '853 can broadly be divided into the following categories:

(a) Claims for a compound per se – claims 1 to 34;

(b) Claims for a composition comprising compound(s) of claim 1 with a pharmaceutically acceptable carrier – claims 35;

(c) Claims for a composition comprising compound(s) of claim 1 with a pharmaceutically acceptable carrier and with one or more other active ingredients – claims 36 to 40.

42. As stated hereinabove, the impugned application has multiple sets of claims. In particular the independent claims 1, 17 and 18 each cover several thousand compounds. Claims 19 and 20 in turn, each cover several hundred compounds separately. Again, it is not the applicants' case that they have allegedly invented

a completely new molecule. The application stipulates that the compounds covered through the claimed Markush structures comprise biphenyl imidazole derivatives with a biphenyl moiety linked at either end to a pyrrolidone alkylglycine.

43. It is submitted that IN '853 is liable to be refused on several counts for not having provided sufficient, adequate and clear description as to the nature and scope of the invention. In this connection, it is submitted that merely filing 634 pages of written description do ensure compliance with this statutory requirement – the content of this disclosure and its' relevance is essential.

44. In the first place, there is absolutely no disclosure of any prior art, let alone directly relevant prior art as to compounds which are useful for treating Hepatitis C. Pages 1 and 2 of the written description merely provide four paragraphs background information – not on compounds useful in the treatment/inhibition of Hepatitis C, but on Hepatitis C itself. This is despite the fact that various biphenyl imidazole derivatives have been known for several years before the priority date of IN '853 for the treatment of Hepatitis C.

45. For example, US Patent Publication 20040152073 (**D5** – hereinafter US '073) teaches and claims p-nitroblue tetrazolium as an antioxidant and for treatment of Hepatitis C. The use of compounds containing a biphenyl heterocycle moiety for treatment of Hepatitis C is also known from US Patent 6,664,255 (**D6** – hereinafter US '255). Pyrrolidinyl – L – valyl carbamate for example, is also widely known as a component of drugs for the treatment of Hepatitis C, and in fact is specifically known for its NS5A protein inhibitory activity – see US Patent 6,900,207 (**D7** – hereinafter US '207).

46. US Patent 7,220,745 (**D8** – hereinafter US '745) for example relates to heterocyclic compounds for treatment of Hepatitis C. US '745 expressly discloses compounds and compositions for treatment of Hepatitis C, and comprise biphenyl heterocycle compounds that inhibit replication and/or proliferation of Hep C virus.

47. As can be seen, IN '853 does not contain any disclosure of any prior art compounds, particularly of compounds containing a biphenyl imidazole moiety and/or a pyrrolidone alkylglycine moiety for treatment of Hepatitis C. Instead, the impugned application purports to give an impression that the alleged 'invention' comprises completely new compound(s), thereby deliberately misleading the Indian Patent Office.

48. The claims relating to compound(s) per se encompass over 1000 different compounds based on the combinations from the Markush structure. Strangely, there is no supporting disclosure for each possible species derivable from this Markush structure. The Indian Patent Office in *Cipla vs. Gilead Sciences (IN 396/DEL/1996),* had expressly held that when the primary independent claim encompasses a wide range of compounds based on the Markush structure, it is essential that an applicant provide not only the IUPAC names, but also actual clear directions as to the method of preparation and advantages of such compounds. Simply put, any possible benefit considered hypothetically possible for one compound derived from a Markush structure cannot automatically be extrapolated to all other compounds that are encompassed in the same Markush structure. This is especially true of pharmaceutical compounds.

49. The written description of IN '853 for example details that the compounds may be administered in any of the known conventional dosage regimens and in any of the conventional dosage forms. This is simply inapplicable, since drug-carrier interactions determine the nature of administration and dosage. Simply put, a person of ordinary skill in the art would receive no guidance as to which compound, from the many thousands encompassed within the structure of Compound I, is actually useful for NS5A protein inhibition, or how it is to be administered. In order to determine this, such a person of ordinary skill in the art would necessarily have to perform a separate range of investigations.

50. It is further submitted that while IN '853 claims several thousand compounds, **none of these** are described in terms of their synthesis or characterisation. The

compounds are defined (if at all) only in terms of their purported activity of Hepatitis C inhibition. Additionally, there is no example which would possibly support this claim of Hepatitis C inhibition through NS5A inhibition. Effectively, the 600 pages of what purport to be methods of synthesis do not provide a person of ordinary skill in the art necessary guidance to practice the invention.

51. Turning specifically to Daclatasvir which has the IUPAC nomenclature of Methyl [(2*S*)-1-{(2*S*)-2-[4-(4'-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-2-pyrrolidinyl]-1*H*-imidazol-4-yl}-4-biphenylyl)-1*H*-imidazol-2-yl]-1-pyrrolidinyl}-3methyl-1-oxo-2-butanyl] carbamate, there is no working example which actually supports the formation or existence of this compound. The closest possible compound is that disclosed in Example 24-23 viz. methyl ((1S)-1-(((2S)2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate dihydrochloride salt. However, again based on Applicant's own conduct, even this compound is an allegedly different polymorphic form (see D4 - IN 806/DELNP/2010).

52. Applicants in IN 806 expressly state that the compound claimed therein is an allegedly novel and inventive polymorphic form which is totally different from the compounds claimed and disclosed in IN '853. Given this dichotomy in Applicants' statements in respect of two separate patent applications, the only conclusion that can possibly be drawn is that Example 24-23 does not relate to the Markush structure of the claims of IN '853, and therefore has no role to play in any determination of adequacy or sufficiency of disclosure. In fact, the very presence of an example which apparently on Applicants' own admission does not relate to the claimed alleged invention renders the impugned application unclear and liable for refusal.

53. It is further submitted that given the literally innumerable possible permutations and combinations encompassed in the Markush structure of the claims, IN '853 simply does not help any person of ordinary skill in the art at arriving at an

understanding of the nature and scope of the invention. Essentially, the written description of IN '853 is a fishing expedition aimed at obtaining protection (without validation) for hypothetical compounds with hypothetical activity – and does not serve the primary purpose of informing the public as to the scope of protection sought and the metes and bounds of the alleged invention.

54. The opening description on pages 2 and 3 of IN '853 purports to assert that the compound(s) of the alleged invention are useful for the treatment of Hepatitis C virus. However, Applicants themselves admit that this assertion is speculative (page 20-26). Additionally, there is no data whatsoever in the written description either in the form of in vitro tests, or in vivo tests (human clinical or animal model) which would support this assertion in respect of the alleged invention. The description admits that any anti-HCV activity is speculative, but continues to assert this as a stated utility. Despite the admitted speculative utility, the impugned application contains not one but 6 claims for a pharmaceutical composition containing the compounds of the alleged invention and a carrier.

55. It is submitted that it is incumbent on an applicant to not merely state a utility, but provide information in support of this utility. In other words, a patent specification cannot be built on a foundation of hypotheses or speculation. If anti-HCV activity is a part of the invention, then the impugned application is liable to be rejected since it does not contain any information or data in support of this assertion. Effectively, merely stating a purported utility (and in a speculative manner at that) cannot meet the requirement to let a person of ordinary skill in the art know that the compound in question does actually work.

56. In similar fashion, claims 36 to 40 attempts to cover a combination of the compounds of the preceding claims with one or two other medicaments useful for the treatment of HCV. However, the preceding written description does not contain any information as to how these formulations should be prepared. Preparing combinatorial drugs requires an assessment of each separate active pharmaceutical ingredient, and the potential interaction with the other(s) as well

as cross-interactions with the excipients in the formulation. The written description merely provides a long list of known medicaments, and asserts that the compounds of the alleged invention can be combined with any or all of them for a combined treatment of HCV. IN '853, however, does not disclose any information regarding compatibility of medicaments or excipients. There is no disclosure in terms of data or working examples to show that such combinations actually provide the claimed benefit of inhibition of the NS5A protein.

57. Applicants' themselves admit that the benefits of such combination are purely speculative (see page 20-26). The disclosure referred to herein clearly establishes that no work has been done at all prior to filing of the impugned application in respect of devising any combinatorial treatments. Indeed, this is not surprising, considering the Applicants' own admission that the potential anti-HCV activity of the allegedly novel compound/composition is itself hypothetical and speculative. It is reiterated that a patent application is not a hunting licence whereby an applicant can simply pen down untested speculations and hypotheses as assertions without providing any demonstrable proof. Indeed, such evidence must be present at the time of filing, and cannot be supplied later.

58. It is further submitted that the purpose of a patent specification is to enable a person of ordinary skill who is reading it, necessary information and guidance to work the invention. As such, the impugned application fails to provide any guidance to a person of ordinary skill in the art in respect of any of the following:

(a) the metes and bounds of the alleged invention in terms of what the prior art was, the problems associated with such prior art compounds and how the compound(s) of the alleged invention overcome such problems;

(b) whether the alleged invention would be useful in any dosage form and dosage regimen, or whether specific dosage forms are recommended;

(c) Any data or information as to how any compound covered or encompassed in the Markush structure of the claims is actually useful if at all, in the treatment of any disease, let alone HCV;

(d) Any data or information as to how any compound encompassed in the Markush structure of the claims is useful, if at all, for the treatment of any disease, let alone HCV when used in combination with one or more other known medicaments for the treatment of HCV.

59. It is submitted that in the absence of this critical information, what is claimed as "invention(s)" is simply not supported by the preceding disclosure, and such description must necessarily be held to be insufficient and unclear. Therefore, on this ground alone, the impugned application is liable to be rejected in toto.

VI. Section 25(1)(f) – subject matter of the claims currently on record are not an invention within the meaning of the Act, or are not patentable under the Act

60. In connection with this ground of opposition, Opponents firstly rely on the provision of Section 2(1)(j) of the Act. Section 2(1)(j) defines an invention as:
"...a new product or process involving an inventive step and capable of industrial application".

61. Without prejudice to any of the submissions in this opposition that the subject matter of the claims lacks inventive step, Opponent submits that claims 1-40 of the impugned application do not meet the requirement of an invention within the meaning of Section 2(1)(j).

62. Even assuming arguendo, which the Opponent disputes, that there is some intrinsic novelty and/or inventive step in the biphenyl benzimidazole derivatives of claims 1 to 34, the Applicants' have not established that either the compounds of claims 1 to 34, or the two separate compositions of claims 35 to 40 are capable of industrial application.

63. IN '853 is liable to be rejected since what is claimed therein is incapable of any industrial application because:

- it does not provide any data as to any activity for the claimed compounds (the asserted uses are all admittedly speculative);

- it does not provide any data as to any activity for any of the claimed combinations of the allegedly invented compounds with any prior art compound

(the listed uses being admittedly speculative).

64. In this connection, it is submitted that the entire written description of IN '853 does not contain any evidence of any form whatsoever of any utility (industrial application) for either the biphenyl benzimidazole derivatives claimed in claims 1 to 34, or for a pharmaceutical composition containing such compound(s) per se, or for any pharmaceutical composition containing such compound(s) with one or more additional known medicaments for treatment of HCV.

There is no disclosure, credible or otherwise of any actual activity

65. As pointed out above under the ground of insufficient disclosure, the Applicants assert that the compound(s) of the alleged invention **may be** useful in the treatment of HCV, particularly by inhibition of the NS5A protein (page 20 – 34). However, there is no data or example supporting this assertion. The sole information that is provided is present in pages 600 – 634 which purport to give the biological activity of some of the compounds. What is essential to note here is that even this so-called working example is silent on the parameters used to test activity of the compounds against NS5A protein in terms of the testing protocols, the test equipment etc. Applicants here baldly state that procedures and protocols disclosed in another patent application were used – which application discloses not one, but a multitude of protocols and procedures. There is no evidence that Applicants actually carried out these tests. Per contra, the probability is higher that the figures given in the tables stretching across six pages are arbitrary numbers.

66. It is also important to note that even this so called working example actually admits that the level of inhibition was 10-fold less in respect of drug resistant strains! As such, this is an admission that the compounds allegedly encompassed within IN '853 have no utility over the prior art.

67. It is submitted that this remains a speculative assertion given the failure by Applicants to provide even in vitro, let alone in vivo data to show any anti-HCV activity for the named compound. It is submitted that industrial application

requirement of Section 2(1)(j) is not met by a mere assertion – but must be backed up with some evidence in the written description. As stated above, a patent is not a hunting licence to provide a monopoly right against any future activity, even if such activity seems extremely likely.

68. There is also no data or example to show that any of the compounds of claims 1-34 were actually formulated as a composition, whether by themselves or in combination with any other active ingredients, or that such combinations were tested for their NS5A protein inhibiting activity, or any other therapeutic activity. Given this absence of information, any utility asserted for such compositions remains in the realms of non-validated hypothesis.

69. While Applicants admit that such activity is a 'potential' activity – they do not provide any basis for this assumption. It is submitted that even if the compounds are taken as being novel and inventive, it would fail the test of "industrial application". On this ground alone, claims 1-40 are liable to be rejected.

70. It is submitted that another facet of industrial applicability is that a reader of the specification must be provided sufficient information as to the 'working of the invention'. This submission is supported by the fact that even the Act mandates that a patentee must file working statements showing the extent of commercial working of an invention. If the disclosure in an application is so insufficient as to provide no guidance to a skilled reader as to the practice of the invention, then the patent application must fall on the ground of lack of 'industrial applicability'.

There is no disclosure of any activity of any combination of the claimed compositions, let alone any synergistic activity

71. Similarly, the composition of claim 35 of IN '853 also lacks industrial application. The written description does not provide any evidence that such a composition was at all made or that it would have any anti-HCV activity, apart from the hypotheses in pages 20-34. There is no information or guidance as to how the compounds of claims 1-34 can be made into any pharmaceutical composition, to the extent that the nature of the carrier is not disclosed at all.

72. The written description on pages 20-34 attempts to set forth what Applicants term as the "utility" of the invention. This portion of the disclosure is speculative. For example, it is stated that the compounds can be made into a pharmaceutical composition that can be administered in "unit dosage form" through means such as "oral, rectal, buccal, sublingual... or parenteral". The 'parenteral' administration route is defined as any one of multiple such routes, such as sub-cutaneous, intra-cutaneous, intravenous, intra-muscular, intra-sternal etc. injection or infusion. Persons of skill in the art will appreciate that each route of administration has specific complexities in terms of formulation preparation. Disclosure of a composition prepared as a tablet for oral administration does not provide guidance towards forming an intra-muscular injection.

73. In the absence of any disclosure as to even one form of formulation preparation, what is stated in pages 20-34 of the written description is no more than a laundry list of various forms of administration. Further, this does not meet the requirement of 'industrial application' that should be present in the application at the time of filing.

74. For the above reasons, claim 35 is also liable to be rejected as not being industrially applicable, specifically since the asserted utility of treatment of HCV is not demonstrated and methods of preparation of such composition are not demonstrated in the written description.

75. Similarly, claims 36-40 which attempt to cover the compounds of claims 1 to 34 and one or two additional anti-HCV medicaments as a pharmaceutical composition are also not an invention within the meaning of Section 2(1)(j).

76. The written description on page 25 – 29 admits that such combinations **can be made**, thereby clearly establishing that they have not so far been made. On page 24-25, Applicant merely states a preferred 'dosage regimen' when compounds of claims 1 to 34 are formulated as a composition with one or more other therapeutic or prophylactic agents. Again, there is no example in the application which will show (a) how this formulation is to be prepared; or (b) whether such a

formulation was prepared at all; or (c) whether such formulation actually has any activity, even in vitro.

77. It is submitted that on pages 25 – 29, Applicants set out a laundry list of additional medicaments that allegedly are usable with the compounds of Claims 1 to 34. However, given the wide range of such medicaments, there is no support or disclosure as to how any interactive side-effects are to be addressed, or indeed even what such side-effects are. It is submitted that it is ordinary routine in pharmaceutical chemistry to assess potential adverse interactions before formulating a composition containing two or more active ingredients.

78. In the absence of even this basic information as to whether such an examination was done, claims 36-40 clearly lack industrial applicability. A person of ordinary skill will have to trawl the entire list provided by applicants, carry out extensive trial and experimentation to determine any potential adverse interactions (this assuming that any of the biphenyl benzimidazole compounds of claims 1 to 34 are an active ingredient in the first place), and then prepare such a formulation. It is submitted that any claim, the working of which requires extensive trial and experimentation, is clearly not industrially applicable.

79. For this reason alone, claims 36-40 are liable to be rejected as lacking industrial applicability.

Section 3(d) and Section 3(e)

80. It is submitted that claims 1-40 are also liable to be rejected under Section 3(d), and claims 35-40 are liable to be rejected also on the basis of Section 3(e).

81. Section 3(d) stipulates that 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 is not a patentable invention. Section 3(d) proviso expressly states that salts, polymorphs, particle size, combinations of known substances shall be considered to be the same substance unless they differ significantly in properties with regard to efficacy.

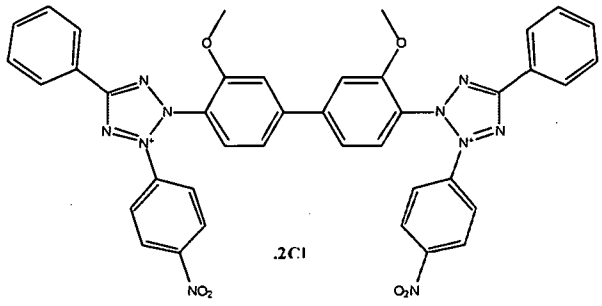
82. Established jurisprudence of the Courts in India, including the Hon'ble Supreme Court in Glivec™ clearly state that the term 'efficacy' in regard to pharmaceutical substances must be read as 'clinical efficacy'.

83. As stated hereinabove, the compounds encompassed by the Markush structure of Claim 1 are fundamentally biphenyl benzimidazole derivatives with a pyrrolidone alkylglycine moiety at each end thereof. As submitted in this opposition, the Hepatitis C inhibitory activity, specifically the NS5A protein inhibitory activity of each respective moiety – the biphenyl benzimidazole and the pyrrolidone alkylglycine are both well known, even if Applicants have not provided this prior art disclosure in the complete specification.

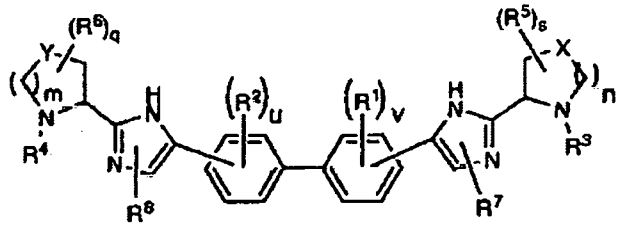
84. Even if the compounds encompassed by the structures of the alleged invention are to be considered a new form of biphenyl benzimidazoles, it is submitted that claims 1 to 34 are liable to be rejected under Section 3(d).

85. Specifically, we rely firstly upon the following documents to demonstrate that the compounds of Claims 1-34 of IN '853 are derivatives of a known substance.

86. US '073 (**D5**) discussed above expressly discloses and claims p-nitroblue tetrazolium as an antioxidant and treatment or preventative for HCV. This disclosure is supplanted by several other publications (for example, US '207 and US '255), which also teach and disclose derivatives of p-nitroblue tetrazolium for the treatment of/inhibition of Hepatitis C, particularly inhibition of NS5A protein. The base structure of this compound is given below:



87. It is submitted that the compound of claims 1-34 of IN '853 are an obvious derivative of p-nitroblue tetrazolium as is evident from a comparison of the two structures.



(I),

88. In particular, Thornber et al (1979, page 564) (**D9**), teaches that 1H-imidazole is a simple bioisosteric switch from 1H-tetrazole and provides similar pharmacological activity. Several anti-HCV drug publications teach derivatives of this compound, starting with the biphenyl – heterocycle moiety.

89. In view of this, and particularly considering that Section 3(d) has been in our statute from 2005, it is surprising that Applicants neither disclosed the above referred prior art, nor have they attempted to provide evidence showing a demonstrable enhancement in efficacy of any of the compounds encompassed in Claims 1 – 34. Indeed, the only reference to any biological activity is on pages 630-634, wherein it is clearly admitted that the compounds of the invention which were apparently tested by some unstated prior art protocol, actually show 10-fold less inhibitory activity in relation to drug resistant cells when compared to activity against wild type cells.

90. What is surprising is that Applicants have not provided any comparative data of the biological activity, let alone efficacy, of the claimed compounds vis a vis prior art biphenyl benzimidazoles which are known to have NS5A and/or NS3A inhibitory activity. Indeed, not only have they not provided this comparison (which is mandated due to Section 3(d) of our Act), they have in fact even failed to advert to any of this prior art in the written description.

91. It is submitted that under Section 3(d) combinations of known substances are also deemed to be the same substance absent any data showing any enhanced

activity of such combinations over the individual substances. In the present case, Claims 35 and 36-40 disclose compositions comprising compounds of formula I with a carrier, and compounds of formula I with one or more other known actives and a carrier respectively. While claims have been included in the impugned application, the preceding written description is silent on whether these compositions were actually prepared and tested, and if yes, the levels of efficacy observed therein, let alone any enhancement in efficacy.

92. It is reiterated that that claims 35-40 for the composition containing the allegedly novel and inventive compounds of formula I with one or more additional active ingredients are also liable to be rejected since 'combinations' are also proscribed under Section 3(d) proviso, particularly given that the impugned application itself admits that the use of such compositions is hypothetical. Admittedly, the written description does not provide any evidence that such a combination actually demonstrates any significant enhancement in the admittedly known efficacy of prior art biphenyl benzimidazole composition containing the same additional known medicaments.

93. For the above reasons, it is respectfully submitted that all of claims 1 through 40 are liable to be rejected under Section 3(d) as not being patentable.

94. Without prejudice to any of the foregoing submissions, it is also submitted that claims 35-40 are liable to be rejected based on Section 3(e) of the Act. Section 3(e) stipulates that a substance obtained by a mere admixture resulting only in the aggregation of the properties of the components thereof is not patentable. It is submitted that established jurisprudence of the Patent Office has crystallised this principle into requiring any composition that is claimed to demonstrate a synergistic interaction between its ingredients.

95. In the present case, the composition of claim 35 is a simple admixture of compound of formula I and a pharmaceutically acceptable carrier.

96. Even assuming arguendo that such a composition had actually been made by Applicants', which evidence is lacking in the written description, there is no data

in the complete specification which would support any assertion of a synergistic interaction between the stated compound(s) and the carrier.

97. It is submitted that in the absence of any such information, the composition of claim 35 has to be construed as a simple admixture, and is liable to be rejected based on Section 3(e).

98. Turning now to the compositions of claims 36-40, the written description is again silent not only on any activity, let alone a synergistic interaction of compositions containing compound of formula I and the other additional one or more actives. There is no evidence that such formulations were even made, let alone whether the stated ingredients actually interact with each other or whether such interaction is synergistic.

99. In view of this missing disclosure, the compositions of Claims 36-40 comprising compounds of formula I and one or two additional medicaments with anti-HCV activity are liable to be rejected based on Section 3(e).

100. It is also of importance to note that Daclatasvir which according to applicants is encompassed in the structure of formula I of claim 1 is not even approved for sole administration in any jurisdiction. The EMEA has given only conditional approval for sale of Daclatasvir with another active ingredient (**D10** – Copy of EMEA Approval). It is submitted that this is in itself is sufficient evidence of the absence of any evidence of enhancement of significant efficacy in Daclatasvir, and ergo in the compounds (and compositions) encompassed by the claims of the present invention.

101. In view of the above, it is respectfully submitted that the absence of any data, particularly comparative data showing enhanced efficacy of the compounds and compositions of the alleged invention, IN '853 is liable to be refused.

VII. Section 25(1)(e) – The claims are obvious and lack inventive step

102. It is submitted that all of claims 1-40 of the impugned application are liable to be rejected on the ground of obviousness and lack of inventive step for the reasons

set out below. It is further submitted, that this ground, as all other grounds in this opposition, are being taken without prejudice to one another.

103. Section 2(1)(ja) of the Act stipulates defines 'inventive step' as that feature of a claimed invention that involves a technical advance as compared to existing knowledge or having economic significance or both and that which makes the invention not obvious to a person of skill in the art.

104. In the present case, as submitted above, the compounds (and compositions) of IN '853 clearly lack any industrial applicability, and are therefore clearly of no economic significance. Ergo, the compound claimed in claims 1-34, and by extension, any composition containing such compound (claimed in claims 35 – 40) also lack any economic significance.

105. Turning now to the question of inventive step, it is submitted that the impugned application fails to set out any 'step' let alone an inventive step as to what the technical problem was with the known compounds, particularly known biphenyl benzimidazoles and known pyrrolidone alkylglycines, both of which are known for the treatment of Hepatitis C, particularly by inhibition of NS5A and NS3A proteins. In point of fact, the written description of IN '853 actually does not even acknowledge the existence of such prior art – clearly in an attempt by the Applicants to mislead the Indian Patent Office that what is claimed is a compound(s) created for the first time.

106. In support of the ground of lack of inventive step, we rely upon the following documents:

(a) US '073 – D5

(b) US '207 – D7

(c) Llinsa Brunet – D11

(d) Thornber et a – D9

(e) WO 2004/005264 (WO '264) – D12

(f) US 7,220,745 (US '745) – D8

(g) WO 2003/099274 (WO '274) – D13

107. In order to address the issue of obviousness or lack of inventive step, we respectfully draw the attention of the Learned Controller to the following. Our submissions on the ground of obviousness are based on the compound(s) of formula I given in claim 1, but would be equally applicable to the structures given in claims 17 and 18. In addition, to a large extent, considering that Applicants have publicly asserted that the impugned application covers Daclatasvir, the question of obviousness will be based on the specific structure of this named compound. This is without prejudice to our submissions above that the impugned application simply does not disclose Daclatasvir, or its method of preparation, let alone the purported activity of NS5A and/or NS3A protein inhibition, thereby leading to treatment/inhibition of Hepatitis C.

108. In order to determine whether or not the claims of the impugned application possess any inventive step, or are obvious, it is also essential to study the written description so that the 'problem(s)' in prior art compounds can be understood, as well as an analysis made of whether the proposed solution overcomes or addresses such problems.

109. Firstly, the written description states that it provides compounds useful as Hepatitis C virus inhibitors. The compounds in question are said to be biphenyl imidazoles with a pyrrolidone alkylglycine moiety. The only prior art compounds identified in the written description are on page 1 (paragraph 3) viz. ribavarin and Pegylated α-Interferon. There is no reference of any other prior art compound, let alone other biphenyl imidazoles or alkylglycines which are known for the treatment of Hepatitis C. The only problem with Peg-α-Intereferon therapy that is identified is the alleged need to 'provide sustained reduction in viral load' (page 1, paragraph 3). The entire discussion of prior art and any problems associated therewith is confined to this single paragraph.

110. On page 2, paragraph 2, it is stated that compounds which inhibit the NS5A protein are desired **based on already available prior art literature**. Surprisingly, there is no reference to several literature references and/or patents which

disclose specifically the use of biphenyl imidazoles or alkylglycines for the inhibition of both NS5A and NS3A proteins. There is also obviously no indication as to exactly why inhibition of NS5A proteins is desirable – not surprisingly, since this requirement was already well known and addressed in the art, and in a manner more efficaciously than by the impugned application.

111. The written description from pages 4 to 626 comprises a listing of various compounds purportedly falling with the Markush structure of formula I, hypothetical and extremely speculative statements about the alleged activity of the named compounds, hypothetical and speculative statements about the alleged activity of compositions containing the named compounds by themselves or in combination with one or more additional active ingredients, admissions that the process of composition formation, compound preparation, crystallisation methods etc. are otherwise well known in the art, and liberal admissions that in actuality, perhaps very few of the compounds falling or encompassed in structure of formula I have been prepared or even tested to determine the lead compound.

112. From pages 627 to 634, the written description purports to provide a 'working example' to justify the activity of the named compounds, which essentially comprises two paragraphs wherein there is no disclosure as to either testing protocols, cell types (including their depository numbers), or any other testing parameters, and seven pages of a Table 2 setting out alleged Ec50 values. There is however, an admission that in terms of activity, when the named compounds were purportedly tested against both wild type cells and drug resistant cells, a noticeable reduction (10-fold) in activity was observed in the case of the latter.

113. In this light, it is submitted that our averments in respect of obviousness and lack of inventive step are with respect to three issues:

(a) Given the stated technical problem of ensuring 'sustained reduction in viral load', is there any evidence that the named compounds/compositions actually provide a technical solution?

(b) Even assuming that the answer to (a) above is in the affirmative, what is the technical solution provided by IN '853, and does the technical solution actually comprise an inventive step – given that biphenyl benzimidazole based compounds were known for the treatment of Hepatitis C;

(c) Even if the answer to both (a) and (b) above is in the affirmative, would it not be obvious for a person of ordinary skill in the art to either:

- combine a biphenyl benzimidazole with an alkylglycine to provide a complex molecule for treatment/inhibition of Hepatitis C virus, since both moieties are individually known to provide the same desired result;
- form a symmetrical combination of a phenyl imidazole bearing an alkylglycine moiety given that individually HCV inhibitory activity of both phenyl imidazoles and alkylglycines were known.

114. It is respectfully submitted that the impugned application fails the test of inventive step or non-obviousness on each of the above-mentioned counts.

Is there any evidence that the impugned application provides any technical solution, let alone a technical solution to the alleged technical problem?

115. As stated above, Applicants identify the alleged technical problem on page 1, paragraph 2 in the following terms:

> "Presently, the most effective HCV therapy employs a combination of alpha interferon and ribavirin, leading to sustained efficacy in 40% of patients. Recent clinical results demonstrate that pegylated alpha-interferon is superior to unmodified alpha-interferon as monotherapy. However, even with experimental therapeutic regimens involving combinations of pegylated alpha-interferon and ribavirin, a substantial fraction of patients do not have a sustained reduction in viral load. Thus, there is a clear and long-felt need to develop effective therapeutics for treatment of HCV infection."

116. There is no disclosure anywhere else in the written description as to any other technical problem with any prior art treatment regimen or prior art compound. It is respectfully submitted that keeping this assertion in mind, it was incumbent on Applicants' to provide sufficient information and data and working examples (even at least in vitro examples) of the alleged "sustained reduction in viral load" when compared with the prior art. It is submitted that this was essential to justify any claim to a technical solution leading to an inventive step, since a deficiency in efficacy in prior art interferon was being touted as the problem.

117. However, instead of providing any comparative data as to the 'sustained reduction viral load', the last eight pages of the written description merely provide arbitrary Ec50 values without providing even the test protocols that were followed. For example, there is no information or data as to whether the reduction in viral load over a preferred treatment regimen was truly 'sustained' or did regression occur.

118. It is submitted that this lapse in data is a clear example that the compounds of the invention do not comprise a technical solution to the alleged technical problem. A review of published literature on Daclatasvir which is allegedly encompassed within the ambit of claim 1 (and specifically covered in claim 20) only shows that it should **not be administered as a monotherapy**. It is submitted that this establishes that there is no 'sustained reduction in viral load' achieved by the compounds of the invention, or even by the alleged lead compound Daclatasvir encompassed in structure 1.

119. In direct contrast, in point of fact, the complete specification on page 626 and 627 admits that the compounds purportedly tested (which incidentally does not include Daclatasvir) actually are ineffective against a specific drug resistant cell type. The relevant portion of the admission is reproduced below:

> "The compounds tested were determined to have **more than 10-fold less inhibitory activity on cells resistant to compound A than wild-type cells** indicating a related mechanism of action between the two compound

series. Thus, the compounds of the present disclosure **can be** effective to inhibit the function of the HCV NS5A protein **and are understood to be as** effective in combinations as previously described in application PCT/US2006/022197 and commonly owned WO/04014852. Further, the compounds of the present disclosure **can be** effective against the HCV Ib genotype. It should also be understood that the compounds of the present disclosure **can inhibit** multiple genotypes of HCV." (***emphasis added)***

120. Quite apart from the fact that there is no information as to which of the test protocols of PCT/US2006/022197 or O'Boyle, et al., *Amimicroh Agents Chemother.* 2005 Apr; 49(4): 1346-53, were adopted, and what exactly "compound A" is, the portions above that are underlined and emphasised clearly establish that:

(a) There is no 'sustained reduction in viral load', and therefore no solution to the alleged technical problem;

(b) That in fact, any activity that is claimed is actually still hypothetical – note the use of 'can be effective' instead of the definitive 'is effective'.

121. It is submitted that in view of this, it is clearly established that the compounds of the invention, even if novel and non-obvious, simply do not provide a technical solution to the alleged technical problem, and therefore lack inventive step.

122. It is again reiterated that the very fact that the Applicants have only been able to secure permission for combinatorial administration of Daclatasvir (assuming that this is encompassed within the present impugned application) both at the EMEA and the US FDA is evidence that a technical solution for the technical problem is not provided.

123. Without prejudice to the foregoing submissions, Applicants' may in response submit that the very factum of approvals by EMEA and USFDA are evidence of "synergistic interaction of compounds of formula I with other active ingredients". However, this would be manifestly incorrect since:

(a) Firstly, there is no evidence that Daclatasvir is actually encompassed within the structure of the claims, or that it is actually enabled (see submissions above on insufficiency and lack of clarity of disclosure);

(b) Even if Daclatasvir per se was so enabled, there is no evidence to show that any data relating to Daclatasvir can be extrapolated to other compounds encompassed within the claims of the impugned application, particularly given the wide variance in the Ec50 values listed on pages 628-634;

(c) Even if such data could be extrapolated, there is no evidence to show that applicants had **ever** actually tried combinatorial treatment in any form of testing – in vitro, in vivo or animal model since this is clearly missing from the written description. The Act requires that such data/evidence in relation to synergy be present at the time of filing, and not be provided during subsequent prosecution.

124. It is therefore submitted that for the above reasons alone, IN '853 is liable to be refused on the ground of lack of inventive step.

Is there an inventive step – given that biphenyl benzimidazole based compounds were known for the treatment of Hepatitis C?

125. Without prejudice to any of the foregoing averments, it is respectfully submitted that even assuming arguendo that the impugned application does provide a technical solution to a technical problem, the compounds of the invention comprise an obvious variant of prior art compounds, all of which are known for the inhibition of Hepatitis C virus, particularly inter alia through the inhibition of NS5A protein.

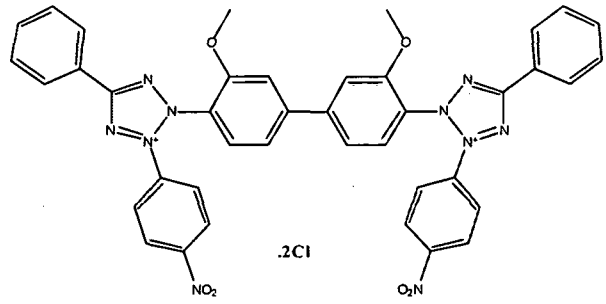
126. In this connection, we respectfully rely on the following documents:

- US '073 – D5
- US '207 – D7
- Llinsa Brunet – D11
- Thornber et a – D9

127. It is submitted that US '073 is admittedly published prior in point of time to the impugned application and is therefore entitled to be considered prior art. It is submitted that US '073 is relevant prior art since it discloses methods for identifying compounds that are useful for the treatment and diagnosis of Hepatitis C. US '073, inter alia expressly discloses the use of p-nitroblue tetrazolium as an antioxidant and for treatment and prevention of Hepatitis C (pages 6 to 9).

128. US '207 was published on August 14, 2003 and admittedly is prior art. This document discloses compounds useful for the treatment of Hepatitis C based on inhibitory activity on cysteine proteases (paragraph 498 et seq). This document teaches various derivatives of p-nitroblue tetrazolium containing the biphenyl heterocycle moiety, all of which are considered useful for the treatment of Hepatitis C.

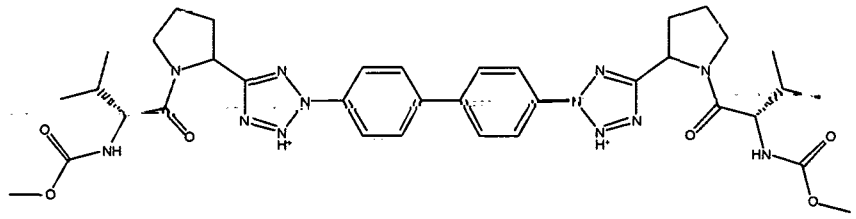
129. In particular, the disclosure of US '073 and US '207 provide a biphenyl imidazole compound of the following structure:



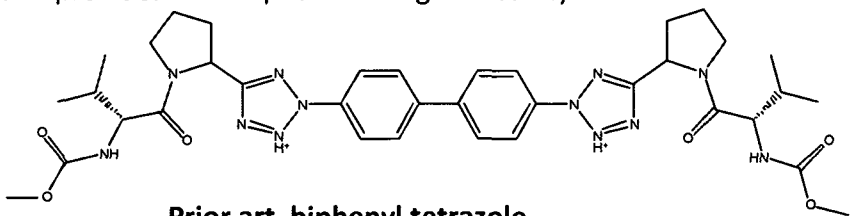
130. We now respectfully draw the Learned Controller's attention to Llinsa-Brunet which was published in 1998. This document expressly discloses pyrrolidinyl-L-valyl-carbamate and (S)-2-amino-3,3-dimethyl-1-(pyrrolidin-1-yl)butan-1-one carbamate as components of many HCV antiviral drugs, as a serine protease inhibitor. This, incidentally, is also taught as NS5A inhibitors in Bailey AR049435 and a phenotypical Hepatitis C treatments (US '207). The 15 most potent peptide based inhibitors HCV serine protease inhibitors taught in Llinsa Brunet contain L-

proline-L-valine moiety with the naturally occurring amino acid enantiomers. Proline-L-valine is a key moiety in the NS5A protein.

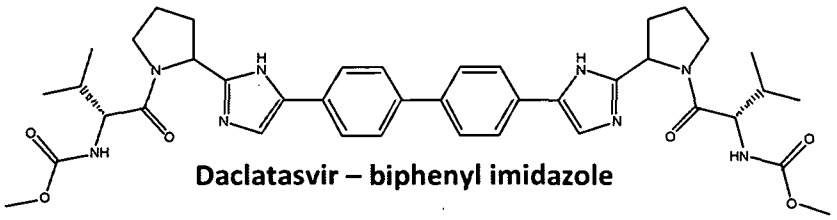
131. It is submitted that reading US '073 and/or US '207 together with Llinsa Brunet would result in a compound of the following structure:



132. It is submitted that if at all there is any difference in the teaching of the above-cited documents from the compounds of the impugned invention, it is that the IN '853 discloses 1H-imidazoles, whereas this art teaches 1H-tetrazoles **(see structural comparison below)**. However, it is submitted that this is an insignificant difference, in as much as the two are considered as bioisosteres in the art (Thornber et al, 1979, page 564). It is submitted that Thornber et al expressly teaches that 1H-imidazole is a simple bioisosteric switch from 1H-tetrazole and provides similar pharmacological activity.



Prior art biphenyl tetrazole



Daclatasvir – biphenyl imidazole

133. In view of the above, it is submitted that any person of ordinary skill in the art would readily take the biphenyl tetrazole compound of the cited art (which is known to possess HCV inhibitory activity), replace the 1H-tetrazole with 1H-imidazole. It is submitted that this is not an inventive or non-obvious

substitution, particularly considering that the pharmacological activity of the two sets of compounds is identical. It is surprising that there is no discussion at all in the impugned application of any biphenyl –heterocycle compounds which are useful for treatment of HCV.

134. In view of the above, it is respectfully submitted that claims 1-40 (compounds, as well as compositions containing inter alia, such compounds) are rendered obvious to a person of ordinary skill in the art. Indeed, a person of ordinary skill in the art seeking any guidance as to the alleged inventive step in the impugned application and teaching as to how to work the invention, would find the necessary information in the cited prior art but not in IN '853.

135. It is submitted that IN '853 is liable to be rejected on this ground alone.

Is it obvious for a person of ordinary skill in the art to combine a biphenyl benzimidazole with an alkylglycine or form a symmetrical combination of a phenyl imidazole bearing an alkylglycine moiety to provide a complex molecule for treatment/inhibition of Hepatitis C virus?

136. Without prejudice to any of the foregoing averments, it is submitted that the claimed compounds are obvious derivatives of prior art disclosures as set forth below. It is reiterated that each averment in this opposition is to be read independent of any other, and is not to be construed as a waiver or abandonment of any of the preceding submissions under any ground.

137. In support of this submission, we rely on the following documents:

- WO 2004/005264 (WO '264) – D23
- US 7,220,745 (US '745) – D8
- WO 2003/099274 (WO '274) – D13

138. For the purpose of support of this assertion, Opponent would rely on Daclatasvir as the primary/lead compound allegedly covered in the impugned application in order to establish obviousness.

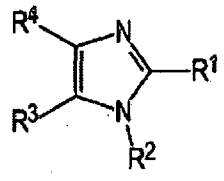
139. Daclatasvir is represented by the structure given above and is also known as Methyl[(2S)-1-{(2S)-2-[4-(4'-{2-[(2S)-1-{(2S)-2[(methoxycarbonyl)amino]-3-

methylbutanoyl}-2-pyrrolidinyl]-1H-imidazol-4-yl}-4biphenylyl)-1H-imidazol-2-yl]-1-pyrrolidinyl}-3-methyl-1-oxo-2 butanyl] carbamate.

140. It is submitted that the structure of Daclatasvir can be seen as a combination of a alkylglycine moiety attached to a biphenyl imidazole, or alternatively as a symmetrical combination (with inversion) of a phenyl imidazole with an alkylglycine moiety attached therewith. It is submitted that this combination is an obvious combination to any person of ordinary skill in the art, particularly because each of these three moieties – the biphenyl imidazole, the alkylglycine and the phenyl imidazole are individually known to possess inhibitory activity against HCV and in particular to the NS5A protein.

141. It is submitted that WO '264 teaches the use of various imidazole compounds for treatment of Hepatitis C virus while using protein kinas casein kinase I Alpha, Delta and Epsilon as targets for medical Intervention. It specifically discloses imidazole compounds which inhibit the NS5A protein. WO '264 also teaches methods for the identification of compounds for prophylaxis and/or treatment of diseases caused by HCV, methods for treatment thereof, as well as pharmaceutical compositions useful for prophylaxis and/or treatment of HCV infections and diseases (page 1-5, and examples).

142. The phenyl imidazole structure disclosed in WO '264 which admittedly possesses Hepatitis C virus inhibitory and in particular NS5A protein inhibitory activity, is given below:

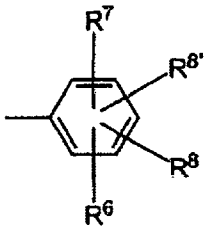


(I)

(page 4 of WO '264)

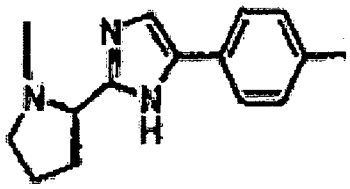
143. It is submitted that WO '264 also stipulates that in the given structure,

- R^3 can be $R^{1'}$ or $R^{1''}$. (pages 4 to 9)
- R^1, $R^{1'}$ and $R^{1''}$ are said to have the following structure: (pages 4-9)



- R^4 can be –H (page 53)
- R^2 can be –H

144. It is submitted that when the above substitutions are made in the Markush structure of WO '264, the following structure is obtained:



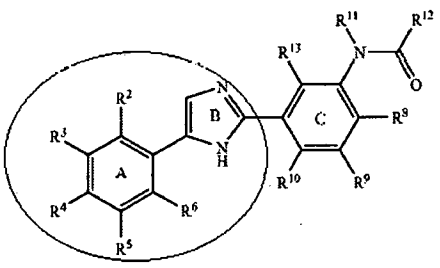
145. The structure enunciated above for WO '264 is evidence that phenyl imidazole pyrrolidine and substituents thereof were known for inhibition of Hepatitis C virus. WO '264 establishes that phenyl imidazole moieties are the core structures of the compounds claimed therein and are known also for NS5A protein inhibition. WO '264 also teaches that phosphorylation of NS5A and homologues thereof, is a preferred feature in members of the *Flaviviridae* family and has a significant role in the HCV replication cycle. This citation also discloses that cellular protein kinases involved, particularly in cellular kinases responsible for NS5A phosphorylation *in vivo,* could therefore serve as promising targets for antiviral therapeutic intervention [page 44).

146. It is therefore submitted that WO '264 establishes that phenyl imidazole containing compounds are useful as NS5A inhibitors.

147. It is submitted that Daclatasvir can be viewed as a symmetrical compound – where one half of the molecule is a phenyimidazole moiety with a pyrrolidine ring attached at 2-position of the imidazole ring. As is clear above, this feature is

already disclosed in WO '264, and for the same stated activity viz. inhibition of NS5A protein.

148. The Opponent now relies on US '745 which relates to diphenyl heterocyclic compounds useful for the inhibition of Hepatitis C virus. US '745 discloses compounds of the following structure:

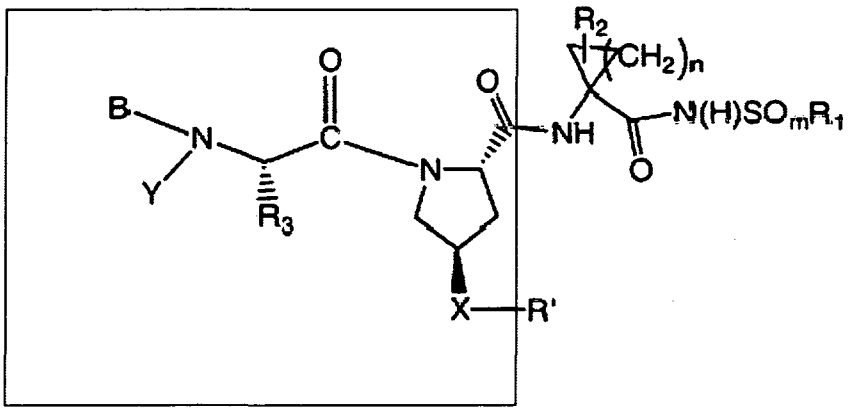


149. US '745 discloses the use of phenyl imidazoles for treatment of Hepatitis C virus by inhibition of the replication thereof (page 8).

150. It is submitted that after a reading of WO '264, it would have been obvious to replace the benzene ring and associated moieties in the benzene imidazole with a pyrrolidine alkylglycine since the activity of such moieties for a similar pharmacological condition is also taught in WO '264. It is therefore submitted that a combined reading of WO '264 and US '745 renders the compounds of the impugned invention obvious – in as much as a person of ordinary skill in the art would adopt the easiest path provided by such reading **and** with full expectation of success. The moieties are analogous, if not identical, the medical condition being treated is identical, the specific protein target (NS5A) is identical, and efficacy is already taught as present.

151. It is therefore submitted that just on this reading alone, IN '853 is liable to be rejected as obvious and lacking in inventive step.

152. Opponent now relies on WO '274 which teaches inter alia compounds for the inhibition of NS3 protease encoded in the HCV. WO '274 discloses compounds of the following structure:



where R_3 is C_{1-8} alkyl; Y is H, B is H, C_{1-6} alkyl, R_4-(C=O)-, R_4O(C=O)-, R_4-N(R_5)-C(=O)-, R_4-N(R_5)-C(=S)-, R_4SO_2-, or R_4-N(R_5)-SO_2-; R_4 is C_{1-10} alkyl optionally substituted with phenyl, carboxyl, C_{1-6} alkanoyl, 1-3 halogen.

153. It is submitted that a combined reading of WO '274 with WO '264 establishes that a combination of benzene imidazole and pyyrolidine moieties are already known for the stated sue of NS5A inhibition. It is submitted that in the impugned invention the alkylglycine moieties are attached to the pyrrolidine ring. It is submitted that the cited art clearly teaches the use of alkylglycine moiety for inhibition of Hepatitis C.

154. In view of the above, it is respectfully submitted that a person of ordinary skill in the art would find this the obvious route to take when looking for further phenyl imidazole compounds for treatment and/or inhibition of Hepatitis C. In particular such a person would automatically look for compounds/structures that are known inter alia for NS5A protein inhibition, and then combine such structures with the reasonable expectation that such combination would work.

155. Given the above, it is respectfully submitted that the subject matter of claims 1-34 are obvious, thereby leading to a finding of obviousness also in respect of the composition claims 35-40.

156. In view of the above, IN 853 is liable to be refused on the ground of obviousness.

157. Our address for service in India is:

LAW CHAMBERS OF G. NATARAJ
D – 804 AASHIANA APARTMENTS
MAYUR VIHAR PHASE 1 EXTENSION
DELHI 110 091
Fax: 011 45038460
Email: mail@gnataraj.com

PRAYERS:

158. In the fact and circumstances of the case, the Opponent prays as follows:

a. that the Controller take the present Opposition on record;

b. that the Indian Patent Application No. 853/DELNP/2009, be rejected under Section 25(1) of the Patents (Amendment) Act, 2005;

c. that the Opponent may be allowed to file further documents as evidence if necessary to support their averments;

d. that the Opponent may be granted an opportunity of being heard in the matter before any final orders are passed;

e. that the Opponent may be allowed to make further submissions in case the Applicant makes any amendments in the claims;

f. any other reliefs considering the facts and circumstances may be granted in favour of the Opponent in the interest of justice

Dated this the 8th day of June 2015.

G.NATARAJ
Attorney for Opponent

To:
The Controller of Patents,
Patent Office, New Delhi.

IN THE MATTER OF

Indian Patent Application 853/DELNP/2009

In the name of

BRISTOL-MYERS SQUIBB COMPANY

AND IN THE MATTER OF

A pre-grant representation by

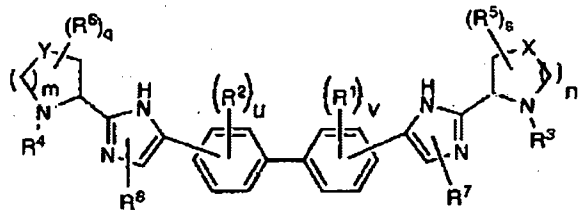
DALVIR SINGH

D1 – Copy of claims currently pending on application

CLAIMS

WHAT IS CLAIMED IS:

1. A compound of Formula (I)



(I),

or a pharmaceutically acceptable salt thereof, wherein

m and n are independently 0, 1, or 2;

q and s are independently 0, 1, 2, 3, or 4;

u and v are independently 0, 1, 2, or 3;

X is selected from O, S, S(O), SO_2, CH_2, CHR^5, and $C(R^5)_2$;

provided that when n is 0, X is selected from CH_2, CHR^5, and $C(R^5)_2$;

Y is selected from O, S, S(O), SO_2, CH_2, CHR^6, and $C(R^6)_2$;

provided that when m is 0, Y is selected from CH_2, CHR^6, and $C(R^6)_2$;

each R^1 and R^2 is independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, arylalkoxycarbonyl, carboxy, formyl, halo, haloalkyl, hydroxy, hydroxyalkyl, $-NR^aR^b$, (NR^aR^b)alkyl, and (NR^aR^b)carbonyl;

R^3 and R^4 are each independently selected from hydrogen and R^9-C(O)-, and R^9-C(S)-;

each R^5 and R^6 is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^aR^b$, wherein the alkyl can optionally form a fused three- to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

R^7 and R^8 are each independently selected from hydrogen, alkoxycarbonyl, alkyl, arylalkoxycarbonyl, carboxy, haloalkyl, (NR^aR^b)carbonyl, and trialkylsilylalkoxyalkyl; and

each R^9 is independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylcarbonylalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, aryloxyalkyl, cycloalkyl, (cycloalkyl)alkenyl, (cycloalkyl)alkyl,

cycloalkyloxyalkyl, haloalkyl, heterocyclyl, heterocyclylalkenyl, heterocyclylalkoxy, heterocyclylalkyl, heterocyclyloxyalkyl, hydroxyalkyl, -NR^cR^d, (NR^cR^d)alkenyl, (NR^cR^d)alkyl, and (NR^cR^d)carbonyl.

2. A compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein m and n are each 1.

3. A compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein

u and v are each independently 0, 1, or 2; and

each R^1 and R^2 is independently selected from alkoxy, alkoxyalkyl, alkyl, arylalkoxycarbonyl, carboxy, formyl, halo, haloalkyl, hydroxyalkyl, (NR^aR^b)alkyl, and (NR^aR^b)carbonyl.

4. A compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein

u and v are each independently 0 or 1; and

when present, R^1 and/or R^2 are halo.

5. A compound of claim 4, or a pharmaceutically acceptable salt thereof, wherein the halo is fluoro.

6. A compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein at least one of X and Y is S.

7. A compound of claim 6, or a pharmaceutically acceptable salt thereof, wherein X and Y are each S.

8. A compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein X is selected from CHR^5, and $C(R^5)_2$; and Y is selected from CH_2, CHR^6, and $C(R^6)_2$.

9. A compound of claim 1, or a pharmaceutically acceptable salt thereof,

wherein R^7 and R^8 are independently selected from hydrogen, alkoxycarbonyl, alkyl, arylalkoxycarbonyl, carboxy, haloalkyl, and (NR^aR^b)carbonyl.

10. A compound of claim 9, or a pharmaceutically acceptable salt thereof, wherein R^7 and R^8 are each hydrogen.

11. A compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein

q and s are independently 0, 1, or 2; and

each R^5 and R^6 is independently selected from alkyl, aryl, halo, and hydroxy, wherein the alkyl can optionally form a fused three- to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups.

12. A compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein

q and s are independently 0 or 1; and

when present, R^5 and/or R^6 are halo.

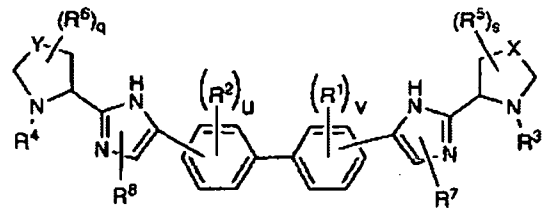
13. A compound of claim 12, or a pharmaceutically acceptable salt thereof, wherein the halo is fluoro.

14. A compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein at least one of R^3 and R^4 is hydrogen.

15. A compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^3 and R^4 are each R^9-C(O)-.

16. A compound of claim 15, or a pharmaceutically acceptable salt thereof, wherein each R^9 is independently selected from alkoxy, alkoxyalkyl, alkyl, alkylcarbonylalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, aryloxyalkyl, cycloalkyl, (cycloalkyl)alkyl, cycloalkyloxyalkyl, heterocyclyl, heterocyclylalkyl, hydroxyalkyl, $-NR^cR^d$, (NR^cR^d)alkenyl, (NR^cR^d)alkyl, and (NR^cR^d)carbonyl.

17. A compound of Formula (II)



(II),

or a pharmaceutically acceptable salt thereof, wherein

q and s are independently 0, 1, or 2;

u and v are independently 0, 1, or 2;

X is selected from S, CH_2, CHR^5, and $C(R^5)_2$;

Y is selected from S, CH_2, CHR^6, and $C(R^6)_2$;

each R^1 and R^2 is independently selected from alkoxy, alkoxyalkyl, alkyl, arylalkoxycarbonyl, carboxy, formyl, halo, haloalkyl, hydroxyalkyl, (NR^aR^b)alkyl, and (NR^aR^b)carbonyl;

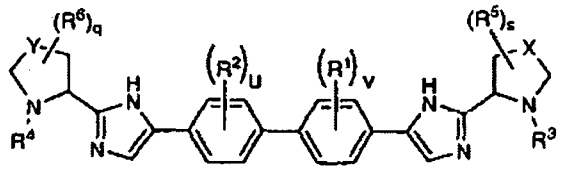
R^3 and R^4 are each independently selected from hydrogen and R^9-C(O)-;

each R^5 and R^6 is independently selected from alkyl, aryl, halo, and hydroxy, wherein the alkyl can optionally form a fused three- to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

R^7 and R^8 are each independently selected from hydrogen, alkoxycarbonyl, alkyl, arylalkoxycarbonyl, carboxy, haloalkyl, and (NR^aR^b)carbonyl; and

each R^9 is independently selected from alkoxy, alkoxyalkyl, alkyl, alkylcarbonylalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, aryloxyalkyl, cycloalkyl, (cycloalkyl)alkyl, cycloalkyloxyalkyl, heterocyclyl, heterocyclylalkyl, hydroxyalkyl, $-NR^cR^d$, (NR^cR^d)alkenyl, (NR^cR^d)alkyl, and (NR^cR^d)carbonyl.

18. A compound of Formula (III)



(III),

or a pharmaceutically acceptable salt thereof, wherein

q and s are independently 0, 1, or 2;

u and v are independently 0 or 1;

X is selected from CH_2, CHR^5, and $C(R^5)_2$;

Y is selected from CH_2, CHR^6, and $C(R^6)_2$;

when present, R^1 and/or R^2 are halo, wherein the halo is fluoro;

R^3 and R^4 are each R^9-C(O)-;

when present, R^5 and/or R^6 are halo, wherein the halo is fluoro; and

each R^9 is independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylcarbonylalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, aryloxyalkyl, cycloalkyl, (cycloalkyl)alkenyl, (cycloalkyl)alkyl, cycloalkyloxyalkyl, haloalkyl, heterocyclyl, heterocyclylalkenyl, heterocyclylalkoxy, heterocyclylalkyl, heterocyclyloxyalkyl, hydroxyalkyl, -NR^cR^d, (NR^cR^d)alkenyl, (NR^cR^d)alkyl, and (NR^cR^d)carbonyl.

19. A compound selected from

di-tert-butyl (2S,2'S)-2,2'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl))di(1-pyrrolidinecarboxylate);

tert-butyl (2S)-2-(4-(3'-(2-((2S)-1-(tert-butoxycarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-3-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate;

5,5'-(4,4'-biphenyldiyl)bis(2-((2S)-2-pyrrolidinyl)-1H-imidazole);

2-((2S)-2-pyrrolidinyl)-4-(3'-(2-((2S)-2-pyrrolidinyl)-1H-imidazol-5-yl)-3-biphenylyl)-1H-imidazole;

(1R,1'R)-2,2'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-dimethyl-2-oxo-1-phenylethanamine);

(1R,1'R)-2,2'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(2-oxo-1-phenylethanol);

(2S,2'S)-1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(1-oxo-2-phenyl-2-propanol);

dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate;

(1S,1'S)-2,2'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-dimethyl-2-oxo-1-phenylethanamine);

5,5'-(4,4'-biphenyldiyl)bis(2-((2S)-1-benzoyl-2-pyrrolidinyl)-1H-imidazole);
5,5'-(4,4'-biphenyldiyl)bis(2-((2S)-1-(phenylacetyl)-2-pyrrolidinyl)-1H-imidazole);
5,5'-(4,4'-biphenyldiyl)bis(2-((2S)-1-((2R)-2-methoxy-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazole);
(2R,2'R)-1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(1-oxo-3-phenyl-2-propanol);
5,5'-(4,4'-biphenyldiyl)bis(2-((2S)-1-propionyl-2-pyrrolidinyl)-1H-imidazole);
5,5'-(4,4'-biphenyldiyl)bis(2-((2S)-1-(cyclopropylcarbonyl)-2-pyrrolidinyl)-1H-imidazole);
5,5'-(4,4'-biphenyldiyl)bis(2-((2S)-1-(cyclopropylacetyl)-2-pyrrolidinyl)-1H-imidazole);
5,5'-(4,4'-biphenyldiyl)bis(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazole);
2,2'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-dimethyl-2-oxoethanamine);
(2R,2'R)-1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(1-oxo-2-propanol);
(2R,2'R)-1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(3-methyl-1-oxo-2-butanol);
5,5'-(4,4'-biphenyldiyl)bis(2-((2S)-1-((2R)-2-phenyl-2-(1-pyrrolidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazole);
4,4'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))dimorpholine;
5,5'-(4,4'-biphenyldiyl)bis(2-((2S)-1-(((3S)-3-fluoro-1-pyrrolidinyl)(phenyl)acetyl)-2-pyrrolidinyl)-1H-imidazole);
5,5'-(4,4'-biphenyldiyl)bis(2-((2S)-1-(((3S)-3-fluoro-1-pyrrolidinyl)(phenyl)acetyl)-2-pyrrolidinyl)-1H-imidazole);
(1R,1'R)-2,2'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-diethyl-2-oxo-1-phenylethanamine);
(1R,1'R)-2,2'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N-ethyl-N-methyl-2-oxo-1-phenylethanamine);
N,N'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))diformamide;

1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediylcarbonyl))dicyclopropanol;

1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))dipiperidine;

1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))bis(4-methyl-4-piperidinol);

dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-1-(2-chlorophenyl)-2-oxo-2,1-ethanediyl)))biscarbamate;

N',N'''-(4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))bis(1,1-dimethylurea);

N',N'''-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))bis(1-methylurea);

N',N'''-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))bis(1-ethylurea);

N',N'''-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))bis(1-cyclopentylurea);

2,2'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N-benzyl-N-methyl-2-oxoethanamine);

(2S,2'S)-1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N-benzyl-N-methyl-1-oxo-2-propanamine);

1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N-benzyl-N,3-dimethyl-1-oxo-2-butanamine);

1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl(2-oxo-1-phenyl-2,1-ethanediyl)))di(4-piperidinol);

1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl((2S,4S)-4-fluoro-2,1-pyrrolidinediyl)((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))dipiperidine;

(1R,1'R)-2,2'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl((2S,4S)-4-fluoro-2,1-pyrrolidinediyl)))bis(N,N-diethyl-2-oxo-1-phenylethanamine);

(1R,1'R)-2,2'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl((2S,4S)-4-fluoro-2,1-pyrrolidinediyl)))bis(N,N-dimethyl-2-oxo-1-phenylethanamine);

1,1'-(4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl((2S)-4,4-difluoro-2,1-pyrrolidinediyl)((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))dipiperidine;

dimethyl (4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl((2S)-4,4-difluoro-2,1-pyrrolidinediyl)((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate;

1-((1R)-2-((2S)-2-(4-(4'-(2-((2S)-4,4-difluoro-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)piperidine;

dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl((2S,4R)-4-hydroxy-2,1-pyrrolidinediyl)((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate;

(3R,5S,3'R,5'S)-5,5'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl))bis(1-((2R)-2-hydroxy-2-phenylacetyl)-3-pyrrolidinol);

N,N'''-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl((2S,4R)-4-hydroxy-2,1-pyrrolidinediyl)((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))bis(3-methylurea);

N',N'''-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl((2S,4R)-4-hydroxy-2,1-pyrrolidinediyl)((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))bis(1-ethylurea);

N',N'''-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl((2S,4R)-4-hydroxy-2,1-pyrrolidinediyl)((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))bis(1-cyclopentylurea);

(3S,5S,3'S,5'S)-5,5'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl))bis(1-((2R)-2-(dimethylamino)-2-phenylacetyl)-3-pyrrolidinol);

dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl((2S,4S)-4-hydroxy-2,1-pyrrolidinediyl)((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate;

(3S,5S,3'S,5'S)-5,5'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl))bis(1-((2R)-2-hydroxy-2-phenylacetyl)-3-pyrrolidinol);

N,N'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))diacetamide;

di-tert-butyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate;

(2R,2'R)-N,N'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))ditetrahydro-2-furancarboxamide;

N,N'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))bis(1-methyl-1H-imidazole-5-carboxamide) (2S,2'S)-N,N'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))bis(1-methyl-2-pyrrolidinecarboxamide);

N,N'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))bis(2-(3-pyridinyl)acetamide);

N,N'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))bis(2-(dimethylamino)acetamide);

N,N'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))di(4-morpholinecarboxamide);

N,N'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))bis(4-methyl-1-piperazinecarboxamide);

N,N''-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))bis(3-(3-pyridinyl)urea);

methyl ((1R)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

(2R,2'R)-1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(3-methyl-1-oxo-2-butanamine);

N-((1R)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-acetamido-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)acetamide;

methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate;

benzyl tert-butyl (2S,2'S)-2,2'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl))di(1-pyrrolidinecarboxylate);

tert-butyl (2S)-2-(5-(4'-(2-((2S)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate;

tert-butyl (2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate;

methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate;

(1R)-N,N-dimethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine;

1-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)piperidine;

methyl ((1R)-1-(2-chlorophenyl)-2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate;

(1R)-1-(2-chlorophenyl)-N,N-dimethyl-2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine;

(1R)-1-(2-fluorophenyl)-N,N-dimethyl-2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine;

(1R)-N,N-dimethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine;

1-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)piperidine;

methyl ((1R)-1-(2-chlorophenyl)-2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate;

(1R)-1-(2-chlorophenyl)-N,N-dimethyl-2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine;

(1R)-1-(2-fluorophenyl)-N,N-dimethyl-2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((4-methyl-1-piperazinyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-glycyl-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(tert-butoxycarbonyl)glycyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-acetyl-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-propionyl-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(cyclopropylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(cyclopropylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-hydroxypropanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N,N-dimethylglycyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(4-morpholinylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl (2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-acetylglycyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-hydroxy-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((1-methyl-4-piperidinyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(tetrahydro-2H-pyran-4-ylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate;

methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(2-pyridinylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate;

methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(3-pyridinylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate;

methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(4-pyridinylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((1-methyl-1H-imidazol-5-yl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(dimethylcarbamoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(1-methyl-D-prolyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(1-methyl-L-prolyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-acetyl-D-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-acetyl-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(methoxyacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-hydroxybutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((4-methyl-1-piperazinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(1-pyrrolidinylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate;

methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((1-hydroxycyclopropyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(1H-imidazol-5-ylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((1-methyl-1H-imidazol-4-yl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(1H-imidazol-2-ylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2 (5-(4'-(2-((2S)-1-((4-hydroxy-1-piperidinyl)(phenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl) 2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(1H-tetrazol-5-ylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate;

methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(2-pyridinylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate;

methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(3-pyridinylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-isonicotinoyl-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((4R)-4-fluoro-1-methyl-L-prolyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(1,3-oxazol-2-ylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(1,3-oxazol-5-ylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((dimethylamino)(oxo)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(tetrahydro-3-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N,N-dimethyl-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl (2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(4-morpholinylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((4S)-4-fluoro-L-prolyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-L-prolyl-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(4,4-difluoro-L-prolyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((4R)-4-fluoro-L-prolyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((1S,3S,5S)-2-azabicyclo[3.1.0]hex-3-ylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-L-alanyl-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-(2-fluorophenyl)-2-hydroxypropanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-(5-oxo-D-prolyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(4-hydroxy-4-methyl-1-piperidinyl)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

tert-butyl (4R)-4-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-1,3-thiazolidine-3-carboxylate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((1-((tert-butoxycarbonyl)amino)cyclopentyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-benzoylglycyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(4-(4-methyl-1-piperazinyl)benzoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((5-phenyl-2-thienyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate;

methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((4-phenyl-1,2,3-thiadiazol-5-yl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate;

methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-phenyl-1,3-thiazol-4-yl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate;

tert-butyl 4-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-4-methyl-1-piperidinecarboxylate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(4-(dimethylamino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((3-hydroxyphenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N,N-dimethyl-beta-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(4-(hydroxymethyl)benzoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(((3R)-1-benzyl-3-pyrrolidinyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

tert-butyl (2S)-2-(2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)-1-pyrrolidinecarboxylate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((5-methyl-1H-pyrazol-3-yl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(((3S)-7-hydroxy-1,2,3,4-tetrahydro-3-isoquinolinyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

tert-butyl (2R)-2-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-1-piperidinecarboxylate;

methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((5-phenyl-4-isoxazolyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(((1R,3S)-3-((tert-butoxycarbonyl)amino)cyclopentyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(3-(1-piperidinyl)propanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(2-benzoylbenzoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-methoxyphenoxy)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

tert-butyl 3-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-1-azetidinecarboxylate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(((3S)-1-benzyl-3-pyrrolidinyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(3-(1-pyrrolidinyl)benzoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(2-((tert-butoxycarbonyl)amino)benzoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

tert-butyl (3R)-3-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-1-piperidinecarboxylate;

methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((1-(trifluoromethyl)cyclopropyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(4-(dimethylamino)benzoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(3-benzoylbenzoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((cis-4-((tert-butoxycarbonyl)amino)cyclohexyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

tert-butyl 4-(((2S)-2-(5-(4'-(2-((2S) 1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-1-piperidinecarboxylate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((cis-4-((tert-butoxycarbonyl)amino)cyclohexyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(diphenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-(4-oxopentanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(2-fluorobenzoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(2-biphenylylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(2-benzylbenzoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2E)-3-(4-(dimethylamino)phenyl)-2-propenoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(1,3-thiazol-4-ylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((((1R,2S,5R)-2-isopropyl-5-methylcyclohexyl)oxy)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((dimethylamino)(2-thienyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((dimethylamino)(3-thienyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((dimethylamino)(2-methyl-1,3-thiazol-4-yl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(1,2-benzisoxazol-3-yl(dimethylamino)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(1-benzothiophen-3-yl(dimethylamino)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((dimethylamino)(1-naphthyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((dimethylamino)(3-quinolinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((dimethylamino)(2-methyl-1,3-benzothiazol-5-yl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((dimethylamino)(3-(trifluoromethyl)phenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((dimethylamino)(2-(trifluoromethyl)phenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-chlorophenyl)(dimethylamino)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((3-chlorophenyl)(dimethylamino)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((4-chlorophenyl)(dimethylamino)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((dimethylamino)(2-fluorophenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((dimethylamino)(3-fluorophenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((dimethylamino)(2-pyridinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(4-(4'-(2-((2S)-1-((dimethylamino)(3-pyridinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((4-methoxyphenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((3-methoxyphenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-methoxyphenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-chlorophenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((3-chlorophenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((4-chlorophenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-methylphenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((4-methylphenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((3-methylphenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-methyl-1,3-thiazol-4-yl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(3-thienylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((3-methyl-5-isoxazolyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(cyclohexylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenylpropanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate;

methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((1-phenylcyclopropyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((1-(4-chlorophenyl)cyclopropyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(2-(4-chlorophenyl)-2-methylpropanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-methoxy-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate;

(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl acetate;

(1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl acetate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-(4-morpholinylmethyl)phenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-(1-piperidinylmethyl)phenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate;

methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-(1-pyrrolidinylmethyl)phenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-((dimethylamino)methyl)phenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

(1R)-N,N-dimethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(3-pyridinylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine;

(1R)-N,N-dimethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine;

(1R)-N,N-dimethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine;

(1R)-N,N-dimethyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((1-methyl-1H-imidazol-4-yl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethanamine;

(1R)-N,N-dimethyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(4-morpholinyl)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethanamine;

(1R)-N,N-dimethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-pyrrolidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine;

methyl (2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

(1R)-N,N-dimethyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(4-morpholinylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethanamine;

(1R)-N,N-dimethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(1-pyrrolidinylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine;

(2S)-1-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-(2-fluorophenyl)-1-oxo-2-propanol;

(5R)-5-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-pyrrolidinone;

1-((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)-4-methyl-4-piperidinol;

tert-butyl (4R)-4-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-1,3-thiazolidine-3-carboxylate;

tert-butyl (1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)cyclopentyl)carbamate;

N-(2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)benzamide;

(1R)-N,N-dimethyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(4-(4-methyl-1-piperazinyl)benzoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethanamine;

(1R)-N,N-dimethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((5-phenyl-2-thienyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine;

(1R)-N,N-dimethyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(4-(4-morpholinyl)benzoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethanamine;

(1R)-N,N-dimethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((4-phenyl-1,2,3-thiadiazol-5-yl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine;

(1R)-N,N-dimethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-phenyl-1,3-thiazol-4-yl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine;

tert-butyl 4-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-4-methyl-1-piperidinecarboxylate;

3-(2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)phenol;

3-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-3-oxo-1-propanamine;

(4-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)phenyl)methanol;

(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(1H-indol-3-ylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine;

(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(((3R)-1-benzyl-3-pyrrolidinyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine;

tert-butyl (2S)-2-(2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)-1-pyrrolidinecarboxylate;

(1R)-N,N-dimethyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((5-methyl-1H-pyrazol-3-yl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethanamine;

tert-butyl (2R)-2-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-1-piperidinecarboxylate;

tert-butyl ((1S,3R)-3-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)cyclopentyl)carbamate;

(1R)-N,N-dimethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(3-(1-piperidinyl)propanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine;

(2-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)phenyl)(phenyl)methanone;

(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-methoxyphenoxy)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine;

tert-butyl 3-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-1-azetidinecarboxylate;

(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(((3S)-1-benzyl-3-pyrrolidinyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine;

(1R)-N,N-dimethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(3-(1-pyrrolidinyl)benzoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine;

tert-butyl (2-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)phenyl)carbamate;

tert-butyl (3R)-3-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-1-piperidinecarboxylate;

(1R)-N,N-dimethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((1-(trifluoromethyl)cyclopropyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine;

4-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-N,N-dimethylaniline;

(3-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)phenyl)(phenyl)methanone;

tert-butyl (cis-4-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)cyclohexyl)carbamate;

'tert-butyl 4-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-1-piperidinecarboxylate;

tert-butyl (cis-4-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)cyclohexyl)carbamate;

(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(diphenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine;

5-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-5-oxo-2-pentanone;

(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(2-fluorobenzoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine;

(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(2-biphenylylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine;

(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(2-benzylbenzoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine;

4-((1E)-3-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-3-oxo-1-propen-1-yl)-N,N-dimethylaniline;

(1R)-N,N-dimethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(1,3-thiazol-4-ylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine;

(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((((1R,2S,5R)-2-isopropyl-5-methylcyclohexyl)oxy)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine;

1-(6-chloro-3-pyridinyl)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxoethanamine;

2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-(3-pyridinyl)ethanamine;

2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-(2-pyridinyl)ethanamine;

(1R)-N,N-dimethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(2-thienylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine;

(1R)-N,N-dimethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(3-thienylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine;

(1R)-N,N-dimethyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(1-naphthylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl) 2-oxo-1-phenylethanamine;

(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(1H-imidazol-5-ylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine;

(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-fluorophenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine;

(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((3-fluorophenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine;

(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((4-fluorophenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine;

(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(1-benzothiophen-3-ylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine;

(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(1,2-benzisoxazol-3-ylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine;

(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(1H-indol-3-ylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine;

2-((2S)-1-((2R)-2-phenyl-2-(1-pyrrolidinyl)acetyl)-2-pyrrolidinyl)-5-(4'-(2-((2S)-1-((2S)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazole;

4-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-pyrrolidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)morpholine;

1-(2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-pyrrolidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)-4-piperidinol;

1-methyl-4-(2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-pyrrolidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)piperazine;

(1R)-N,N-diethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-pyrrolidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine;

methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-pyrrolidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate;

methyl ((1S)-1-methyl-2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-pyrrolidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate;

methyl (2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-pyrrolidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate;

(2S)-N,N-dimethyl-1-oxo-1-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-pyrrolidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-propanamine;

1-(2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)-4-phenylpiperidine;

1-(2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)-4-phenylpiperidine;

1-methyl-4-(2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)piperazine;

1-methyl-4-(2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)piperazine;

benzyl 4-(2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)-1-piperazinecarboxylate;

benzyl 4-(2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)-1-piperazinecarboxylate;

1-(2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)piperazine;

4-(2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)-2-piperazinone;

1-methyl-3-((1R)-2-oxo-1-phenyl-2-((2S)-2-(4-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)urea;

1-ethyl-3-((1R)-2-oxo-1-phenyl-2-((2S)-2-(4-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)urea;

1-cyclopentyl-3-((1R)-2-oxo-1-phenyl-2-((2S)-2-(4-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)urea;

1,1-dimethyl-3-((1R)-2-oxo-1-phenyl-2-((2S)-2-(4-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)urea;

1-methyl-4-(2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)piperazine;

4-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)morpholine;

(1R)-N,N-diethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine;

(1R)-N-ethyl-N-methyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine;

(1S)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl acetate;

4-methyl-1-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)-4-piperidinol;

1-((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(2-fluorobenzoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)piperidine;

N,N-dimethyl-4-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)aniline;

5-oxo-5-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-pentanone;

1-((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(diphenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)piperidine;

1-(3-oxo-3-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)propyl)piperidine;

1-((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-methoxyphenoxy)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)piperidine;

tert-butyl 4-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-1-piperidinecarboxylate;

4-(4-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)phenyl)morpholine;

1-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(1,3-thiazol-4-ylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)piperidine;

tert-butyl 3-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-1-azetidinecarboxylate;

tert-butyl (cis-4-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)cyclohexyl)carbamate;

tert-butyl 4-methyl-4-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-1-piperidinecarboxylate;

1-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((1-(trifluoromethyl)cyclopropyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)piperidine;

1-((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((5-methyl-1H-pyrazol-3-yl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)piperidine;

1-((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(((3R)-1-benzyl-3-pyrrolidinyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)piperidine;

1-((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(((3S)-1-benzyl-3-pyrrolidinyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)piperidine;

1-((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-methoxy-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)piperidine;

1-((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-methoxy-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)piperidine;

(1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl acetate;

1-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((1-phenylcyclopropyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)piperidine;

N,N-dimethyl-1-(2-(2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)phenyl)methanamine;

1-((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((3-methyl-5-isoxazolyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)piperidine;

1-((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-methyl-1,3-thiazol-4-yl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)piperidine;

4-(2-(2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)benzyl)morpholine;

1-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-(1-pyrrolidinylmethyl)phenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)piperidine;

1-((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-fluorophenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)piperidine;

1-((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-acetyl-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)piperidine;

1-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(2-thienylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)piperidine;

(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-(2-fluorophenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine;

(1R)-1-(2-fluorophenyl)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-methoxy-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxoethanamine;

(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-(2-fluorophenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl acetate;

(1R)-1-(2-fluorophenyl)-N,N-dimethyl-2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-((1-phenylcyclopropyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine;

(1R)-1-(2-chlorophenyl)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxoethanamine;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(2-chlorophenyl)-2-(dimethylamino)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

(1R)-1-(2-chlorophenyl)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-methoxy-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxoethanamine;

(1R)-1-(2-chlorophenyl)-N,N-dimethyl-2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine;

methyl ((1R)-1-(2-chlorophenyl)-2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate;

methyl ((1R)-1-(2-chlorophenyl)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(2-chlorophenyl)-2-((methoxycarbonyl)amino)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-1-(2-chlorophenyl)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(4-hydroxy-4-methyl-1-piperidinyl)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate;

methyl ((1R)-1-(2-chlorophenyl)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-methoxy-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate;

methyl ((1R)-1-(2-chlorophenyl)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(2-chlorophenyl)-2-(dimethylamino)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(ethylcarbamoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

dibenzyl (2S,2'S)-2,2'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl))di(1-pyrrolidinecarboxylate);

benzyl (2S)-2-(5-(4'-(2-((2S)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate;

(2R)-N-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)tetrahydro-2-furancarboxamide;

(1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine;

(2R)-N-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)tetrahydro-2-furancarboxamide;

N-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-tetrahydro-2-*furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2*-yl)-1-pyrrolidinyl)ethyl)-4-morpholinecarboxamide;

(2S)-N-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)tetrahydro-2-furancarboxamide;

1-methyl-N-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)-L-prolinamide;

1-methyl-N-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)-4-piperidinecarboxamide;

N-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)tetrahydro-2H-pyran-4-carboxamide;

(4R)-4-fluoro-1-methyl-N-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol 5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)-L-prolinamide;

4-methyl-N-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)-1-piperazinecarboxamide;

N-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)acetamide;

(2R)-N-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)tetrahydro-2-furancarboxamide;

N-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)-4-morpholinecarboxamide;

1-methyl-N-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)-1H-imidazole-5-carboxamide;

1-methyl-N-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)-L-prolinamide;

N-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)-2-(3-pyridinyl)acetamide;

N^2,N^2-dimethyl-N-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)glycinamide;

1-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)-3-(3-pyridinyl)urea;

(1R,1'R)-2,2'-((2,2'-dimethyl-4,4'-biphenyldiyl)bis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-dimethyl-2-oxo-1-phenylethanamine);

dimethyl ((2,2'-dimethyl-4,4'-biphenyldiyl)bis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate;

(1R,1'R)-2,2'-((2-methyl-4,4'-biphenyldiyl)bis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-dimethyl-2-oxo-1-phenylethanamine);

dimethyl ((2-methyl-4,4'-biphenyldiyl)bis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate;

(1R,1'R)-2,2'-((2-methyl-4,4'-biphenyldiyl)bis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(2-oxo-1-phenylethanol);

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2'-methyl-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(2'-methyl-4'-(2-((2S)-1-(3-pyridinylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(2'-methyl-4'-(2-((2S)-1-((2S)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2,2'-dimethyl-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

(1R,1'R)-2,2'-((2-(trifluoromethyl)-4,4'-biphenyldiyl)bis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-dimethyl-2-oxo-1-phenylethanamine);

(1R,1'R)-2,2'-((2-(trifluoromethyl)-4,4'-biphenyldiyl)bis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-dimethyl-2-oxo-1-phenylethanamine);

5,5'-(2-(trifluoromethyl)-4,4'-biphenyldiyl)bis(2-((2S)-1-((2R)-2-phenyl-2-(1-pyrrolidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazole);

(1R,1'R)-2,2'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(4R)-1,3-thiazolidine-4,3-diyl))bis(N,N-dimethyl-2-oxo-1-phenylethanamine);

dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(4R)-1,3-thiazolidine-4,3-diyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate;
(4R,4'R)-4,4'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl))bis(3-((2R)-tetrahydro-2-furanylcarbonyl)-1,3-thiazolidine);
(1R,1'R)-2,2'-(4,4'-biphenyldiylbis((1-methyl-1H-imidazole-4,2-diyl)(2S)-2,1-pyrrolidinediyl))bis(N,N-dimethyl-2-oxo-1-phenylethanamine);
(1S,1'S)-2,2'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(1-cyclohexyl-2-oxoethanol);
(2S,2'S)-1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(4-methyl-1-oxo-2-pentanol);
(2S,2'S)-1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(3-methyl-1-oxo-2-butanol);
3-buten-1-yl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-(((3-buten-1-yloxy)carbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;
methyl ((1S)-2-methyl-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-methylglycyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate;
(2S,2'S)-1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N-methyl-1-oxo-2-propanamine);
(4S,4'S)-4,4'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediylcarbonyl))bis(1,3-oxazinan-2-one);
methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate;
methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-ethylglycyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;
methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-benzylglycyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-isobutylglycyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-sec-butylglycyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-isopropylglycyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N,N-diisopropylglycyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-(3-oxetanyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-2-(3-oxetanyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-2-methyl-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S,2R)-2-methoxy-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-O-methyl-L-threonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-2-methyl-1-pyrrolidinyl)carbonyl)propyl)carbamate;

methyl ((1R)-2-((2R)-2-(5-(4'-(2-((2S,5R)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-5-phenyl-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

rel-(1R)-2-((2S)-2-(4-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)octahydro-1H-indol-2-yl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine;

methyl rel-((1R)-2-((2S)-2-(4-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)octahydro-1H-indol-2-yl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

(1R)-N-ethyl-2-((2S)-2-(4-(4'-(2-((2S)-1-((2R)-2-(ethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethanamine;

(1R)-N-methyl-2-((2S)-2-(4-(4'-(2-((2S)-1-((2R)-2-(methylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethanamine;

N-((1R)-2-oxo-1-phenyl-2-((2S)-2-(4-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(propylamino)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)-1-propanamine;

N-((1R)-2-((2S)-2-(4-(4'-(2-((2S)-1-((2R)-2-(butylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)-1-butanamine;

ethyl ((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-2-((ethoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

propyl ((1S)-1-methyl-2-oxo-2-((2S)-2-(4-(4'-(2-((2S)-1-(N-(propoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate;

butyl ((1S)-2-((2S)-2-(4-(4'-(2-((2S)-1-(N-(butoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

(2S)-2-hydroxy-N-((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-((2S)-2-hydroxy-3-methylbutanoyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)-3-methylbutanamide;

ethyl ((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-2-((ethoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

isopropyl ((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-2-((isopropoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

(2S)-1-((2S)-2-(4-(4'-(2-((2S)-1-((2S)-2-hydroxypropanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-oxo-2-propanol;

tert-butyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((tert-butoxycarbonyl)(methyl)amino)-4-methylpentanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-3-methylbutyl)methylcarbamate;

tert-butyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((tert-butoxycarbonyl)(methyl)amino)-3-methylpentanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylbutyl)methylcarbamate;

tert-butyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((tert-butoxycarbonyl)(methyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)methylcarbamate;

tert-butyl ((1S,2R)-1-(((2S)-2-(4-(4'-(2-((2S)-1-(N-(tert-butoxycarbonyl)-N-methyl-L-alloisoleucyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylbutyl)methylcarbamate;

(2S)-N,4-dimethyl-1-((2S)-2-(4-(4'-(2-((2S)-1-((2S)-4-methyl-2-(methylamino)pentanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-oxo-2-pentanamine;

(2S)-N,3-dimethyl-1-((2S)-2-(4-(4'-(2-((2S)-1-((2S)-3-methyl-2-(methylamino)pentanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-oxo-2-pentanamine;

(2S)-N,3-dimethyl-1-((2S)-2-(4-(4'-(2-((2S)-1-((2S)-3-methyl-2-(methylamino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-oxo-2-butanamine;

(2S,3R)-N,3-dimethyl-1-((2S)-2-(4-(4'-(2-((2S)-1-((2S,3R)-3-methyl-2-(methylamino)pentanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-oxo-2-pentanamine;

methyl ((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-2,3-dimethylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-1,2-dimethylpropyl)carbamate;

methyl ((1S)-2-((2S)-2-(4-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-

1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate;

methyl (2-((2S)-2-(4-(4'-(2-((2S)-1-(((methoxycarbonyl)amino)(tetrahydro-2H-pyran-4-yl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate;

methyl ((1S)-2-((2S)-2-(4-(4'-(2-((2S)-1-((2R)-2-(ethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-1,2-dimethylpropyl)carbamate;

methyl ((1S)-2-methyl-1-(((2S)-2-(4-(4'-(2-((2S)-1-(N-(tetrahydro-2H-pyran-4-yl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate;

methyl ((1S)-2-methyl-1-(((2S)-2-(4-(4'-(2-((2S)-1-(N-(tetrahydro-2H-pyran-4-yl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate;

methyl ((1S)-2-methyl-1-(((2S)-2-(4-(4'-(2-((2S)-1-(N-(tetrahydro-2H-pyran-4-yl)glycyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate;

methyl ((1S)-2-methyl-1-(((2S)-2-(4-(4'-(2-((2S)-1-(N-(tetrahydro-2H-pyran-4-yl)-D-valyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate;

methyl ((1S)-2-methyl-1-(((2S)-2-(4-(4'-(2-((2S)-1-(N-(tetrahydro-2H-pyran-4-yl)-D-alanyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate;

(3S)-tetrahydro-3-furanyl ((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

tetrahydro-2H-pyran-4-yl ((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

(3R)-tetrahydro-3-furanyl ((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

N-((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-2-acetamido-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)acetamide;

N-((1S)-2-methyl-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-3-methyl-2-(propionylamino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)propanamide;

2-methoxy-N-((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-2-((methoxyacetyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)acetamide;

1-methyl-3-((1S)-2-methyl-1-(((2S)-2-(4-(4'-(2-((2S)-1-(N-(methylcarbamoyl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)urea;

1-ethyl-3-((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-2-((ethylcarbamoyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)urea;

N-((1S)-2-methyl-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-3-methyl-2-((methylsulfonyl)amino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)methanesulfonamide;

N-((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-2-((ethylsulfonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)ethanesulfonamide;

N-((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-2-((cyclopropylsulfonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)cyclopropanesulfonamide;

N-((1S)-1-methyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methylsulfonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)methanesulfonamide;

methyl ((1S)-2-methyl-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-2-pyrimidinyl-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate;

methyl ((1S)-1-methyl-2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-2-pyrimidinyl-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate;

methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-2-pyrimidinyl-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate;

N-((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)-2-pyrimidinamine;

methyl ((1S)-2-methyl-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(1-methyl-4,5-dihydro-1H-imidazol-2-yl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(4,5-dihydro-1H-imidazol-2-yl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(4,5-dihydro-1H-imidazol-2-yl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

N-((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)-4,5-dihydro-1H-imidazol-2-amine;

methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-2-pyrimidinyl-D-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate;

methyl ((1S)-2-methyl-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-2-pyrimidinyl-D-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate;

methyl ((1S)-1-methyl-2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-2-pyrimidinyl-D-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate;

N-((1R)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)-2-pyrimidinamine;

methyl ((1S)-2-methyl-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(1-methyl-4,5-dihydro-1H-imidazol-2-yl)-D-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(4,5-dihydro-1H-imidazol-2-yl)-D-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-cyclopropyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(4,5-dihydro-1H-imidazol-2-yl)-D-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate;

N-((1R)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)-4,5-dihydro-1H-imidazol-2-amine;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(5-amino-1-methyl-1H-1,2,4-triazol-3-yl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(4,5-dihydro-1,3-thiazol-2-yl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-2-methyl-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-4-pyrimidinyl-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(5-amino-1,2,4-oxadiazol-3-yl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(cyano(dimethyl)carbamimidoyl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-2-methyl-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-3-pyridinyl-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate;

methyl ((1S)-1-methyl-2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-3-pyridinyl-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate;

methyl ((1S,2R)-2-methoxy-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-3-pyridinyl-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate;

N-((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)-3-pyridinamine;

methyl ((1S)-2-methyl-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-5-pyrimidinyl-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(1H-1,2,3-triazol-4-ylmethyl)ethyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(1H-1,2,3-triazol-4-ylmethyl)ethyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-(1H-1,2,3-triazol-4-yl)propanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S,3R)-3-methoxy-2-((methoxycarbonyl)amino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(1H-1,2,3-triazol-4-ylmethyl)ethyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(1H-pyrazol-1-ylmethyl)ethyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(1H-pyrazol-1-ylmethyl)ethyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-(1H-pyrazol-1-yl)propanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-O-methyl-L-threonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(1H-pyrazol-1-ylmethyl)ethyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-((1-methyl-1H-imidazol-4-yl)methyl)-2-oxoethyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-((1-methyl-1H-imidazol-4-yl)methyl)-2-oxoethyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-(1-methyl-1H-imidazol-4-yl)propanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S,3R)-3-methoxy-2-((methoxycarbonyl)amino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-((1-methyl-1H-imidazol-4-yl)methyl)-2-oxoethyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-((1-methyl-1H-imidazol-5-yl)methyl)-2-oxoethyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-((1-methyl-1H-imidazol-5-yl)methyl)-2-oxoethyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-(1-methyl-1H-imidazol-5-yl)propanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S,3R)-3-methoxy-2-((methoxycarbonyl)amino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-

biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-((1-methyl-1H-imidazol-5-yl)methyl)-2-oxoethyl)carbamate;

methyl ((1S)-1-methyl-2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-(((2S)-4-oxo-2-azetidinyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate;

methyl (2S)-2-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-1-azetidinecarboxylate;

methyl (2S)-2-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-1-azetidinecarboxylate;

methyl ((1S)-3-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-3-oxopropyl)carbamate;

methyl ((1R)-3-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-isopropyl-3-oxopropyl)carbamate;

methyl ((1S)-1-benzyl-3-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-3-oxopropyl)carbamate;

methyl ((1R)-3-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-3-oxo-1-(2-thienylmethyl)propyl)carbamate;

methyl ((1R)-3-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-3-oxo-1-(3-thienylmethyl)propyl)carbamate;

methyl ((1S)-3-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-3-oxo-1-(2-thienylmethyl)propyl)carbamate;

methyl ((1S,3R)-3-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)cyclopentyl)carbamate;

methyl ((1R)-1-benzyl-3-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-3-oxopropyl)carbamate;

methyl ((1R)-3-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-(2-fluorobenzyl)-3-oxopropyl)carbamate;

methyl ((1R,3S)-3-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)cyclopentyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(((1R,3S)-3-((methoxycarbonyl)amino)cyclopentyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(((1S,3R)-3-((methoxycarbonyl)amino)cyclopentyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(((1R,3S)-3-((methoxycarbonyl)amino)cyclopentyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(((1S,3R)-3-((methoxycarbonyl)amino)cyclopentyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-(2-pyridinyl)propanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(2-pyridinylmethyl)ethyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S,3R)-3-methoxy-2-((methoxycarbonyl)amino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(2-pyridinylmethyl)ethyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(2-pyridinylmethyl)ethyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((cis-4-((methoxycarbonyl)amino)cyclohexyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((trans-4-((methoxycarbonyl)amino)cyclohexyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((cis-4-(diethylamino)cyclohexyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S,2R)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((cis-4-(diethylamino)cyclohexyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methoxypropyl)carbamate;

cis-4-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-N,N-diethylcyclohexanamine;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((cis-4-(diethylamino)cyclohexyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

methyl ((1S)-1-((1-benzyl-1H-imidazol-4-yl)methyl)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S,3R)-3-methoxy-2-((methoxycarbonyl)amino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-3-(1-benzyl-1H-imidazol-4-yl)-2-((methoxycarbonyl)amino)propanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-3-(1-benzyl-1H-imidazol-4-yl)-2-((methoxycarbonyl)amino)propanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S,3R)-3-methoxy-2-((methoxycarbonyl)amino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(1,3-thiazol-4-ylmethyl)ethyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-(1,3-thiazol-4-yl)propanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(1,3-thiazol-4-ylmethyl)ethyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(1,3-thiazol-4-ylmethyl)ethyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S,3R)-3-methoxy-2-((methoxycarbonyl)amino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(3-pyridinylmethyl)ethyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(3-pyridinylmethyl)ethyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(3-pyridinylmethyl)ethyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(3-pyridinylmethyl)ethyl)carbamate;

methyl ((1R,3S)-3-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-3-methoxy-2-((methoxycarbonyl)amino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)cyclopentyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S,3R)-3-methoxy-2-((methoxycarbonyl)amino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(4-pyridinylmethyl)ethyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(4-pyridinylmethyl)ethyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(4-pyridinylmethyl)ethyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(4-pyridinylmethyl)ethyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(O-(hydroxy(methoxy)phosphoryl)-N-(methoxycarbonyl)-L-tyrosyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S,2R)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(O-(hydroxy(methoxy)phosphoryl)-N-(methoxycarbonyl)-L-tyrosyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methoxypropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(((1S,2R)-2-((methoxycarbonyl)amino)cyclohexyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1R,2S)-2-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)cyclohexyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(((1S,2R)-2-((methoxycarbonyl)amino)cyclohexyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R,2S)-2-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)cyclohexyl)carbamate;

methyl ((1R,2S)-2-(((2S)-2-(5-(4'-(2-((2S)-1-((cis-4-(diethylamino)cyclohexyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)cyclohexyl)carbamate;

methyl ((1R,2S)-2-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-acetamido-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)cyclohexyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-3-(1H-indol-3-yl)-2-((methoxycarbonyl)amino)propanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(1H-indol-3-ylmethyl)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S,3R)-3-methoxy-2-((methoxycarbonyl)amino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-(1H-indol-3-ylmethyl)-2-oxoethyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-3-(1H-indol-3-yl)-2-((methoxycarbonyl)amino)propanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

methyl ((1S)-1-(4-(aminomethyl)benzyl)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(O-benzyl-N-(methoxycarbonyl)-L-tyrosyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S,2R)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(O-benzyl-N-(methoxycarbonyl)-L-tyrosyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methoxypropyl)carbamate;

methyl ((1S)-1-(4-(benzyloxy)benzyl)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate;

methyl ((1S)-1-(4-(benzyloxy)benzyl)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate;

methyl ((1R,2R)-2-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)cyclopentyl)carbamate;

methyl ((1R,2R)-2-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)cyclopentyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(((1R,2R)-2-((methoxycarbonyl)amino)cyclopentyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1S)-1-(4-hydroxybenzyl)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-(4-hydroxybenzyl)-2-oxoethyl)carbamate;

methyl ((1S)-1-(4-hydroxybenzyl)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate;

methyl ((1S)-1-(4-(acetamidomethyl)benzyl)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate;

methyl ((1S)-1-(4-(((ethylcarbamoyl)amino)methyl)benzyl)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate;

methyl ((1S,2S)-2-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)cyclopentyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(((1S,2S)-2-((methoxycarbonyl)amino)cyclopentyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1S,2S)-2-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)cyclopentyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-O-methyl-L-homoseryl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-3-methoxy-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate;

methyl ((1S,2R)-2-methoxy-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-O-methyl-L-homoseryl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate;

methyl ((1S,2S)-2-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-O-methyl-L-homoseryl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)cyclopentyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-(1H-1,2,3-triazol-4-yl)propanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(1H-1,2,3-triazol-4-ylmethyl)ethyl)carbamate;

dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((2S)-4-oxo-4,2-butanediyl)))biscarbamate;

dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((3R)-4-methyl-1-oxo-1,3-pentanediyl)))biscarbamate;

methyl ((1R)-3-((2S)-2-(5-(4'-(2-(1-((3R)-3-((methoxycarbonyl)amino)-3-phenylpropanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-3-oxo-1-phenylpropyl)carbamate;

methyl ((1S)-3-((2S)-2-(5-(4'-(2-(1-((3S)-3-((methoxycarbonyl)amino)-3-phenylpropanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-3-oxo-1-phenylpropyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-(2-pyridinyl)propanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(2-pyridinylmethyl)ethyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-3-(1H-imidazol-4-yl)-2-((methoxycarbonyl)amino)propanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-(1H-imidazol-4-ylmethyl)-2-oxoethyl)carbamate;

(6S,6'S)-6,6'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediylcarbonyl))didihydro-2,4(1H,3H)-pyrimidinedione;
(4S,5R,4'S,5'R)-4,4'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediylcarbonyl))bis(5-methyl-1,3-oxazolidin-2-one);
N-(3-((2S)-2-(5-(4'-(2-((2S)-1-(3-acetamidopropanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-3-oxopropyl)acetamide;
dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((3R)-1-oxo-5-phenyl-1,3-pentanediyl)))biscarbamate;
dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((2R)-4-oxo-1-(2-thienyl)-4,2-butanediyl)))biscarbamate;
dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((2R)-4-oxo-1-(3-thienyl)-4,2-butanediyl)))biscarbamate;
dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((2S)-4-oxo-1-(2-thienyl)-4,2-butanediyl)))biscarbamate;
dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediylcarbonyl(1R,2R)-2,1-cyclohexanediyl))biscarbamate;
di-tert-butyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((2S)-4-(dimethylamino)-1-oxo-1,2-butanediyl)))biscarbamate;
dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediylcarbonyl(1R,2S)-2,1-cyclohexanediyl))biscarbamate;
(3S,3'S)-4,4'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N~1~,N~1~-dimethyl-4-oxo-1,3-butanediamine);
dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((2R)-4-oxo-1-phenyl-4,2-butanediyl)))biscarbamate;
dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediylcarbonyl(1R,3S)-3,1-cyclopentanediyl))biscarbamate;
methyl ((1R)-1-benzyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-3-phenylpropanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate;
dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((2S)-4-(dimethylamino)-1-oxo-1,2-butanediyl)))biscarbamate;
(2R,2'R)-1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-dimethyl-1-oxo-3-phenyl-2-propanamine);

methyl ((1S)-1-benzyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-phenylpropanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate;

dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediylcarbonyl(1R,3S)-3,1-cyclopentanediyl))biscarbamate;

dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediylcarbonylcis-4,1-cyclohexanediyl))biscarbamate;

dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediylcarbonyltrans-4,1-cyclohexanediyl))biscarbamate;

({cis)-4,4'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediylcarbonyl))bis(N,N-diethylcyclohexanamine);

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-(1,3-thiazol-4-yl)propanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(1,3-thiazol-4-ylmethyl)ethyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-3-(1-benzyl-1H-imidazol-4-yl)-2-((methoxycarbonyl)amino)propanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-((1-benzyl-1H-imidazol-4-yl)methyl)-2-oxoethyl)carbamate;

dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediylcarbonyl(1S,2S)-2,1-cyclopentanediyl))biscarbamate;

methyl ((1S)-3-methoxy-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-O-methyl-L-homoseryl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate;

methyl ((1S)-2-((2S,4R)-4-fluoro-2-(5-(4'-(2-((2S,4R)-4-fluoro-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

methyl ((1S)-2-((2S,4R)-4-hydroxy-2-(5-(4'-(2-((2S,4R)-4-hydroxy-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

methyl ((1S)-1-(((2S,4R)-4-hydroxy-2-(5-(4'-(2-((2S,4R)-4-hydroxy-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl((2S,4R)-4-hydroxy-2,1-pyrrolidinediyl)((1S)-1-cyclopropyl-2-oxo-2,1-ethanediyl)))biscarbamate;
(3S,5S,3'S,5'S)-5,5'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl))bis(1-((2R)-2-(diethylamino)-2-phenylacetyl)-3-pyrrolidinol);
methyl ((1S)-2-((2S,4S)-4-hydroxy-2-(5-(4'-(2-((2S,4S)-4-hydroxy-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;
methyl ((1S)-1-(((2S,4S)-4-hydroxy-2-(5-(4'-(2-((2S,4S)-4-hydroxy-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;
methyl ((1S)-1-(((2S,4S)-4-fluoro-2-(5-(4'-(2-((2S,4S)-4-fluoro-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;
methyl ((1S)-1-(((2S,4R)-4-fluoro-2-(5-(4'-(2-((2S,4R)-4-fluoro-1-((2S)-2-((methoxycarbonyl)amino)-4-methylpentanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-3-methylbutyl)carbamate;
methyl ((1S)-2-((2S,4S)-4-fluoro-2-(5-(4'-(2-((2S,4S)-4-fluoro-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;
methyl ((1S)-2-((2S,4S)-2-(5-(4'-(2-((2S,4S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-4-fluoro-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-4-fluoro-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;
methyl ((1S)-1-(((2S,4S)-2-(5-(4'-(2-((2S,4S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-4-fluoro-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-4-fluoro-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;
methyl ((1S)-1-(((2S,4R)-4-fluoro-2-(5-(4'-(2-((2S,4R)-4-fluoro-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;
(1R,1'R)-2,2'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl((2S,4R)-4-fluoro-2,1-pyrrolidinediyl)))bis(N,N-diethyl-2-oxo-1-phenylethanamine);
3-((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-2-((dimethylcarbamoyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)-1,1-dimethylurea;

3-((1S)-2-((2S)-2-(4-(4'-(2-((2S)-1-(N-(dimethylcarbamoyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)-1,1-dimethylurea;

2-fluoroethyl ((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-2-(((2-fluoroethoxy)carbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-2-ethyl-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-3-ethyl-2-((methoxycarbonyl)amino)pentanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)butyl)carbamate;

1,1'-(4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl(2S)-2,1-pyrrolidinediyl((2S)-3-methyl-1-oxo-1,2-butanediyl)))ditetrahydro-2(1H)-pyrimidinone;

methyl ((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-4-methylpentanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-3-methylbutyl)carbamate;

methyl ((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-4,4-difluoro-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-4,4-difluoro-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

(1R,1'R)-2,2'-(4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl((2S)-4,4-difluoro-2,1-pyrrolidinediyl)))bis(N,N-dimethyl-2-oxo-1-phenylethanamine);

(1R,1'R)-2,2'-(4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl((2S)-4,4-difluoro-2,1-pyrrolidinediyl)))bis(N,N-diethyl-2-oxo-1-phenylethanamine);

methyl ((1S,2R)-1-(((2S)-2-(4-(4'-(2-((2S)-4,4-difluoro-1-(N-(methoxycarbonyl)-O-methyl-L-threonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-4,4-difluoro-1-pyrrolidinyl)carbonyl)-2-methoxypropyl)carbamate;

methyl ((1S)-2-((2S)-2-(4-(4'-(2-((2S)-4,4-difluoro-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-4,4-difluoro-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

methyl ((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-4,4-difluoro-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

rac-(1R)-2-((2S)-2-(4-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-4,4-difluoro-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-diethyl-2-oxo-1-phenylethanamine;

methyl ((1S)-1-(((2R,3S)-3-hydroxy-2-(4-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-2-((2S)-2-(4-(4'-(2-((2R,3S)-3-hydroxy-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

methyl ((1S)-1-(((2R)-3-hydroxy-2-(4-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl 2-((2S)-1-(tert-butoxycarbonyl)-2-pyrrolidinyl)-5-(4'-(2-((2S)-1-(tert-butoxycarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazole-4-carboxylate;

ethyl 2-((2S)-1-(tert-butoxycarbonyl)-2-pyrrolidinyl)-5-(4'-(2-((2S)-1-(tert-butoxycarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazole-4-carboxylate;

benzyl 2-((2S)-1-(tert-butoxycarbonyl)-2-pyrrolidinyl)-5-(4'-(2-((2S)-1-(tert-butoxycarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazole-4-carboxylate;

tert-butyl (2S)-2-(5-(4'-(2-((2S)-1-(tert-butoxycarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-4-(methylcarbamoyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate;

methyl 2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazole-4-carboxylate;

methyl 2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazole-4-carboxylate;

methyl 2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazole-4-carboxylate;

ethyl 2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazole-4-carboxylate;

ethyl 2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazole-4-carboxylate;

benzyl 2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazole-4-carboxylate;

benzyl 2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazole-4-carboxylate;

benzyl 2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazole-4-carboxylate;

benzyl 2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazole-4-carboxylate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-4-(methylcarbamoyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-N-methyl-1H-imidazole-4-carboxamide;

N-methyl-2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazole-4-carboxamide;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-4-(methylcarbamoyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

methyl ((1R)-2-((2S)-2-(4-carbamoyl-5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazole-4-carboxylic acid;

2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazole-4-carboxylic acid;

tert-butyl (2S)-2-(5-(4'-(2-((2S)-1-(tert-butoxycarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-4-(trifluoromethyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate;

tert-butyl (2S)-2-(5-(4'-(2-((2S)-1-((benzyloxy)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-4-(trifluoromethyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-4-(trifluoromethyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-4-(trifluoromethyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-4-(trifluoromethyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-4-(trifluoromethyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-diethyl-2-oxo-1-phenylethanamine;

methyl ((1S)-1-cyclopropyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-cyclopropyl-2-((methoxycarbonyl)amino)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-4-(trifluoromethyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate;

methyl ((1S,2R)-2-methoxy-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-O-methyl-L-threonyl)-2-pyrrolidinyl)-4-(trifluoromethyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate;

benzyl (2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-4-(trifluoromethyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-4-(trifluoromethyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

tert-butyl (2S)-2-(4-(4'-(2-((2S)-1-(tert-butoxycarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-methoxy-3-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate;

di-tert-butyl (2S,2'S)-2,2'-((3-fluoro-4,4'-biphenyldiyl)bis(1H-imidazole-4,2-diyl))di(1-pyrrolidinecarboxylate);

tert-butyl (2S)-2-(4-(4'-(2-((2S)-1-(tert-butoxycarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2,5-difluoro-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate;

di-tert-butyl (2S,2'S)-2,2'-((3,3'-difluoro-4,4'-biphenyldiyl)bis(1H-imidazole-5,2-diyl))di(1-pyrrolidinecarboxylate);

tert-butyl (2S)-2-(4-(4'-(2-((2S)-1-((benzyloxy)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-3-fluoro-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate;

tert-butyl (2S)-2-(4-(4'-(2-((2S)-1-((benzyloxy)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-3,3'-difluoro-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate;

tert-butyl (2S)-2-(5-(3-fluoro-4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate;

tert-butyl (2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-3-fluoro-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate;

tert-butyl (2S)-2-(5-(3-fluoro-4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate;

tert-butyl (2S)-2-(5-(3,3'-difluoro-4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate;

tert-butyl (2S)-2-(5-(3,3'-difluoro-4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate;

tert-butyl (2S)-2-(5-(3-fluoro-4'-(2-((2S)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate triacetate;

tert-butyl (2S)-2-(5-(3,3'-difluoro-4'-(2-((2S)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate;
methyl ((1R)-2-((2S)-2-(5-(3'-fluoro-4'-(2-((2S)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;
methyl ((1S)-1-(((2S)-2-(5-(3'-fluoro-4'-(2-((2S)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;
(1R)-N,N-diethyl-2-((2S)-2-(5-(3'-fluoro-4'-(2-((2S)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethanamine;
methyl ((1S)-1-(((2S)-2-(5-(3,3'-difluoro-4'-(2-((2S)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;
methyl ((1R)-2-((2S)-2-(5-(3,3'-difluoro-4'-(2-((2S)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;
5,5'-(4-methoxy-3,4'-biphenyldiyl)bis(2-((2S)-2-pyrrolidinyl)-1H-imidazole);
5,5'-(3-fluoro-4,4'-biphenyldiyl)bis(2-((2S)-2-pyrrolidinyl)-1H-imidazole) tetraacetate;
5,5'-(2,5-difluoro-4,4'-biphenyldiyl)bis(2-((2S)-2-pyrrolidinyl)-1H-imidazole);
(1R,1'R)-2,2'-((4-methoxy-3,4'-biphenyldiyl)bis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-dimethyl-2-oxo-1-phenylethanamine);
dimethyl ((4-methoxy-3,4'-biphenyldiyl)bis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate;
methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-3-fluoro-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;
methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-3-fluoro-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;
methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-3-fluoro-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(3'-fluoro-4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-3'-fluoro-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(3'-fluoro-4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(3'-fluoro-4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S,2R)-1-(((2S)-2-(5-(3-fluoro-4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methoxypropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N,N-diethyl-D-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-3'-fluoro-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-3'-fluoro-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(3'-fluoro-4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

dimethyl ((3-fluoro-4,4'-biphenyldiyl)bis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate;

(1R,1'R)-2,2'-((3-fluoro-4,4'-biphenyldiyl)bis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-diethyl-2-oxo-1-phenylethanamine);

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N,N-diethyl-D-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-3'-fluoro-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1S)-1-cyclopropyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-3-fluoro-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate;

methyl ((1S)-1-cyclopropyl-2-((2S)-2-(5-(3-fluoro-4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N,N-diethyl-D-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-3'-fluoro-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2 oxo-1-phenylethyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(2',5'-difluoro-4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

dimethyl ((2,5-difluoro-4,4'-biphenyldiyl)bis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate;

(1R,1'R)-2,2'-((2,5-difluoro-4,4'-biphenyldiyl)bis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-diethyl-2-oxo-1-phenylethanamine);

methyl ((1S)-1-cyclopropyl-2-((2S)-2-(5-(3,3'-difluoro-4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate;

methyl ((1S,2R)-1-(((2S)-2-(5-(3,3'-difluoro-4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methoxypropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(3,3'-difluoro-4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(3,3'-difluoro-4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N,N-diethyl-D-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-3,3'-difluoro-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(3,3'-difluoro-4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(3,3'-difluoro-4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2 pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(3,3'-difluoro-4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N,N-diethyl-D-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-3,3'-difluoro-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-3,3'-difluoro-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1S,2R)-1-(((2S)-2-(5-(3,3'-difluoro-4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methoxypropyl)carbamate bis(trifluoroacetate);

methyl ((1S)-1-cyclopropyl-2-((2S)-2-(5-(3,3'-difluoro-4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate;

7,7'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl(2-oxo-1-phenyl-2,1-ethanediyl)))bis(7-azabicyclo[2.2.1]heptane);

7,7'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl(2-oxo-1-phenyl-2,1-ethanediyl)))bis(7-azabicyclo[2.2.1]heptane);

N,N'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))bis(N-ethylcyclopropanamine);

ethyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(ethoxycarbonyl)-D-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

ethyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(ethoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediylcarbonyl-1,1-cyclopropanediyl))biscarbamate;

methyl (2-((2S)-2-(5-(4'-(2-((2S)-1-(2-((methoxycarbonyl)amino)-2-methylpropanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1,1-dimethyl-2-oxoethyl)carbamate;

(2R,2'R)-1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-dimethyl-1-oxo-2-propanamine);

(2R,2'R)-1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-diethyl-1-oxo-2-propanamine);

(2R,2'R)-1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-diethyl-3-methyl-1-oxo-2-butanamine);

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)(methyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)methylcarbamate;

dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1S)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate;

N,N'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((2R)-1-oxo-1,2-propanediyl)))bis(N-propyl-1-propanamine);

methyl ((1S)-2-hydroxy-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-3-hydroxy-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S,2R)-2-hydroxy-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S,3R)-3-hydroxy-2-((methoxycarbonyl)amino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate;

methyl ((1S,2S)-2-hydroxy-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S,3S)-3-hydroxy-2-((methoxycarbonyl)amino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-D-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

(2S,2'S)-1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-dimethyl-1-oxo-2-propanamine);

dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((2R)-1-oxo-1,2-butanediyl)))biscarbamate;

dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((2S)-1-oxo-1,2-butanediyl)))biscarbamate;

dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-1-cyclopropyl-2-oxo-2,1-ethanediyl)))biscarbamate;

dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1S)-1-cyclopropyl-2-oxo-2,1-ethanediyl)))biscarbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3,3-dimethylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2,2-dimethylpropyl)carbamate;

dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((4S)-5-oxo-1-pentene-5,4-diyl)))biscarbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-O-methyl-L-seryl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-(methoxymethyl)-2-oxoethyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)pentanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)butyl)carbamate;

methyl ((1S)-1-(((2R)-2-(5-(4'-(2-((2R)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2R)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2R)-2,1-pyrrolidinediyl((1R)-1-cyclopropyl-2-oxo-2,1-ethanediyl)))biscarbamate;

ethyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

ethyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

(5S)-5-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-pyrrolidinone;

methyl (1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)cyclopropyl)carbamate;

methyl (2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1,1-dimethyl-2-oxoethyl)carbamate;

(2R)-1-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-diethyl-1-oxo-2-propanamine;

(2S)-1-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-diethyl-1-oxo-2-propanamine;

(1R)-N,N-diethyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(1,3-oxazol-2-ylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethanamine;

(1R)-N,N-diethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(3-pyridinylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine;

(2R)-1-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-oxo-2-propanol;

(2S)-1-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-oxo-2-propanol;

methyl (1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)cyclobutyl)carbamate;

methyl (1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)cyclopentyl)carbamate;

N-((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)-N-propyl-1-propanamine;

(4S)-4-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-1,3-oxazolidin-2-one;

(2R)-1-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-diethyl-3-methyl-1-oxo-2-butanamine;

N-((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)-N-propyl-1-propanamine;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

(1R)-N,N-diethyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(4-morpholinyl)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethanamine;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

methyl (2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate;

(1R)-N,N-diethyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(4-morpholinylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethanamine;

(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol 2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

methyl ((1R)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate;

methyl ((1R)-1-cyclopropyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate;

methyl ((1S)-1-cyclopropyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2,2-dimethylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-3-buten-1-yl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-(methoxymethyl)-2-oxoethyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)butyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N,N-diethyl-D-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N,N-dipropyl-D-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(1H-imidazol-5-ylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

M66a: methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(4-(diethylamino)-2-((methoxycarbonyl)amino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(4-(diethylamino)-2-((methoxycarbonyl)amino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-3-(4-morpholinyl)propyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N,N-diethyl-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N,N-diethyl-D-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-(methoxymethyl)-2-oxoethyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3,3-dimethylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl (2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl) 4 biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)butyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-3-buten-1-yl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-cyclopropyl-2-((methoxycarbonyl)amino)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(ethyl(methyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N,N-diethyl-D-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-2-methyl-1-(((2S)-2-(5-(4'-(2-((2S)-1-(3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate;

methyl ((1S)-2-methyl-1-(((2S)-2-(5-(4'-(2-((2S)-1-((4-methyl-1-piperazinyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N,N-dipropyl-D-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N,N-dipropyl-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-(diethylamino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(1H-imidazol-4-ylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N,N-diethyl-O-methyl-L-seryl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N^2,N^2-diethyl-D-asparaginyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2R)-1-((2R)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N,N-diethyl-O-methyl-D-seryl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N,N-diethyl-3-methyl-D-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-3-amino-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-3-oxopropyl)carbamate ;

methyl ((1S)-1-methyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(1,3-oxazol-2-ylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate;

methyl ((1S)-1-cyclopropyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)propanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)butyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2,2-dimethylpropyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N,N-diethyl-D-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(7-azabicyclo[2.2.1]hept-7-yl(phenyl)acctyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-hydroxy-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(ethyl(methyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-(methoxymethyl)-2-oxoethyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N,N-diethyl-D-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N,N-dipropyl-D-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N,N-dipropyl-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(3-hydroxy-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-3-hydroxy-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S,3R)-4-hydroxy-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S,3S)-4-hydroxy-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-2-methyl-1-(((2S)-2-(5-(4'-(2-((2S)-1-L-valyl-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate;

benzyl (3S)-3-((methoxycarbonyl)amino)-4-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-4-oxobutanoate;

methyl (3S)-3-((methoxycarbonyl)amino)-4-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-4-oxobutanoate;

(3S)-3-((methoxycarbonyl)amino)-4-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-4-oxobutanoic acid;

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-4-(4-methyl-1-piperazinyl)-4-oxobutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-3-(dimethylamino)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-3-oxopropyl)carbamate;

4,4'-bis(2-((2S)-1-(N-(methoxycarbonyl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-biphenylcarboxylic acid;

4,4'-bis(2-((2S)-1-((2R)-2-cyclopropyl-2-((methoxycarbonyl)amino)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-biphenylcarboxylic acid;

4,4'-bis(2-((2S)-1-((2S)-2-cyclopropyl-2-((methoxycarbonyl)amino)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-biphenylcarboxylic acid;

4,4'-bis(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-biphenylcarboxylic acid;

methyl ((1S)-1-(((2S)-2-(5-(2'-carbamoyl-4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(2-(hydroxymethyl)-4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(2-((dimethylamino)methyl)-4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

dimethyl ((2-((dimethylamino)methyl)-4,4'-biphenyldiyl)bis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate;

methyl ((1S)-1-(((1S,3S,5S)-3-(5-(4'-(2-((1S,3S,5S)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate;

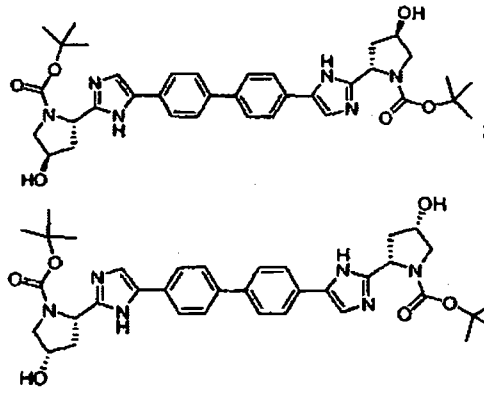
methyl ((1R)-1-(((1S,3S,5S)-3-(5-(4'-(2-((1S,3S,5S)-2-((2R)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate;

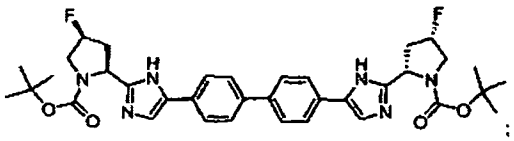
dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(1S,3S,5S)-2-azabicyclo[3.1.0]hexane-3,2-diyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate;

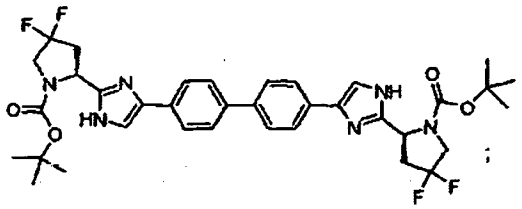
methyl ((1S)-2-hydroxy-1-(((1S,3S,5S)-3-(5-(4'-(2-((1S,3S,5S)-2-((2S)-3-hydroxy-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-

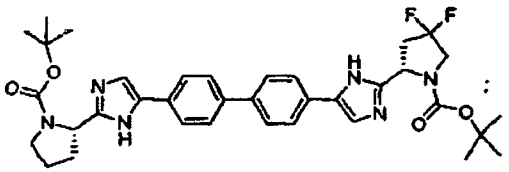
imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate;
dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(1S,3S,5S)-2-azabicyclo[3.1.0]hexane-3,2-diyl((2S)-1-oxo-1,2-butanediyl)))biscarbamate;
dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(1S,3S,5S)-2-azabicyclo[3.1.0]hexane-3,2-diyl((1S)-1-cyclopropyl-2-oxo-2,1-ethanediyl)))biscarbamate;
methyl ((1S)-1-(((1S,3S,5S)-3-(5-(4'-(2-((1S,3S,5S)-2-((2S)-2-((methoxycarbonyl)amino)-3,3-dimethylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2,2-dimethylpropyl)carbamate;
methyl (2-((1S,3S,5S)-3-(5-(4'-(2-((1S,3S,5S)-2-(((methoxycarbonyl)amino)acetyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-2-oxoethyl)carbamate;
methyl ((1S)-2-((1S,3S,5S)-3-(5-(4'-(2-((1S,3S,5S)-2-(N-(methoxycarbonyl)-L-alanyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-1-methyl-2-oxoethyl)carbamate; and
methyl ((1S)-1-(((1R,3R,5R)-3-(5-(4'-(2-((1R,3R,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate;
or a pharmaceutically acceptable salt thereof.

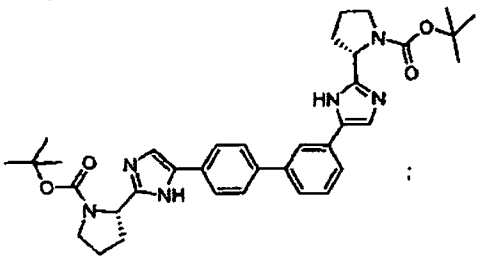
20. A compound selected from

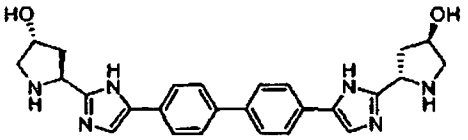


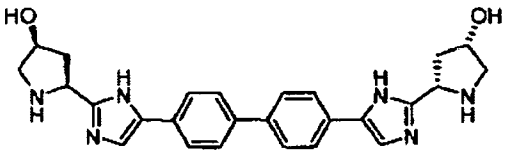


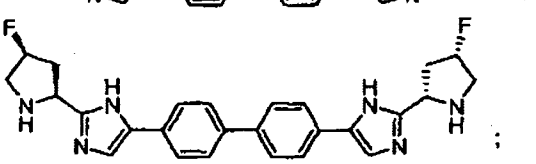


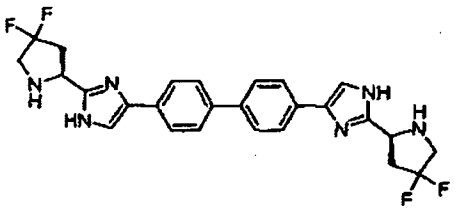


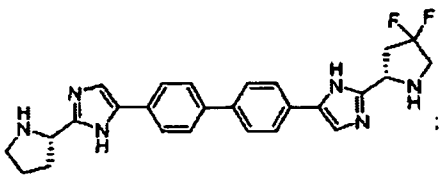


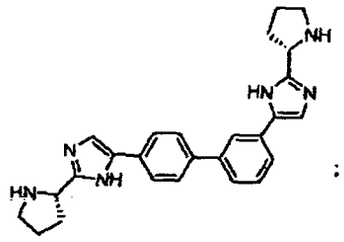


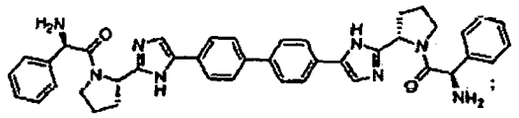


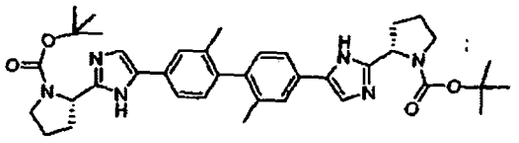


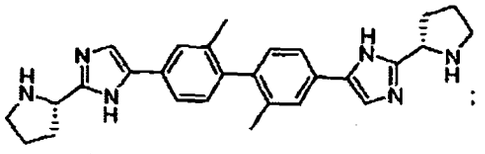


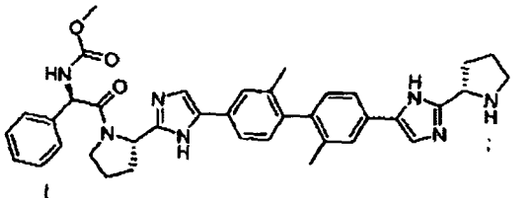


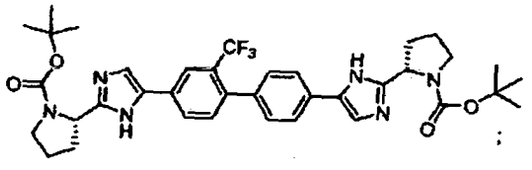


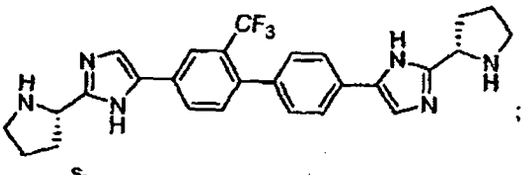


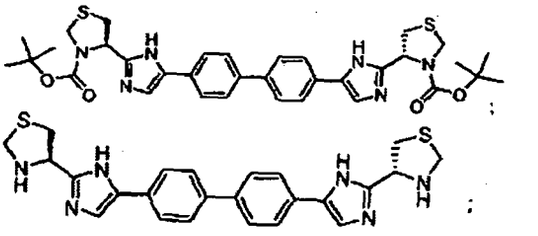


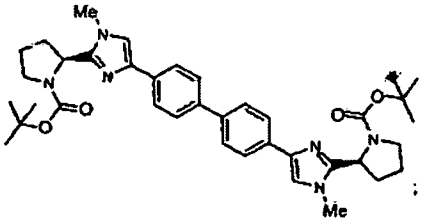


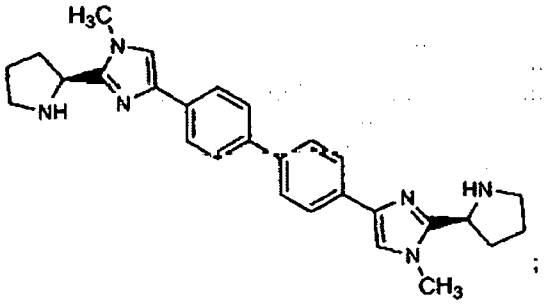


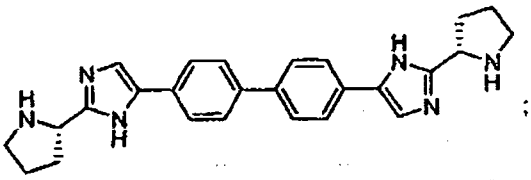


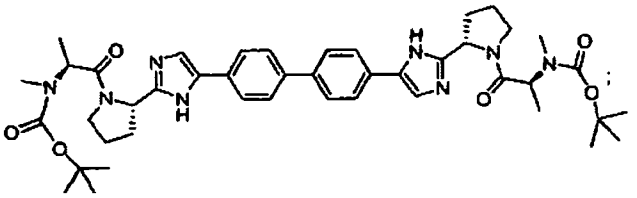


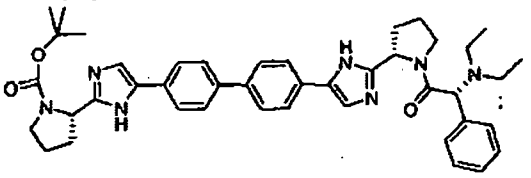


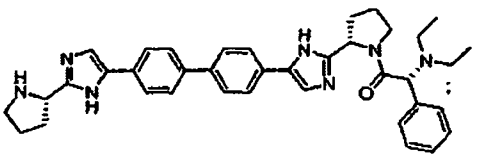


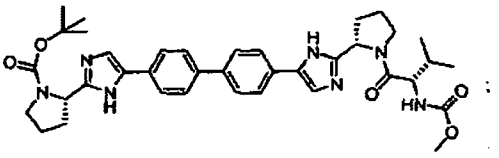


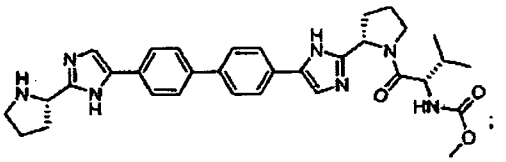


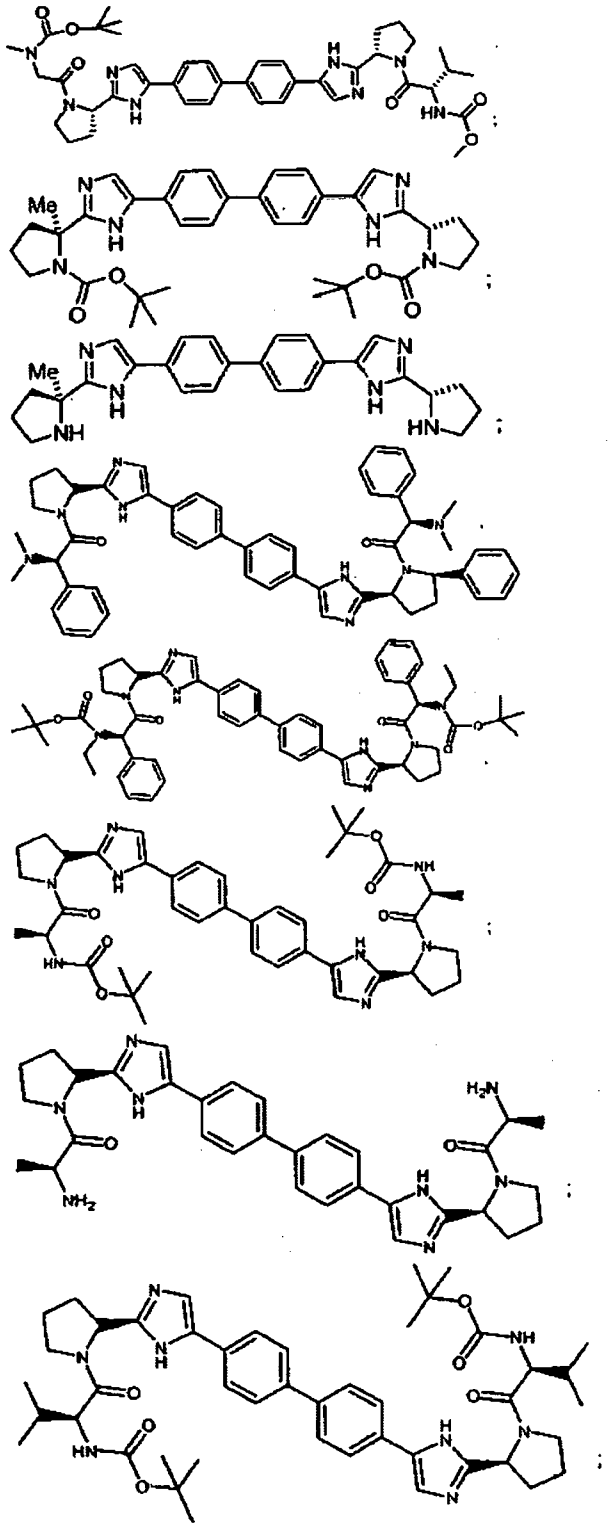


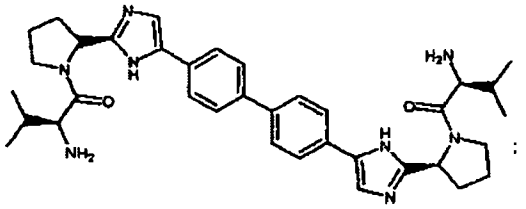


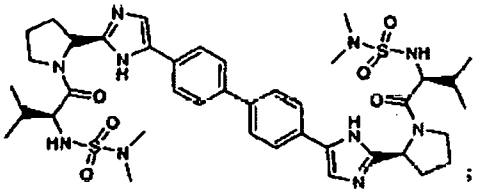


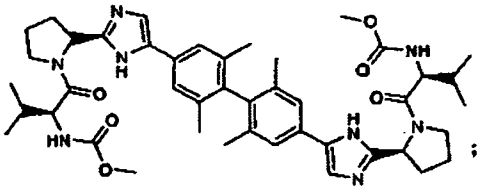


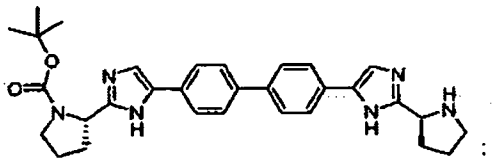


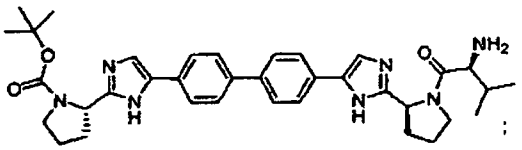


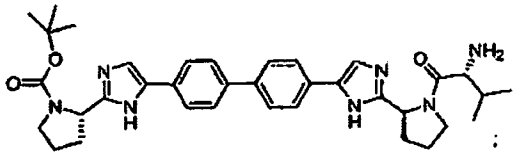


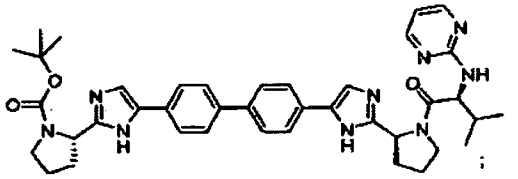


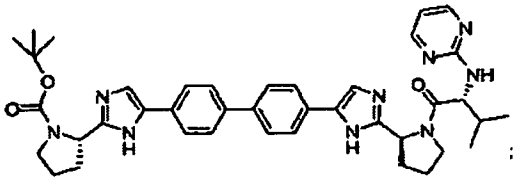


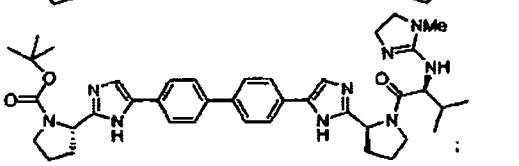


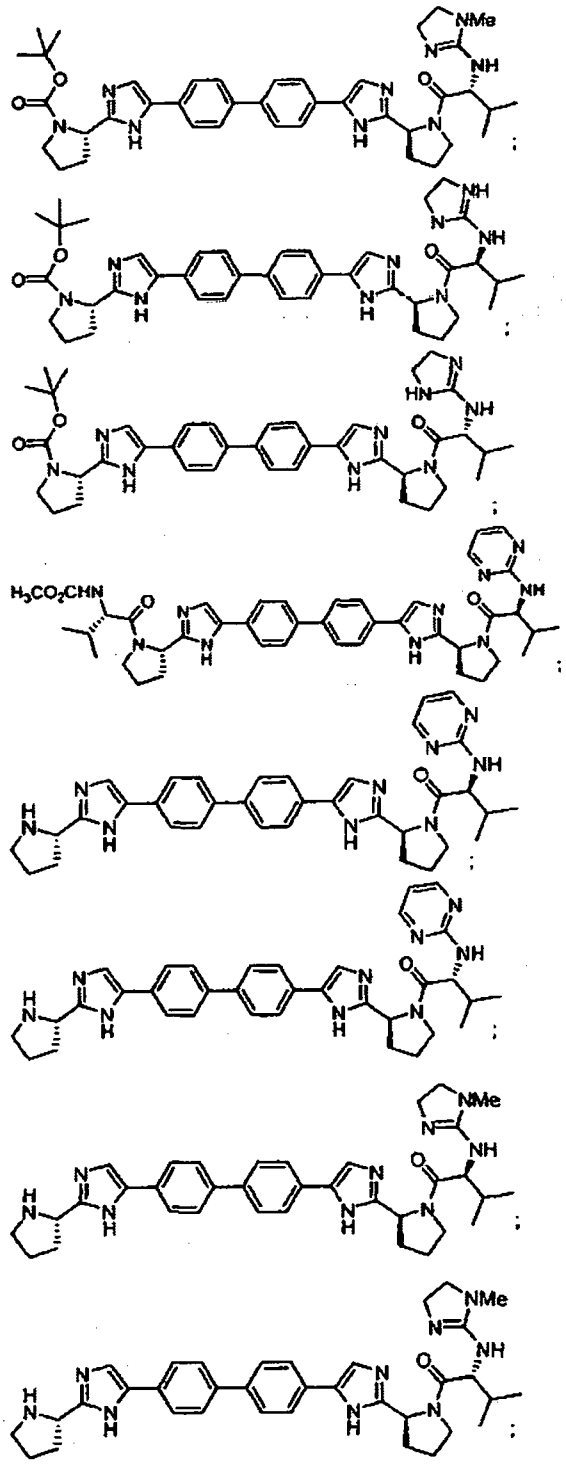


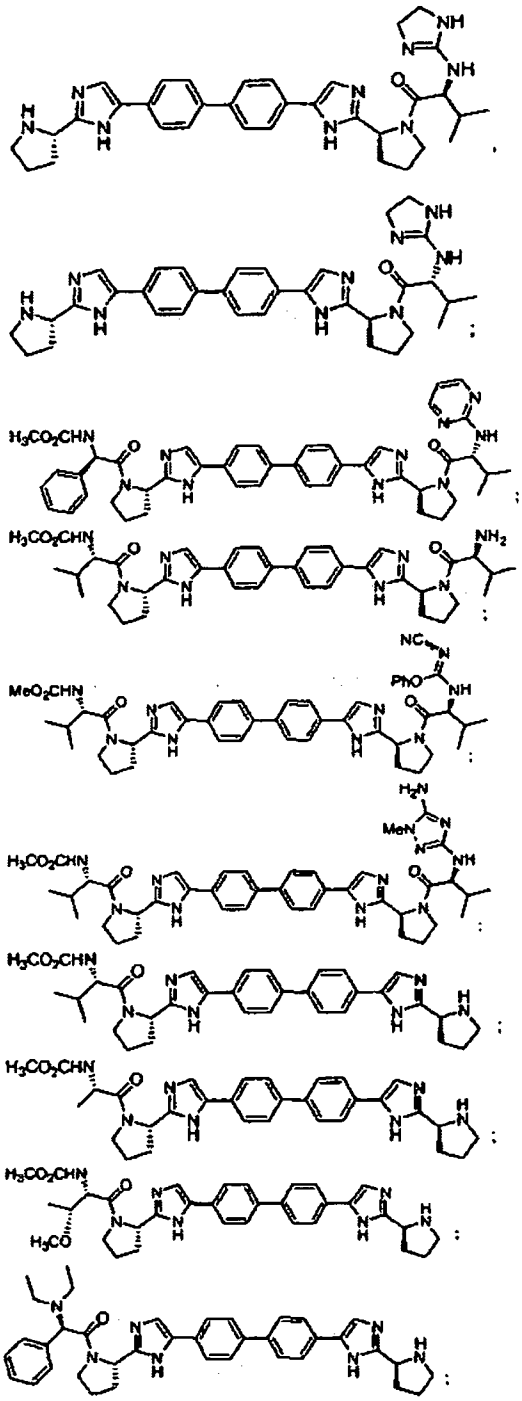


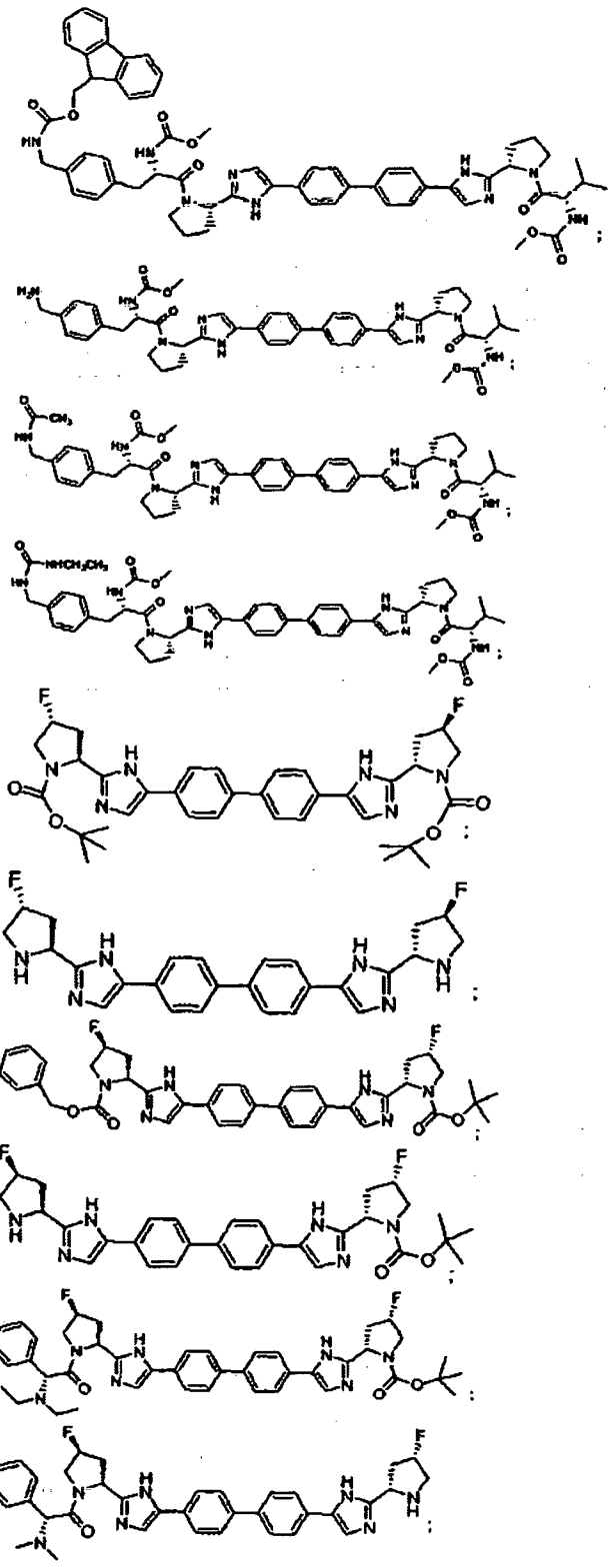


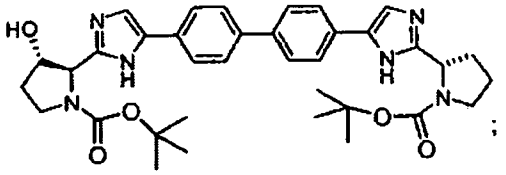








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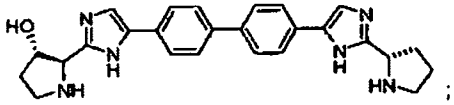
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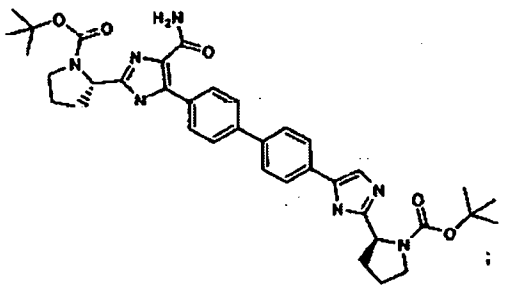
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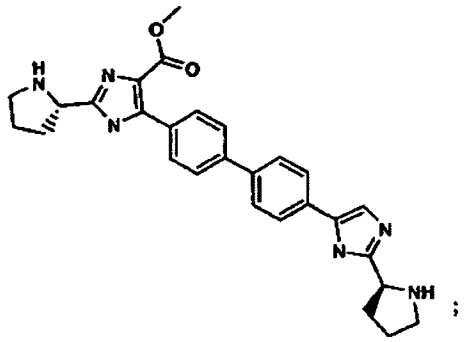
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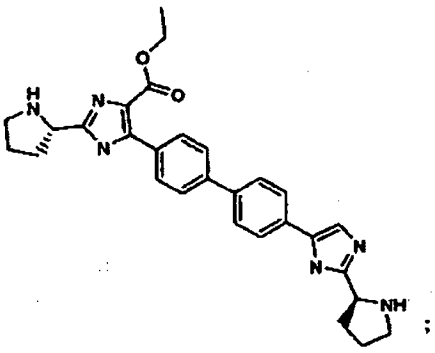
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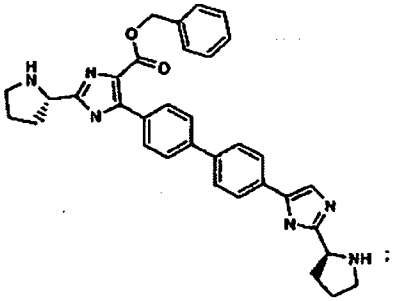
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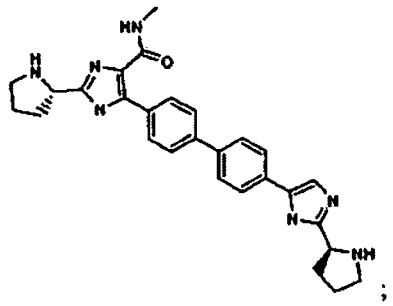
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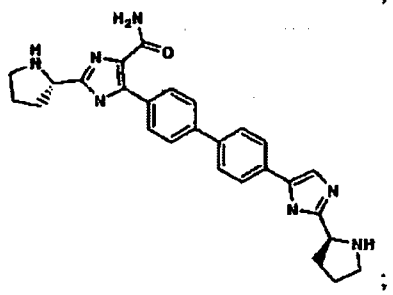
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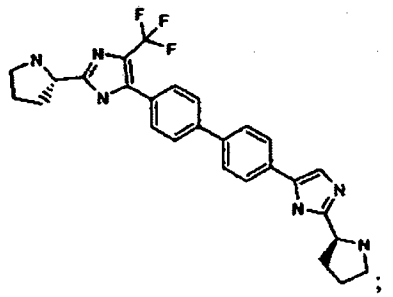
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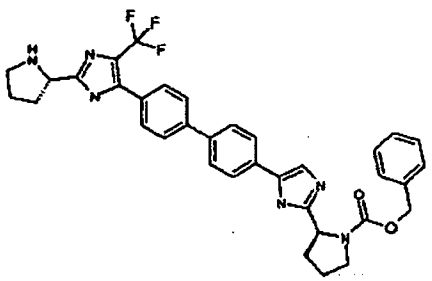
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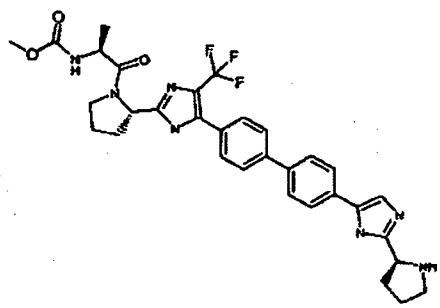
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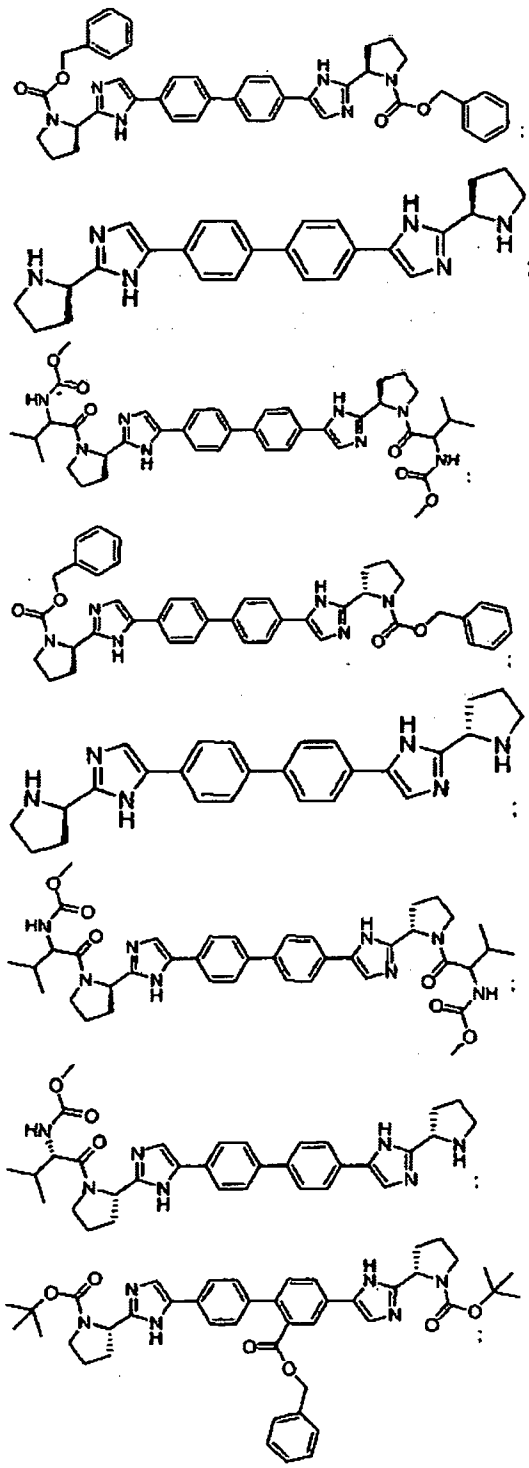

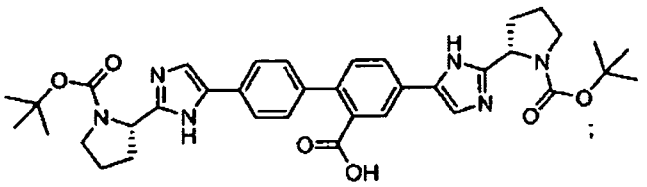

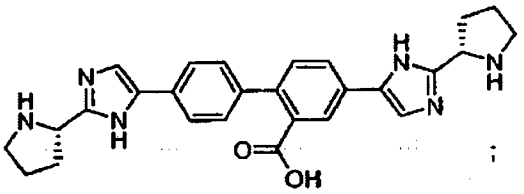

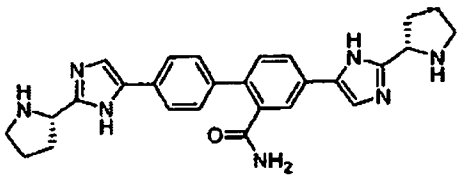

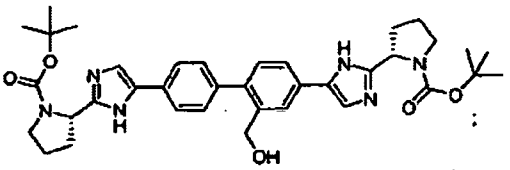

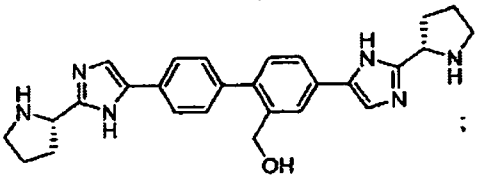

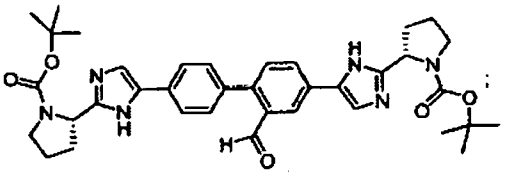

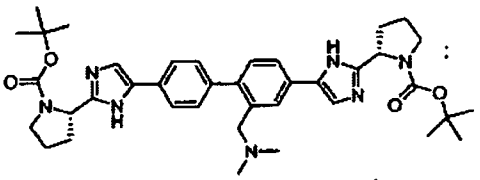

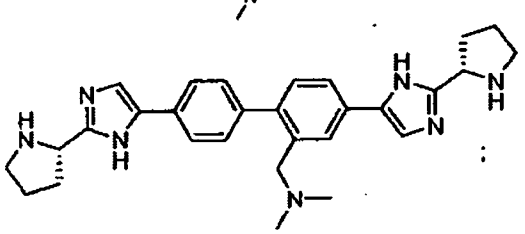

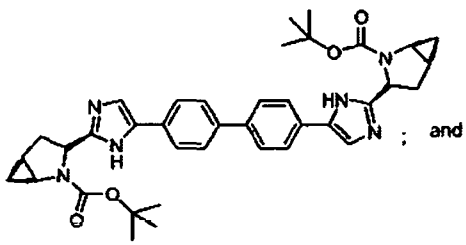
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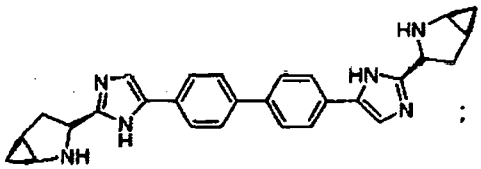
;

or a pharmaceutically acceptable salt thereof.

21. A compound selected from

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

(1R,1'R)-2,2'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-dimethyl-2-oxo-1-phenylethanamine);

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

methyl ((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-4,4-difluoro-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-4,4-difluoro-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((1R,3R,5R)-3-(5-(4'-(2-((1R,3R,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate;

methyl ((1S)-2-methyl-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-2-pyrimidinyl-D-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate;
methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;
dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate;
(1R)-N,N-dimethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine;
methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate; and
methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3,3-dimethylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2,2-dimethylpropyl)carbamate;
or a pharmaceutically acceptable salt thereof.

22. A pharmaceutically acceptable salt of a compound of claim 21, wherein the salt is a dihydrochloride salt.

23. A compound which is methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate; or a pharmaceutically acceptable salt thereof.

24. A compound which is (1R,1'R)-2,2'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-dimethyl-2-oxo-1-phenylethanamine); or a pharmaceutically acceptable salt thereof.

25. A compound which is methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-

imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate; or a pharmaceutically acceptable salt thereof.

26. A compound which is methyl ((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-4,4-difluoro-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-4,4-difluoro-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate; or a pharmaceutically acceptable salt thereof.

27. A compound which is methyl ((1S)-1-(((1R,3R,5R)-3-(5-(4'-(2-((1R,3R,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate; or a pharmaceutically acceptable salt thereof.

28. A compound which is methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate; or a pharmaceutically acceptable salt thereof.

29. A compound which is methyl ((1S)-2-methyl-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-2-pyrimidinyl-D-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate; or a pharmaceutically acceptable salt thereof.

30. A compound which is methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate; or a pharmaceutically acceptable salt thereof.

31. A compound which is dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate; or a pharmaceutically acceptable salt thereof.

32. A compound which is (1R)-N,N-dimethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine; or a pharmaceutically acceptable salt thereof.

33. A compound which is methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate; or a pharmaceutically acceptable salt thereof.

34. A compound which is methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3,3-dimethylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2,2-dimethylpropyl)carbamate; or a pharmaceutically acceptable salt thereof.

35. A composition comprising a compound of claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

36. The composition of claim 35 further comprising one or two additional compounds having anti-HCV activity.

37. The composition of claim 36 wherein at least one of the additional compounds is an interferon or a ribavirin.

38. The composition of claim 37 wherein the interferon is selected from interferon alpha 2B, pegylated interferon alpha, consensus interferon, interferon alpha 2A, and lymphoblastiod interferon tau.

39. The composition of claim 36 wherein at least one of the additional compounds is selected from interleukin 2, interleukin 6, interleukin 12, a compound that enhances the development of a type 1 helper T cell response, interfering RNA, anti-sense RNA, Imiqimod, ribavirin, an inosine 5'-monophospate dehydrogenase inhibitor, amantadine, and rimantadine.

40. The composition of claim 36 wherein at least one of the additional compounds is effective to inhibit the function of a target selected from HCV metalloprotease, HCV serine protease, HCV polymerase, HCV helicase, HCV NS4B protein, HCV entry, HCV assembly, HCV egress, HCV NS5A protein, and IMPDH for the treatment of an HCV infection.

Dated this 5th day of February, 2009.

(HRISHIKESH RAY CHAUDHURY)
OF REMFRY & SAGAR
ATTORNEY FOR THE APPLICANTS.

IN THE MATTER OF

Indian Patent Application 853/DELNP/2009

In the name of

BRISTOL-MYERS SQUIBB COMPANY

AND IN THE MATTER OF

A pre-grant representation by

DALVIR SINGH

D2 – WHO paper on Daclatasvir Patent Landscape,

published April 2014

PATENT SITUATION OF KEY PRODUCTS FOR TREATMENT OF HEPATITIS C

DACLATASVIR

WORKING PAPER

Prepared for the
World Health Organization (WHO) by
Thomson Reuters

August 2014

World Health Organization

This report was prepared for the WHO Department of Essential Medicines and Health Products by Thomson Reuters. It is available for free download: http://www.who.int/phi/en/. If you have questions or feedback, please write to phidepartment@who.int.

WHO/HIS/EMP/PHI/14.1

INTRODUCTION

The World Health Organization's (WHO) 2014 *Guidelines for the screening, care and treatment of persons with hepatitis C infection* state that worldwide more than 185 million people are infected with the hepatitis C virus (HCV). Of these people, 350 000 to 500 000 die each year. An estimated one third of those who become chronically infected develop liver cirrhosis or hepatocellular carcinoma. HCV infection can be cured, but most people infected with the virus are unaware of their infection and so do not seek timely treatment. Furthermore, treatment remains unavailable for many who have been diagnosed. Several medicines are available to treat HCV, including pegylated interferon and ribavirin but treatment duration is long, involves weekly injections, and side effects are considerable. With the development of new direct-acting antivirals, the treatment landscape is rapidly changing. These new antivirals are expected to reach cure rates of more than 90% in persons with HCV infection across different genotypes, with fewer side effects and a shorter duration of treatment.[1] Two new compounds, simeprevir and sofosbuvir, have recently been approved in the United States and Europe and are recommended by the new WHO treatment guidelines. Many others are in various stages of development.

Resolution WHA67.6 adopted by the Sixty-Seventh World Health Assembly, requested the Director-General "to work with national authorities, upon their request, to promote comprehensive, equitable access to prevention, diagnosis and treatment for viral hepatitis" and "to assist Member States to ensure equitable access to quality, effective, affordable and safe hepatitis B and HCV treatments and diagnostics, in particular in developing countries". Ensuring access to new treatments is a challenging task. In order for countries to identify ways of increasing access and affordability of new HCV medicines, they need clarity about patent status. To assess whether a medicine is patent protected in a certain country requires expert knowledge and access to specialized databases that are not easily available. The WHO Global strategy and plan of action on public health, innovation and intellectual property provides WHO with a mandate to support efforts to determine the patent status of health products (element 5.1c). Despite the possibility of filing patents under the World Intellectual Property Organization (WIPO) Patent Cooperation Treaty (PCT) in 148 jurisdictions, there is no such thing as a worldwide patent. Patents are granted individually under each jurisdiction, depending on the national patent law and the outcome of the examination process. National patents that relate to the same basic patent (i.e. the same invention) are called family members and together build a patent family. In the present study, patent families are based on the Derwent World Patent Index (DWPI).[2]

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[1] Guidelines for the screening, care and treatment of persons with hepatitis C infection. Geneva: World Health Organization; 2014 (http://www.who.int/hiv/pub/hepatitis/hepatitis-c-guidelines/en, April 2014).

[2] The Derwent World Patents Index (or DWPI) is a database containing patent applications. Each patent family is grouped around a basic patent, which is usually the first published example of the invention.

The WHO Secretariat has mandated Thomson Reuters to carry out an analysis of the patent situation of seven new hepatitis treatments[3]:

International nonproprietary name	Sponsor
ABT-450	AbbVie Inc.
daclatasvir	Bristol-Myers Squibb Company
dasabuvir	AbbVie Inc.
ledipasvir	Gilead Sciences, Inc.
ombitasvir	AbbVie Inc.
simeprevir	Janssen Pharmaceutical Companies of Johnson & Johnson
sofosbuvir	Gilead Sciences Inc.

The draft reports were shared with the respective sponsor companies before publication.

OBJECTIVE

The objective of the patent working papers was to:

(1) identify the most relevant patents with respect to the medicines
(2) identify in which countries these patents have been filed and granted

One will often find numerous patents relating to one medicine. These patents will cover different aspects and innovations around the same product. Not all however are equally relevant, as many will cover variations or production processes but would not prevent somebody else to produce the medicine, e.g. by using a different process.

These patent working papers identify the most relevant patents for each medicine. The patents are categorized in primary and secondary patents. The patent publication covering the base compound is considered the "primary patent" and patents on specific pharmaceutical formulations, method of use, product derivatives, and processes are considered "secondary patents". Secondary patents are generally easier to circumvent ("to invent around"), meaning to make the medicine without infringing the secondary patents. For example, a patent on the aqueous solution would not prevent competitors to produce a tablet, and a combination patent would not prevent competitors to produce the combined products separately.

[3] Initially two additional candidate medicines were included in the project (faldaprevir and deleobuvir), but development of these has been discontinued and thus the patent landscapes were not finalized.

The following are different types of patents:

Product patents claim the chemical molecule/the active pharmaceutical ingredient. Product patents are usually the strongest patents as the patent holder can use product claims to prevent others from making, selling, or importing the chemical product.

Product-by-process patents define the product by its process of preparation.

Process patents claim a (new) production process for an active pharmaceutical ingredient.

Formulation patents relate to the specific dosage form (e.g. coated tablet, soft gel capsule, syrup etc.).

Combination patents claim the combination of new or existing medicines.

Patents on product derivatives claim a specific form or derivative, e.g. a salt of an existing compound.

Patents containing Markush claims refer to a chemical structure with multiple alternatives in a format such as "chemical compound A wherein X^1 is selected from a group consisting of a, b and c".

This list is simplified and not exhaustive. Detailed explanations can be found in Philip Grubb, Peter Thomsen, *Patents for Chemicals, Pharmaceuticals, and Biotechnology*, 5th Edition Oxford 2010 as well as in the patenting guidelines of the respective national or regional patent offices.

Interpretation of patentability criteria varies, in particular with respect to the so-called secondary patents. Some jurisdictions are more restrictive to prevent a proliferation of secondary patents covering minor modifications of existing medicines. In those jurisdictions, for example India and Argentina, many of the secondary patents may not be granted as they do not fulfil their specific requirements. Further information can be found in the draft *Guidelines for the examination of pharmaceutical patents: developing a public health perspective* which provides detailed information on the different forms of patents in the pharmaceutical sector (www.who.int/phi/publications/category/en/).

HOW TO USE THIS WORKING PAPER?

The working papers identify the relevant patents and provide data where these patents have been filed or granted. They allow countries to carry out a first assessment on whether a medicine is patent protected and to assess their possibilities for rendering the new treatments more affordable. The data is also essential to allow WHO to fulfil its mandate under Resolution WHA67.6 which requests WHO to assist Member States in ensuring equitable access to quality, effective, affordable and safe HCV treatments. Assisting countries in accessing the new hepatitis treatments at an affordable price requires knowledge about the patent situation in the respective jurisdictions as this determines the various options countries have.

The working papers can also help other interested parties to negotiate transfer of technology or license agreements, research ways to enhance or improve the current drug or treatment modality, and facilitate the development of generics.

Although being public domain information, patent information in many countries is difficult to retrieve, as is reflected by the gaps in the Annex. N/A indicates that no information could be retrieved for the relevant patents in the databases that were used in this working paper. This can either mean that the information in the databases is not up-to-date or complete, or that the patents were not filed in these jurisdictions. While the latter may often be the case, certainty can only be achieved by checking the information with the local patent office. This can be done by using the patent numbers provided in this report, as they allow retrieval of information through national patent offices and/or national patent registries. The following WIPO page provides links to all national online patent search tools to search national patent registries:

http://www.wipo.int/branddb/portal/portal.jsp

LIMITATIONS

While endeavours have been made to make the content of this study accessible to the non-expert, the highly technical nature of the subject matter and the singularities of the patent system require a certain expertise to make full use of this study.

This study sets out relevant patents and patent applications in the countries included in this study as of March 2014 (see the Annex). Every effort has been made to obtain comprehensive and accurate information, including on the legal status of the patents. However, in many countries patent information is not readily available or not updated on a regular basis. In addition, some patent applications may have been published only after the searches were conducted and thus may not be included in this study. As this study endeavours to identify the most relevant patents, it does not include the many additional patents and application filed by various entities that may also relate to the compound.

It should also be noted that this study is not a freedom-to-operate analysis. The information provides useful guidance, but only reflects the situation at a particular point in time. Neither WHO nor Thomson Reuters accept any responsibility for the accuracy of data, nor guarantee that it is complete or up-to-date. Users are advised, before taking any investment or other legally relevant decision, to consult a local patent expert to provide a full assessment of the patent situation in a given country.

METHODOLOGY

Relevant patents and patent applications were identified by searching patent and non-patent databases, comprising Thomson Innovation, Newport, Thomson Pharma, Questel, Scientific Technology Network (STN) and Cortellis. Additional bibliographic details were collected from publicly available databases, comprising the United States Patent and Trademark Office (USPTO), Espacenet and relevant national patent office websites.

Legal status and oppositions, if any, were retrieved from respective patent offices (to the extent that information was available). Patent Offices in Brazil, African Regional Intellectual Property Organization (ARIPO), India, Russian Federation, and Ukraine have been directly contacted.

Litigation data were retrieved from WestLaw, PACER, and pharma-related publicly available sources. The study differentiates between patents held by Sponsors and non-Sponsors. Sponsors are the entities developing the medicines and are filing for or already hold market authorization. Non-Sponsor entities include other pharmaceutical companies, public research institutes and other applicants. The patent position of the Sponsors is assessed. Patents of non-Sponsor entities are included in the complete data collection in form of an Excel file that can be made available on demand. Please send any requests to: phidepartment@who.int.

Wherever available, the application submitted under the WIPO PCT is used as a primary source, both because it is generally the favoured priority application for the pharmaceutical industry, and also because the WIPO International Search Report (ISR) include examiner references that are coded for relevance and for which initial rejections (an indicator of possible novelty issues) can be identified.

Thomson Reuters' technical experts analysed the claims and determined whether the scope of each of the claims are broad or narrow. Where available, the outcome of the WIPO ISR on novelty and inventive step is described. It should be noted that quotes from the ISR are only examples and do not preclude objections or outcomes under national jurisdictions.

The expected time of expiration for all the patents was calculated and can be found in the respective Annexes.

GEOGRAPHIC SCOPE

Family members of the Sponsor patent collection have been searched for in the following jurisdictions. It would have been beyond the scope of this study to include patent information of all WHO Member States, thus a selection was made taking into account disease burden, local manufacturing capacities and regional representation:

Argentina (AR), African Regional Intellectual Property Organization (AP), Australia (AU), Brazil (BR), Canada (CA), Chile (CL), China (CN), China, Hong Kong SAR (HK), Colombia (CO), Costa Rica (CR), Ecuador (EC), Egypt (EG), European Patent Office (EPO), Ethiopia (ET), Eurasian Patent Office (EAPO), Georgia (GE), India (IN), Indonesia (ID), Iran (Islamic Republic of) (IR), Israel, (IL), Japan, Jordan (JO), Malaysia (MY), Mexico (MX), Morocco (MA), New Zealand (NZ), Nigeria (NG), African Intellectual Property Organization (OA), Pakistan (PK), Patent Office of the Cooperation Council for the Arab States of the Gulf (GCC), Peru (PE), Philippines (PH), Republic of Korea (KR), Russian Federation (RU), Singapore (SG), South Africa (ZA), Thailand (TH), Tunisia (TN), Ukraine (UA), the United States of America (US), Uruguay (UY), and Viet Nam (VN).

FURTHER RESOURCES

The WHO publication *How to Conduct Patent Searches for Medicines: A Step-by-Step Guide* provides guidance on how to identify the patent status of medicines.[4]

The draft *Guidelines for the examination of pharmaceutical patents: developing a public health perspective* provides detailed information on the different forms of patents in the pharmaccutical sector.[5]

Information on the relationship between public health and intellectual property can be found in the document *Promoting Access to Medical Technologies and Innovation. Intersections between public health, intellectual property and trade.*[6]

These publications as well as other relevant publications on issues related to public health and intellectual property can be found here:
www.who.int/phi/publications/category/en/

More information on HCV and the recommended treatments can be found here: www.who.int/topics/hepatitis/en/

[4] How to Conduct Patent Searches for Medicines: A Step-by-Step Guide. Delhi: World Health Organization; 2010 (http://www.wpro.who.int/publications/PUB_9789290223757/en/, April 2014).
[5] Guidelines for the examination of pharmaceutical patents: developing a public health perspective. Geneva: World Health Organization; 2006 (http://apps.who.int/medicinedocs/documents/s21419en/s21419en.pdf, April 2014).
[6] Promoting Access to Medical Technologies and Innovation. Intersections between public health, intellectual property and trade. Geneva: World Health Organization, World Trade Organization, World Intellectual Property Organization; 2013. (http://www.who.int/phi/promoting_access_medical_innovation/en/, April 2014)

DACLATASVIR

Daclatasvir (formerly BMS-790052; tradename: Daklinza) is an investigational drug candidate for the treatment of HCV. It is being developed by Bristol-Myers Squibb (hereby *referred to as the 'Sponsor'*).

Daclatasvir belongs to a class of new directly acting antivirals that inhibit non-structural protein NS5A. It has been tested in combination regimens with pegylated interferon and ribavirin, as well as with other direct-acting antiviral agents including asunaprevir and sofosbuvir.[7] Bristol-Meyers Squibb filed for marketing approval for a combination therapy of daclatasvir and asunaprevir with the United States Food and Drug Administration (FDA) in early 2014. The FDA has granted the regimen Breakthrough Therapy Designation for use in the treatment of genotype 1b chronic HCV. Bristol-Meyers Squibb has also filed for marketing authorization in Europe for the use of daclatasvir in the treatment of adults with HCV. The European Medicines Agency approved daclatasvir in August 2014 in combination with other drugs for use across genotypes for the treatment of chronic hepatitis C virus infection in adults.[8]

CHEMICAL NAME

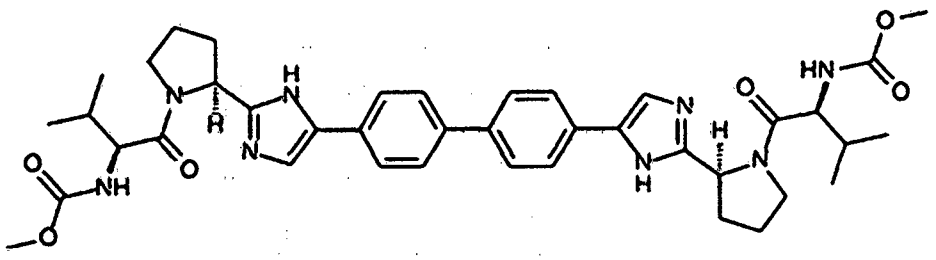
Systematic (IUPAC) name.

Methyl [(2*S*)-1-{(2*S*)-2-[4-(4'-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-2-pyrrolidinyl]-1*H*-imidazol-4-yl}-4-biphenylyl)-1*H*-imidazol-2-yl]-1-pyrrolidinyl}-3-methyl-1-oxo-2-butanyl]carbamate

MOLECULAR FORMULA

$C_{40}H_{50}N_8O_6$

MOLECULAR STRUCTURE



[7] http://www.hivandhepatitis.com/hepatitis-c/hepatitis-c-topics/hcv-treatment/3378-aasld-Daclatasvir-with-pegylated-interferonribavirin-produces-high-rates-of-hcv-suppression

[8] http://www.firstwordpharma.com/node/1231982#axzz3CFzwqvbl

SUMMARY

The search revealed patents filed with respect to daclatasvir by the Sponsor.

The daclatasvir Sponsor patent collection comprises 8 different patents (patent families) with 129 family members published in 33 jurisdictions. The majority of these patent applications are still pending in the respective national and regional patent offices, 42 patents are granted, (see Patents 1 to 8 in the Annex).

Patent 1 is the primary patent claiming the base compound through a Markush claim, along with various substituents. Where granted, this patent can serve to prevent competitors from making daclatasvir.

Patent 2 is covering a process to make daclatasvir and thus if granted will require competitors to design around this patent and use other production processes. The chemical product itself is not protected.

Patent 3 claims specific derivatives of daclatasvir. Seeking subsequent patents on derivatives of existing drugs is a common strategy of companies (i.e., obtaining multiple patents that cover various aspects of the same product).

Patent 4 is a formulation patent, claiming the pharmaceutical dosage form (pharmaceutical composition).

Patents 5, 7 and 8 claim daclatasvir for the use in combination therapy with other HCV protease inhibitors. Co-administration of known drugs can have a synergistic effect in treating a disease and therefore provides an advantage over a single-agent therapy.

Patent 6 is a method patent for the screening of NS5A-targeting compounds to inhibit HCV replication.

There is competition and patents on daclatasvir have been filed by six non-Sponsor entities and one individual inventor.

Note: The search also revealed two patents that are relevant for all seven reports. Patent applications WO2013059630A1 and WO2013059638A1 inter alia claim the use of combinations of unnamed direct-acting antiviral agents for treating HCV, where the treatment does not include administration of interferon or ribavirin, and the treatment lasts between 8-12 weeks. The description and the dataset for these two patents can be found in the Working Paper on ombitasvir (Patents No 3 and 4). These patents are in litigation. Detailed information can be found in the Working Paper on sofosbuvir under Patent No 2.

DACLATASVIR PATENT SITUATION

SPONSOR PATENTS

Patent searches revealed eight Sponsor patents (referred to as Patent 1 to 8 in the following analysis section and in the Annex).

Patent 1 is the primary patent, claiming the base compound. Patents 2 to 8 are secondary patents, claiming formulation, method of use, process, product derivatives, or method for identifying NS5A-targeting compounds. All patents were filed and remain in the name of Sponsor entity Bristol-Myers Squibb.

PATENT 1

Patent application WO2008021927A2 discloses the base compound of daclatasvir (primary patent). The patent claims a general structural formula of the basic compound along with various substituents. This patent, if granted, serves as a blocking patent preventing competitors from making the product. Also disclosed are their salts, pharmaceutical compositions and combinations containing such compounds and methods for using these compounds in the treatment of HCV infection.

As per the WIPO ISR, the patent application is novel and not obvious in comparison to the closest prior art retrieved during the search. The application relates to biphenyl-imidazole compounds which inhibit HCV replication or inhibit the NS5A protein. According to the report, the novelty of the present invention resides in the saturated N-containing rings depicted in the claimed structure.

Prosecution at the USTPO

There are four patents granted in the United States: US8303944B2, US8329159B2, US8574563B2, and US8642025B2. US8303944B2 is a continuation-in-part of US8329159B2. It relates to substituted imidazole compounds and their salts. US8574563B2 is a divisional of US8303944B2 and continuation-in-part of US8329159B2. It relates to imidazole substituted biphenyl derivatives or their salts for the treatment of HCV infection. US8642025B2 is a continuation application of US8329159B2. It relates to biphenyl-imidazole compounds which inhibit HCV replication or inhibit the NS5A protein.

There are no litigation or opposition procedures reported.

PATENT 2

Patent application WO2009020825A1 is a process patent. The patent claims a process for the preparation of antiviral compounds or a pharmaceutically acceptable salt, describing a specific reaction and deprotection process of diacetylbiphenyl. The process is stated to provide an efficient large-scale synthesis of the antiviral compounds. The claims are broad

and cover a set of compounds specifically synthesized by the claimed process, therefore limiting the application of the process to these specific compounds only.

As per the WIPO ISR, the patent application is novel and not obvious in comparison to the closest prior art retrieved during the search.

As per the available legal status information (details available in the Annex):

- The patent has been granted in Australia, China, Hong Kong SAR, the EAPO, the EPO, Japan, and the United States.
- The patent (or a related patent thereof) is pending in Argentina, Canada, China, India, Japan, and Republic of Korea.
- Legal status is not available for Colombia and Mexico

There are no litigation or opposition procedures reported.

PATENT 3

Patent application WO2008021928A2 claims specific daclatasvir derivatives and their salts. The compounds include a core structure consisting of six directly linked systems. The claims are very broad, covering a Markush structure of the antiviral agents.

As per the WIPO ISR, the patent application is novel and not obvious in comparison to the closest prior art retrieved during the search. Though the prior art discloses similar compounds, the novelty lies in the core structure consisting of six directly linked core systems claimed.

As per the available information (details available in the Annex):

- The patent has been granted in Australia, China, Hong Kong SAR, the EAPO, the EPO, Israel, New Zealand, Singapore, and the United States.
- The patent is pending in Brazil, Canada, China, India, and Republic of Korea.
- Legal status is not available for Japan, and Mexico.

There are no litigation or opposition procedures reported.

PATENT 4

Patent application WO2009020828A1 claims new crystalline forms of substituted imidazole compounds, their composition and use in the treatment of HCV infection, comprising administration of a therapeutically-effective amount of a crystalline form of the compound to a patient. The claimed crystalline forms are subject to limitations of cell structure dimensions, temperature, and other structural parameters.

As per the WIPO ISR, the patent application is novel and not obvious in comparison to the closest prior art retrieved during the search. However, the report concludes that although it

claims compounds for HCV treatment, the specific compound claimed in the present application is not disclosed.

As per the available information (details available in the Annex):

- The patent has been granted in Australia, China, as well as China, Hong Kong SAR, the EAPO, New Zealand, Singapore, South Africa, and the United States.
- The patent is pending in Argentina, Canada, Israel, India, and Republic of Korea.
- An EPO patent EP2183244B1 ceased on 28 February 2014.
- Legal status is not available for Colombia, Egypt, Japan, Mexico, and Peru.

There are no litigation or opposition procedures reported.

PATENT 5

Patent application WO2011046811A1 is a formulation patent disclosing a combination of daclatasvir and a HCV NS3 protease inhibitor, asunaprevir. The application claims compositions thereof, exhibiting synergistic activity in the treatment of HCV infection. It is further claimed that the compositions may be administered in combination with an additional anti-HCV agent, preferably interferon or ribavirin.

As the composition claims a combination of two known compounds without claiming any substituent, the scope of the claims narrows down to only the combination of the claimed compounds.

As per the WIPO ISR, the patent application is novel but lacks an inventive step. Lack of inventive step relates to the synergetic combination claimed in the present invention, and according to the ISR, this is obvious from existing prior art.

As per the available information (details available in the Annex):

- The patent has been granted in New Zealand and the United States.
- The patent (or a related patent thereof) is pending in Australia, Canada, China, as well as China, Hong Kong SAR, the EPO, India, Israel, Japan, Republic of Korea, Singapore, South Africa, Thailand, and the United States.
- Legal status is not available for the EAPO, Mexico, Peru, Philippines, and Viet Nam.

There are no litigation or opposition procedures reported.

PATENT 6

Patent application WO2012009394A2 is a method patent for the screening of NS5A-targeting compounds to inhibit HCV replication. The invention is based on the finding that pairs of HCV NS5A-targeting inhibitors can be identified which display similar resistance profiles yet, when combined, exhibit synergistic inhibition of HCV wild type replicons and/or HCV replicons carrying mutations conferring resistance to the HCV NS5A-targeting inhibitor.

In addition, combinations of these molecules result in a higher genetic barrier to resistance, demonstrating their potential utility as novel combination therapies for treatment of HCV. As the application claims a general methodology of screening and testing the combinations, the claims have a broader scope.

As per the WIPO ISR, the invention is novel but lacks an inventive step. Thus the present invention is considered to be obvious over cited non-patent prior art.

As per the available information (details available in the Annex):

- The patent has not been granted yet, and is pending at the EPO and the United States.

There are no litigation or opposition procedures reported.

PATENT 7

Patent application WO2012018829A1 is another formulation patent, claiming a formulation comprising one or two HCV polymerase inhibitors and a pharmaceutically acceptable carrier. The composition shows synergistic effect, effectively inhibits HCV, achieves maximum efficacy, and potentially eradicates the HCV. Combinations comprise a HCV NS5A inhibitor, e.g. daclatasvir, a HCV NS3 inhibitor, e.g. asunaprevir, and a HCV NS5B inhibitor (compound of formula 3). As the claimed composition is a combination of one or two compounds without claiming any substituents in the claimed structure, the scope of the claims narrows down to only the claimed set of compounds.

As per the WIPO ISR, the patent application lacks novelty and is obvious in comparison to the closest prior art retrieved during the search.

As per the available information (details available in the Annex):

- The patent has not been granted yet, and is pending in Australia, Canada, China, as well as China, Hong Kong SAR, the EPO, Israel, Republic of Korea, Singapore, and the United States.
- Legal status is not available for the EAPO, Japan, and Mexico.

There are no litigation or opposition procedures reported.

PATENT 8

Patent application WO2013106520A1 is another formulation patent. The claimed formulation comprises a combination of an NS5A-targeting compound and a NS5A synergist, which provides synergistic anti-HCV activity against variants that contain mutation(s) conferring resistance to the NS5A-targeting compound alone. It is claimed that combinations may be used with additional compounds such as interferon or ribavirin.

As per the WIPO ISR, the patent application lacks novelty and is obvious in comparison to closest prior art retrieved during the search, including patent and non-patent publications which disclose combinations of compounds which can inhibit HCV.

As per the available information (details available in the Annex):

- The patent has not been granted yet, and is pending in the United States (ready for examination).
- Legal status is not available for Uruguay.

NON-SPONSOR PATENTS

There is competition, and patents on daclatasvir have been filed by six non-Sponsor entities and one individual inventor.

- AbbVie Inc.
- Boehringer Ingelheim GmbH
- Catabasis Pharmaceuticals
- INSERM
- Instituto di Ricerche di Biologia Molecolare Pietro Angeletti / Merck Sharp & Dohme Corp.
- Santaris Pharma

A total of eleven inventions (patent families) are counted, including method of use, formulation and product patents.

Patents of non-Sponsor entities are included in the complete data collection in form of an Excel file that can be made available on demand. Please send any requests to: phidepartment@who.int.

ANNEX - DACLATASVIR PATENT SITUATION

	Patent 1	Patent 2	Patent 3	Patent 4	Patent 5	Patent 6	Patent 7	Patent 8
Subject Matter	Patent application WO2008021927 covers the base *compound of* daclatasvir.	Patent application WO2009020825 covers a process for synthesizing daclatasvir for the treatment of HCV.	Patent application WO2008021928 covers a novel HCV inhibitor or *its salts useful for* the treatment of HCV infection.	Patent application WO2009020828 covers crystalline *forms of* daclatasvir.	Patent application WO2011046811 covers a formulation comprising a *combination of* daclatasvir and asunaprevir.	Patent application WO2012009394 is related to the method of *identifying* NS5A-targeting compounds.	Patent application WO2012018829 covers a formulation comprising one or two HCV polymerase inhibitors.	Patent application WO2013106520 covers a formulation comprising a *combination which* provides synergistic anti-HCV activity.
Applicant	*Bristol-Myers* Squibb Co.	*Bristol-Myers* Squibb Co.	*Bristol-Myers* Squibb Co.	*Bristol-Myers* Squibb Co.	*Bristol-Myers* Squibb Co.	*Bristol-Myers* Squibb Co.	*Bristol-Myers* Squibb Co.	*Bristol-Myers* Squibb Co.
Int'l Patent Publication Number	WO2008021927	WO2009020825	WO2008021928	WO2009020828	WO2011046811	WO2012009394	WO2012018829	WO2013106520
Priority Number	US2006836996P	US2007954595P	US2006836999P	US2007954592P	US2009250648P	US2010364851P	US2010371399P	US2012586558P
Expected expiry[1]	8 Aug 2027	30 Jul 2028	8 Aug 2027	30 Jul 2028	7 Oct 2030	12 Jul 2031	1 Aug 2031	9 Jan 2033
PATENT STATUS								
ARIPO (AP)[2]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Argentina (AR)	Pending Pub No: AR63684A1	Pending Pub No: AR67896A1	N/A	Pending Pub No: AR070016A1	N/A	N/A	N/A	N/A
Australia (AU)	Granted Pub No: AU2007286222B2	Granted Pub No: AU2008284097B2	Granted Pub No: AU2007286223B2	Granted Pub No: AU2008284100B2	Pending Pub No: AU2010307144A1	N/A	Pending Pub No: AU2011285890A1	N/A
Brazil (BR)	N/A	N/A	Pending Pub No: BRPI0716220	N/A	N/A	N/A	N/A	N/A

	Patent 1	Patent 2	Patent 3	Patent 4	Patent 5	Patent 6	Patent 7	Patent 8
Canada (CA)	Pending Pub No: CA2660520A1	Pending Pub No: CA2695711A1	Pending Pub No: CA2660628A1	Pending Pub No: CA2695729A1	Pending Pub No: CA2777560A1	N/A	Pending Pub No: CA2807589A1	N/A
Chile (CL)	Pending Pub No: CL23272007A1	N/A	N/A	N/A	N/A	N/A	N/A	N/A
China (CN)	Pending Pub No: CN101558059A	Pending Pub No: CN101778841A	Pending Pub No: CN101528232A	Granted Pub No: CN101778840B	Pending Pub No: CN102655873A	N/A	Pending Pub No: CN103153280A	N/A
China, Hong Kong SAR (HK)	N/A	Granted Pub No: HK1137454A1	Granted Pub No: HK1125576A1	Granted Pub No: HK1144089A1	Pending Pub No: HK1172237A0	N/A	Pending Pub No: HK1180211A0	N/A
Colombia (CO)	Status: N/A Pub No: CO6150171A2	Status: N/A Pub No: CO6251317A2	N/A	Status: N/A Pub No: CO6160327A2	N/A	N/A	N/A	N/A
Costa Rica (CR)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Ecuador (EC)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Egypt (EG)	N/A	N/A	N/A	Status: N/A Pub No: EG2010020177	N/A	N/A	N/A	N/A
Ethiopia (ET)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
EAPO (EA)[3]	Granted Pub No: EA15756B1	Granted Pub No: EA17173B1	Granted Pub No: EA17348B1	Granted Pub No: EA018152B1	Status: N/A Pub No: EA201270555A1	N/A	Status: N/A Pub No: EA201390155A1	N/A
EPO (EP)[4]	Pending Pub No: EP2049522A2 Withdrawn Pub No: EP2385048A1	Granted Pub No: EP2178863B1	Granted Pub No: EP2049116B1	Ceased Pub No: EP2183244B1	Pending Pub No: EP2488192A1	Pending Pub No: EP2593565A2	Pending Pub No: EP2600835A1	N/A
GCC[5]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Georgia (GE)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

	Patent 1	Patent 2	Patent 3	Patent 4	Patent 5	Patent 6	Patent 7	Patent 8
India (IN)	Pending Pub No: IN200900853P1 Indian National Patent Number: 853/DELNP/2009	Pending Pub No: IN201000854P1 Indian National Patent Number: 854/DELNP/2010	Pending Pub No: IN200900753P1 Indian National Patent Number: 753/DELNP/2009	Pending Pub No: IN201000806P1 Indian National Patent Number: 806DELNP/2010	Pending Pub No: IN201203372P1 Indian National Patent Number: 3372/CHENP/2012	N/A	N/A	N/A
Indonesia (ID)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Iran (Islamic Republic of) (IR)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Israel (IL)	Granted Pub No: IL196813A	N/A	Granted Pub No: IL196815A	Pending Pub No: IL203684	Pending Pub No: IL219123	N/A	Pending Pub No: IL224369	N/A
Japan (JP)	Granted Pub No: JP05235882B2 Pending Pub No: JP2013151535A	Granted Pub No: JP05324574B2 Pending Pub No: JP2013231072A	Status: N/A Pub No: JP05306203B2	Status: N/A Pub No: JP05244179B2	Pending Pub No: JP2013507439A	N/A	Status: N/A Pub No: JP2013535487A	N/A
Jordan (JO)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Malaysia (MY)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Mexico (MX)	Status: N/A Pub No: MX2009001426A	Status: N/A Pub No: MX290356B	Status: N/A Pub No: MX283096B	Status: N/A Pub No: MX307552B	Status: N/A Pub No: MX2012003835A	N/A	Status: N/A Pub No: MX2013001170A	N/A
Morocco (MA)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
New Zealand (NZ)	Granted Pub No: NZ574805A	N/A	Granted Pub No: NZ574769A	Granted Pub No: NZ583148A	Granted Pub No: NZ599284A	N/A	N/A	N/A
Nigeria (NG)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
OAPI[6]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

	Patent 1	Patent 2	Patent 3	Patent 4	Patent 5	Patent 6	Patent 7	Patent 8
Pakistan (PK)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Peru (PE)	Status: N/A Pub No: PE20080542A1	N/A	N/A	Status: N/A Pub No: PE09402009A1	Status: N/A Pub No: PE14322012A1	N/A	N/A	N/A
Philippines (PH)	N/A	N/A	N/A	N/A	Status: N/A Pub No: PH12012500571A1	N/A	N/A	N/A
Republic of Korea (KR)	Pending Pub No: KR2009040909A	Pending Pub No: KR2010045992A	Pending Pub No: KR2009040910A	Pending Pub No: KR20100042641A	Pending Pub No: KR2012088743A	N/A	Pending Pub No: KR2014002611A	N/A
Russian Federation (RU)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Singapore (SG)	N/A	N/A	Granted Pub No: SG150105B	Granted Pub No: SG159059B	Pending Pub No: SG179814A1	N/A	Pending Pub No: SG187193A1	N/A
South Africa (ZA)	Granted Pub No: ZA200900962A	N/A	Granted Pub No: ZA200900935	Granted Pub No: ZA201000843A	Granted Pub No: ZA201203451A	N/A	N/A	N/A
Thailand (TH)	N/A	N/A	N/A	N/A	Pending Pub No: TH1201001642	N/A	N/A	N/A
Tunisia (TN)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Ukraine (UA)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

	Patent 1	Patent 2	Patent 3	Patent 4	Patent 5	Patent 6	Patent 7	Patent 8
The United States (US)	Abandoned Pub No: US20100158862A1 Abandoned Pub No: US20110268697A1 Granted Pub No: US201300345201 Granted Pub No: US8303944B2 Granted Pub No: US8329159B2 Granted Pub No: US8574563B2	Granted Pub No: US7728027B2	Granted Pub No: US7659270B2	Granted Pub No: US8629171B2	Pending Pub No: US20130259832A1 Granted Pub No: US8415374B2	Pending Pub No: US20130157894A1	Pending Pub No: US20120196794A1	Pending Pub No: US20130183269A1
Uruguay (UY)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Status: N/A Pub No: UY34570A
Viet Nam (VN)	N/A	N/A	N/A	N/A	Status: N/A Pub No: VN31028A	N/A	N/A	N/A

[1] If granted and not subject to patent term extension.

[2] **The African Regional Intellectual Property Organization (ARIPO) includes the following countries:** Botswana, Ghana, Gambia, Kenya, Liberia, Lesotho, Malawi, Mozambique, Namibia, Sudan, Sierra Leone, Swaziland, the United Republic of Tanzania, Uganda, Zambia and Zimbabwe.

[3] **The Eurasian Patent Organization (EAPO) includes the following countries:** Armenia, Azerbaijan, Belarus, Kazakhstan, Kyrgyzstan, Russian Federation, Tajikistan and Turkmenistan.

[4] **The European Patent Office (EPO) includes the following countries:** Albania, Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Iceland, Italy, Liechtenstein, Lithuania, Luxemburg, Latvia, Malta, Monaco, Netherlands, Norway, Poland, Portugal, Romania, San Marino, Serbia, Slovenia, Slovakia, Spain, Sweden, Switzerland, The former Yugoslav Republic of Macedonia, Turkey and the United Kingdom.

[5] **The Patent Office of the Cooperation Council for the Arab States of the Gulf (Gulf Cooperation Council - GCC) includes the following countries:** Bahrain, Kuwait, Oman, Qatar, Saudi Arabia and United Arab Emirates.

[6] **The African Intellectual Property Organization (OAPI) includes the following countries:** Benin, Burkina Faso, Cameroon, Central African Republic, Chad, The Congo, Equatorial Guinea, Gabon, Guinea, Guinea Bissau, Côte d'Ivoire, Mali, Mauritania, Niger, Senegal and Togo.

GLOSSARY

INTERFERENCE PROCEEDING: An interference proceeding is a proceeding to determine the priority issues of multiple patent applications. Based on the (previous) first-to-invent system of the United States, a party which has failed to file a patent application on time is allowed to challenge the inventorship of another party which has a granted or pending patent.

N/A: Patent information was not available for this country at the time the patent searches were conducted, in March 2014.

NOTICE OF ALLOWANCE: During a USTPO examination, if it appears to the examiner that the applicant is entitled to a patent under the law, a notice of allowance is sent to the applicant. The notice of allowance specifies a sum constituting the issue fee which must be paid within a given time from the date of mailing of the notice of allowance to avoid abandonment of the application.

PATENT FAMILY MEMBER: All patent publications that relate to the same basic patent (that is, invention) are members of this patent family. In the present study patent families are based on the Derwent World Patent Index (DWPI).

PENDING or GRANTED: Indicates a patent's legal status.

PRIORITY NO: Earliest application number.

PUB NO: Patent publication number.

SPONSOR: The term "Sponsor" refers to the entities that are developing the medicines and are holding or filing for market authorization. Note that a Sponsor is not necessarily the patent assignee or applicant.

THE WIPO INTERNATIONAL SEARCH REPORT (ISR): After an applicant files a PCT application with WIPO, a search is conducted by an authorised International Searching Authority (ISA) to find the most relevant prior art documents regarding the claimed subject matter. The search results in an International Search Report (ISR), together with a written opinion regarding patentability.

IN THE MATTER OF

Indian Patent Application 853/DELNP/2009

In the name of

BRISTOL-MYERS SQUIBB COMPANY

AND IN THE MATTER OF

A pre-grant representation by

DALVIR SINGH

D3 – print out from website of Applicants'

Bristol-Myers Squibb

Bristol-Myers Squibb Receives Complete Response Letter from U.S. Food and Drug Administration for Daclatasvir, an Investigational Treatment for Hepatitis C

Wednesday, November 26, 2014 11:34 am EST

PRINCETON, N.J.--(BUSINESS WIRE)--Bristol-Myers Squibb Company (NYSE:BMY) today announced that the U.S. Food and Drug Administration (FDA) has issued a Complete Response Letter (CRL) regarding the New Drug Application (NDA) for daclatasvir, an NS5A complex inhibitor, in combination with other agents for the treatment of hepatitis C (HCV).

"Despite the recent advances in the treatment of hepatitis C there remain significant areas of unmet high need in this disease area"

The initial daclatasvir NDA submitted to the FDA focused on its use in combination with asunaprevir, an NS3/4A protease inhibitor. Given the withdrawal of asunaprevir by Bristol-Myers Squibb in October, the FDA is requesting additional data for daclatasvir in combination with other antiviral agents for the treatment of HCV. Bristol-Myers Squibb is in discussions with the FDA about the scope of these data.

"Despite the recent advances in the treatment of hepatitis C there remain significant areas of unmet high need in this disease area," said Francis Cuss, Executive Vice President and Chief Scientific Officer, R&D, Bristol-Myers Squibb. "Our commitment remains to make daclatasvir-based regimens available to help these difficult-to-treat patients achieve cure, and we will continue to collaborate with the FDA to bring daclatasvir to patients in the U.S. as quickly as possible."

Ongoing Daclatasvir Clinical Development

Bristol-Myers Squibb is dedicated to the ongoing clinical development program for daclatasvir, a potent, pan-genotypic NS5A complex inhibitor (*in vitro*), which is currently being investigated globally in multiple treatment regimens for HCV patients with high unmet need. The company continues to progress its daclatasvir clinical trial program focused on difficult-to-treat patients, including pre- and post-liver transplant (ALLY-1), HCV patients co-infected with HIV (ALLY-2) and patients with genotype 3 (ALLY-3). The Phase 3 UNITY studies investigating Bristol-Myers Squibb's investigational all-oral fixed-dose-combination DCV-TRIO regimen (daclatasvir/asunaprevir/beclabuvir) are also ongoing and include study populations of non-cirrhotic naïve, cirrhotic naïve and previously treated patients.

About Bristol-Myers Squibb

Bristol-Myers Squibb is a global biopharmaceutical company whose mission is to discover, develop and deliver innovative medicines that help patients prevail over serious diseases. For more information, please visit http://www.bms.com or follow us on Twitter at http://twitter.com/bmsnews.

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Business Wire NewsHQ

IN THE MATTER OF

Indian Patent Application 853/DELNP/2009

In the name of

BRISTOL-MYERS SQUIBB COMPANY

AND IN THE MATTER OF

A pre-grant representation by

DALVIR SINGH

D4 – IN 806/DELP/2010

8016 DELNP 2011 ORIGINAL 160

FORM 1 THE PATENTS ACT, 1970 [39 OF 1970] & THE PATENTS (AMENDMENT) RULES, 2006 APPLICATION FOR GRANT OF PATENT [See Sections 7, 135 and rule 20 (1)]	Application No: Filing date: Amount of Fee paid: Received Rs 7,600/- Cheque / M.O./I.P.O. / DD on CBR No. Signature: 08 FEB 2010 Vide Entry No. 1030 in the Register of Valuables Cashier

1. APPLICANT (S)

Name	Nationality	Address
BRISTOL-MYERS SQUIBB COMPANY,	a corporation of the State of Delaware,	Route 206 and Province Line Road, Princeton, New Jersey 08543, United States of America,

2. INVENTOR (S)

Name	Nationality	Address
SOOJIN KIM,	a US citizen,	23 Country Club Way, Demarest, New Jersey 07627, USA,
QI GAO,	a US citizen,	c/o Bristol-Myers Squibb Company, 1 Squibb Drive, New Brunswick, New Jersey 08903, USA,
FUKANG YANG,	a Chinese citizen,	c/o Bristol-Myers Squibb Company, 5 Research Parkway, Wallingford, CT 06492, USA,

3. TITLE OF THE INVENTION

"CRYSTALLINE FORM OF METHYL ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((METHOXYCARBONYL)AMINO)-3-METHYLBUTANOYL)-2-PYRROLIDINYL)-1H-IMIDAZOL-5-YL)-4-BIPHENYLYL)-1H-IMIDAZOL-2-YL)-1-PYRROLIDINYL)CARBONYL)-2-METHYLPROPYL)CARBAMATE DIHYDROCHLORIDE SALT"

4. ADDRESS FOR CORRESPONDENCE OF APPLICANT/ AUTHORISED PATENT AGENT IN INDIA

REMFRY & SAGAR
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Millennium Plaza
Sector 27, Gurgaon 122 002,
India. - Telephone No. 91-124-280-6100
Telefax No. 91-124-280 6101

5. PRIORITY PARTICULARS OF THE APPLICATION (S) FILED IN CONVENTION COUNTRY

Country	Application Number	Filing Date	Name of the applicant	Title of the invention
U.S.A.	60/954,592	08/08/2007	SOOJIN KIM, QI GAO and FUKANG	"CRYSTALLINE FORM OF METHYL ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-

			YANG	((METHOXYCARBONYL)AMINO)-3-METHYLBUTANOYL)-2-PYRROLIDINYL)-1H-IMIDAZOL-5-YL)-4-BIPHENYLYL)-1H-IMIDAZOL-2-YL)-1-PYRROLIDINYL)CARBONYL)-2-METHYLPROPYL)CARBAMATE DIHYDROCHLORIDE` SALT"

6. PARTICULARS FOR FILING PATENT COOPERATION TREATY (PCT) NATIONAL PHASE APPLICATION

PCT/US2008/071734	31/07/2008

7. DECLARATIONS:

i) Declaration by the applicant(s) in the convention country

I/We, SOOJIN KIM, a US citizen, of 23 Country Club Way, Demarest, New Jersey 07627, USA, QI GAO, a US citizen, c/o Bristol-Myers Squibb Company, 1 Squibb Drive, New Brunswick, New Jersey 08903, USA and FUKANG YANG, a Chinese citizen, c/o Bristol-Myers Squibb Company, 5 Research Parkway, Wallingford, CT 06492, USA, the applicant(s) in the convention country declare that the applicant(s) herein is/are my/our assignee or legal representative.

SOOJIN KIM, QI GAO, FUKANG YANG,

ii) Declaration by the applicant(s):

I/We, the applicant(s) hereby declare(s) that:-

- I am/we are in possession of the above-mentioned invention
- The complete specification relating to the invention is filed with this application.
- There is no lawful ground of objection to the grant of the Patent to me/us.
- The application or each of the applications, particulars of which are given in Para 5 was the first application in convention country/countries in respect of my/our invention.
- I/we claim the priority from the above mentioned application(s) filed in convention country/countries and state that no application for protection in respect of the invention had been made in a convention country before that date by me/us or by any person from which I/we derive the title.
- My/our application in India is based on International application under Patent Cooperation Treaty (PCT) as mentioned in Para-6.

Following are the attachment with the application:

(a) Complete specification in conformation with the International application/as amended before the International Preliminary Examination Authority (IPEA), as applicable (2 copies), No. of pages 44 No. of claims 20.

[b] Drawing(s) in conformation with the international application/as amended before the International Preliminary Examination Authority (IPEA), as applicable (2 copies), No. of sheets (3).

[c] Statement and undertaking on Form 3

[d] Declaration of inventorship on Form 5

[e] Fee Rs. 17600/- by cheque

I/We hereby declare that to the best of my/our knowledge, information and belief the fact

and matters stated herein are correct and I/we request that a patent may be granted to me/us for the said invention.

Dated this 05/02/2010

BRISTOL-MYERS SQUIBB COMPANY,

(HRISHIKESH RAY CHAUDHURY)
OF REMFRY & SAGAR
ATTORNEY FOR THE APPLICANT[S]

THE CONTROLLER OF PATENTS,
THE PATENT OFFICE, DELHI

FORM 2
THE PATENTS ACT 1970
[39 OF 1970]
&
THE PATENTS (AMENDMENT) RULES, 2006
COMPLETE SPECIFICATION

[See Section 10; rule 13]

"CRYSTALLINE FORM OF METHYL ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((METHOXYCARBONYL)AMINO)-3-METHYLBUTANOYL)-2-PYRROLIDINYL)-1H-IMIDAZOL-5-YL)-4-BIPHENYLYL)-1H-IMIDAZOL-2-YL)-1-PYRROLIDINYL)CARBONYL)-2-METHYLPROPYL)CARBAMATE DIHYDROCHLORIDE SALT"

BRISTOL-MYERS SQUIBB COMPANY, a corporation of the State of Delaware, of Route 206 and Province Line Road, Princeton, New Jersey 08543, United States of America,

The following specification particularly describes the invention and the manner in which it is to be performed:

CRYSTALLINE FORM OF METHYL ((1*S*)-1-(((2*S*)-2-(5-(4'-(2-((2*S*)-1-((2*S*)-2-((METHOXYCARBONYL)AMINO)-3-METHYLBUTANOYL)-2-PYRROLIDINYL)-1*H*-IMIDAZOL-5-YL)-4-BIPHENYLYL)-1*H*-IMIDAZOL-2-YL)-1-PYRROLIDINYL)CARBONYL)-2-METHYLPROPYL)CARBAMATE DIHYDROCHLORIDE SALT

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S Provisional Application Serial Number 60/954,592 filed August 8, 2007.

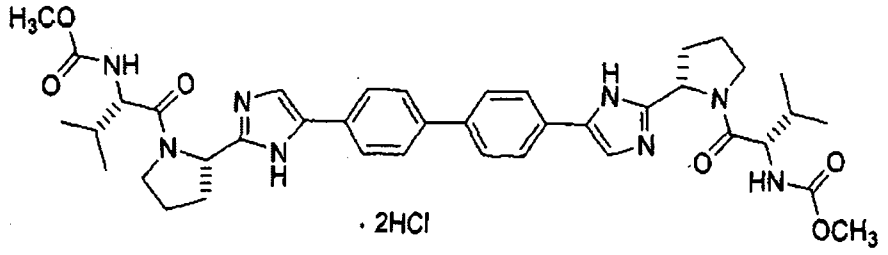
The present disclosure generally relates to a crystalline form of methyl ((1*S*)-1-(((2*S*)-2-(5-(4'-(2-((2*S*)-1-((2*S*)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1*H*-imidazol-5-yl)-4-biphenylyl)-1*H*-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate dihydrochloride salt. The present disclosure also generally relates to a pharmaceutical composition comprising a crystalline form, as well of methods of using a crystalline form in the treatment of Hepatitis C virus (HCV) and methods for obtaining such crystalline form.

Hepatitis C virus (HCV) is a major human pathogen, infecting an estimated 170 million persons worldwide - roughly five times the number infected by human immunodeficiency virus type 1. A substantial fraction of these HCV infected individuals develop serious progressive liver disease, including cirrhosis and hepatocellular carcinoma.

Presently, the most effective HCV therapy employs a combination of alpha-interferon and ribavirin, leading to sustained efficacy in 40 percent of patients. Recent clinical results demonstrate that pegylated alpha-interferon is superior to unmodified alpha-interferon as monotherapy. However, even with experimental therapeutic regimens involving combinations of pegylated alpha-interferon and ribavirin, a substantial fraction of patients do not have a sustained reduction in viral load. Thus, there is a clear and unmet need to develop effective therapeutics for treatment of HCV infection.

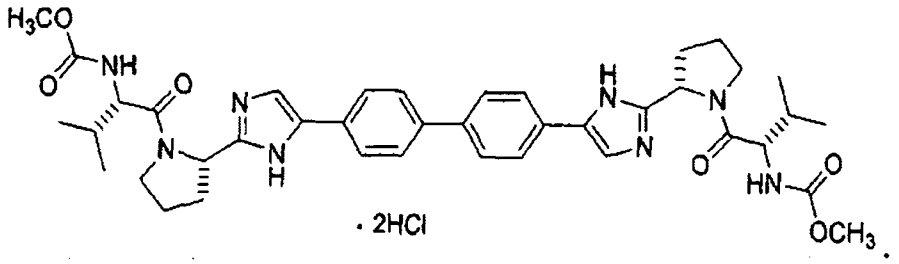
The compound methyl ((1*S*)-1-(((2*S*)-2-(5-(4'-(2-((2*S*)-1-((2*S*)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1*H*-imidazol-5-yl)-4-

biphenylyl)-1*H*-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate is useful for the treatment of HCV infection. Due to the difficulty in crystallizing this compound, formation of pure product has not been reproducible. It has been found that the dihydrochloride salt, represented by formula (I) and herein referred to as Compound (I), can be repeatedly crystallized into one particular polymorph, herein referred to as Form N-2, that offers high aqueous solubility and excellent purification capacity.

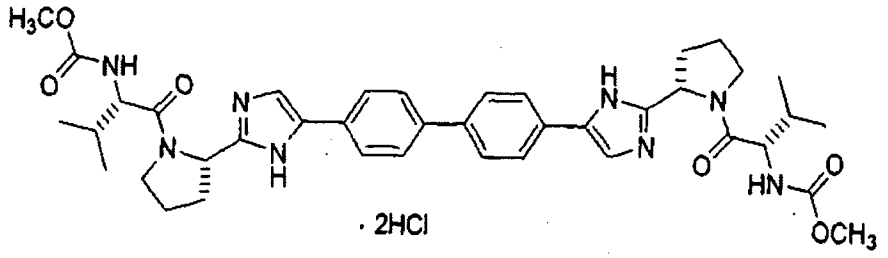


Compound (I)

In its first aspect the present disclosure provides Form N-2 of



In a second aspect the present disclosure provides Form N-2 of



characterized by the following unit cell parameters:

Cell dimensions: a = 7.5680 Å

b= 9.5848 Å

c = 16.2864 Å

α = 74.132 degrees

β = 84.132 degrees

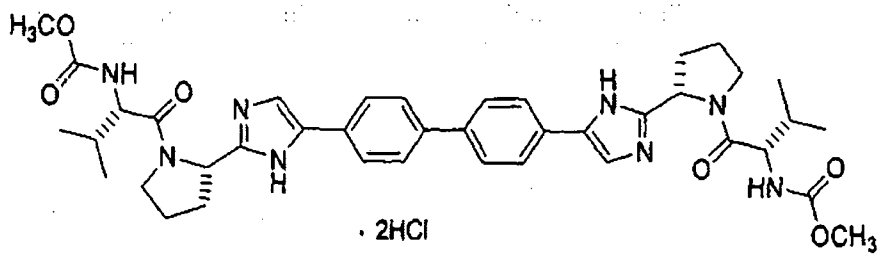
γ = 70.646 degrees

Space group P1

Molecules/unit cell 1

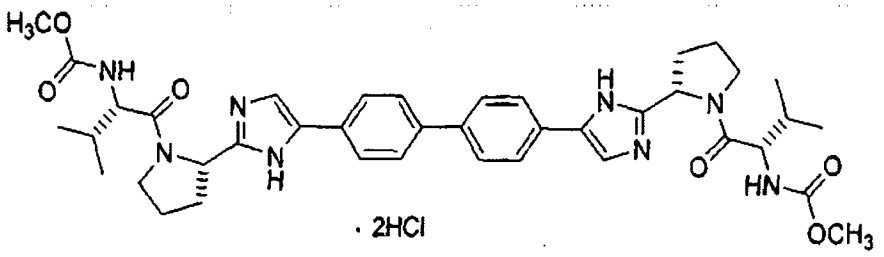
wherein measurement of said crystalline form is at a temperature between about 20 °C to about 25 °C.

In a third aspect the present disclosure provides Form N-2 of



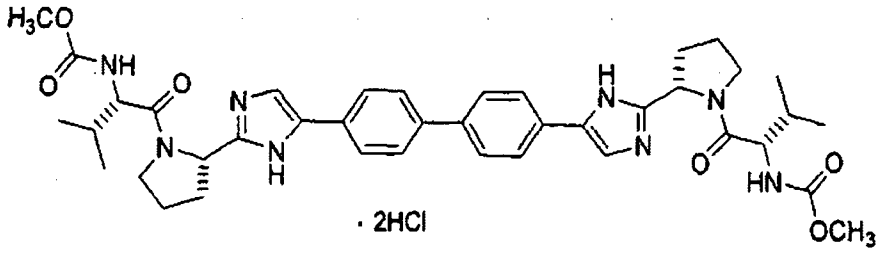
characterized by fractional atomic coordinates within the unit cell as listed in Table 3.

In a fourth aspect the present disclosure provides Form N-2 of



with characteristic peaks in the powder X-Ray diffraction pattern at values of two theta of 10.3 ± 0.1, 12.4 ± 0.1, 12.8 ± 0.1, 13.3 ± 0.1, 13.6 ± 0.1, 15.5 ± 0.1, 20.3 ± 0.1, 21.2 ± 0.1, 22.4 ± 0.1, 22.7 ± 0.1, and 23.7 ± 0.1 at a temperature between about 20°C and about 25 °C, based on a high quality pattern collected with a diffractometer (CuKα) with a spinning capillary with 2θ calibrated with a NIST other suitable standard.

In a fifth aspect the present disclosure provides Form N-2 of



characterized by one or more of the following:

a) a unit cell with parameters substantially equal to the following:

Cell dimensions: a = 7.5680 Å

b= 9.5848 Å

c = 16.2864 Å

α = 74.132 degrees

β = 84.132 degrees

γ = 70.646 degrees

Space group P1

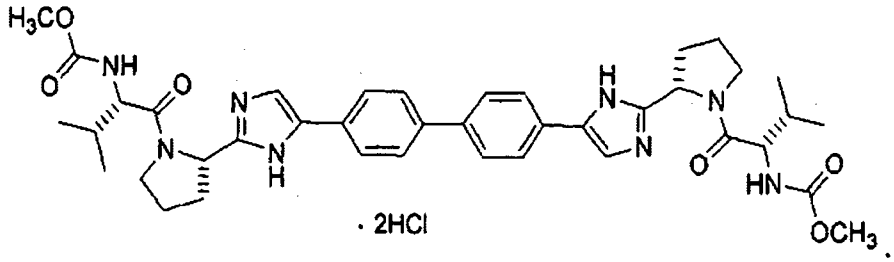
Molecules/unit cell 1

wherein measurement of said crystalline form is at a temperature between about 20 °C to about 25 °C;

b) characteristic peaks in the powder X-Ray diffraction pattern at values of two theta of 10.3 ± 0.1, 12.4 ± 0.1, 12.8 ± 0.1, 13.3 ± 0.1, 13.6 ± 0.1, 15.5 ± 0.1, 20.3 ± 0.1, 21.2 ± 0.1, 22.4 ± 0.1, 22.7 ± 0.1, and 23.7 ± 0.1 at a temperature between about 20°C and about 25 °C, based on a high quality pattern collected with a diffractometer (CuKα) with a spinning capillary with 2θ calibrated with a NIST other suitable standard; and/or

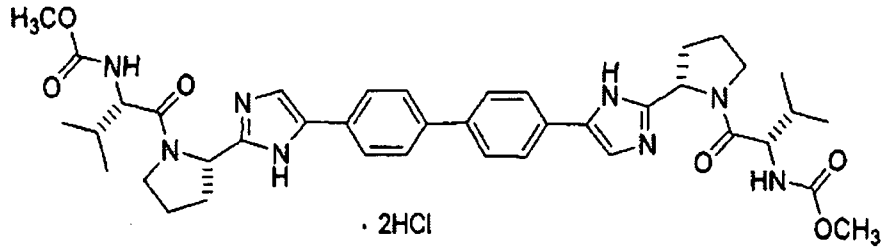
c) a melt with decomposition endotherm with onset typically in the range of 225-245 °C.

In a sixth aspect the present disclosure provides substantially pure Form N-2 of



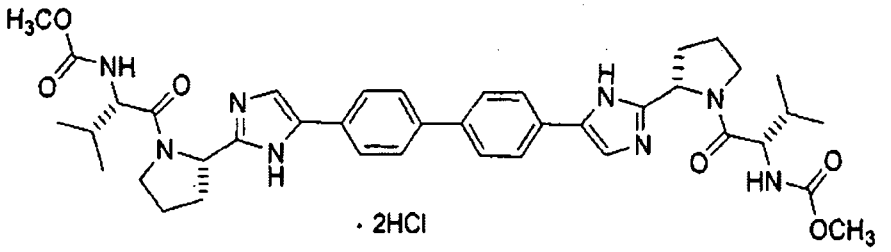
In a first embodiment of the sixth aspect said Form N-2 has a purity of at least 95 weight percent. In a second embodiment of the sixth aspect said Form N-2 has a purity of at least 99 weight percent.

In a seventh aspect the present disclosure provides substantially pure Form N-2 of



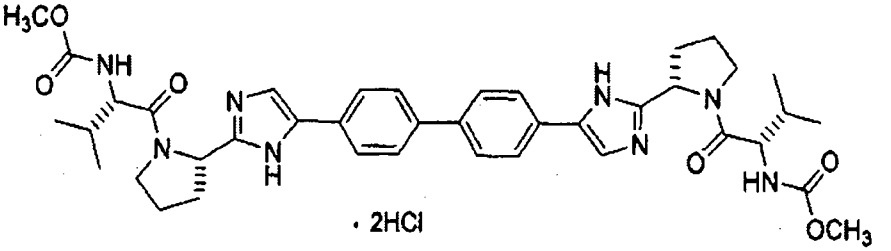
with characteristic peaks in the powder X-Ray diffraction pattern at values of two theta of 10.3 ± 0.1, 12.4 ± 0.1, 12.8 ± 0.1, 13.3 ± 0.1, 13.6 ± 0.1, 15.5 ± 0.1, 20.3 ± 0.1, 21.2 ± 0.1, 22.4 ± 0.1, 22.7 ± 0.1, and 23.7 ± 0.1 at a temperature between about 20°C and about 25 °C, based on a high quality pattern collected with a diffractometer (CuKα) with a spinning capillary with 2θ calibrated with a NIST other suitable standard.

In an eighth aspect the present disclosure provides a pharmaceutical composition comprising Form N-2 of



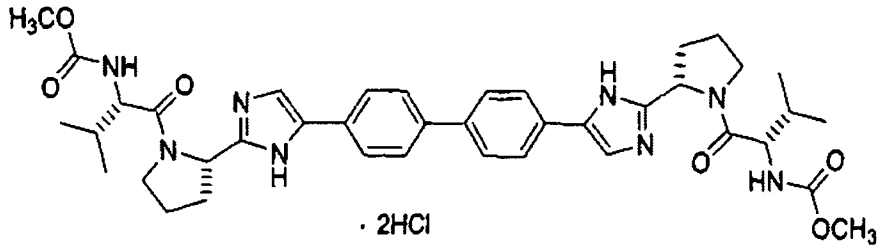
and a pharmaceutically acceptable carrier or diluent.

In a ninth aspect the present disclosure provides a pharmaceutical composition comprising substantially pure Form N-2 of



and a pharmaceutically acceptable carrier or diluent. In a first embodiment of the ninth aspect said Form N-2 has a purity of at least 95 weight percent. In a second embodiment of the ninth aspect said Form N-2 has a purity of at least 99 weight percent.

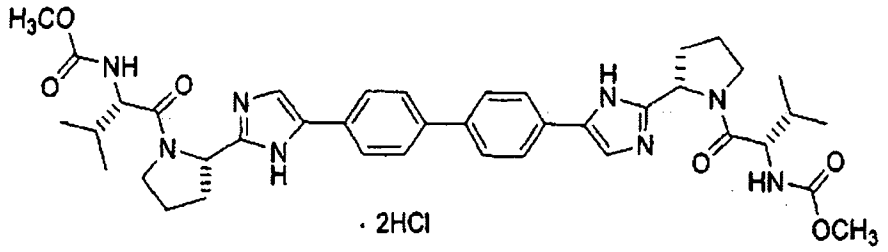
In a tenth aspect the present disclosure provides a pharmaceutical composition comprising Form N-2 of



in combination with one or two additional compounds having anti-HCV activity. In a first embodiment of the tenth aspect said Form N-2 has a purity of at least 90 weight percent. In a second embodiment of the tenth aspect said Form N-2 has a purity of at least 95 weight percent. In a third embodiment of the tenth aspect said Form N-2 has a purity of at least 99 weight percent.

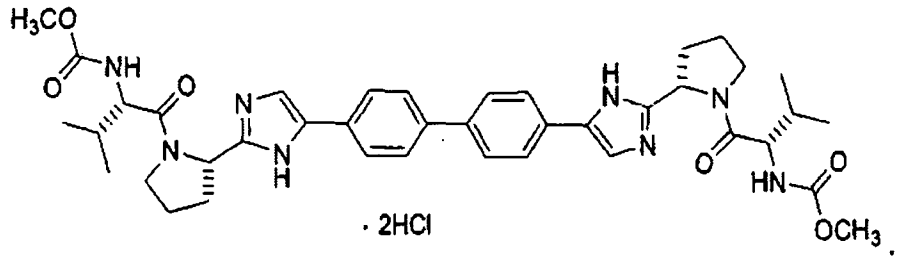
In a fourth embodiment of the tenth aspect at least one of the additional compounds having anti-HCV activity is an interferon or ribavirin. In a fifth embodiment of the tenth aspect the interferon is selected from interferon alpha 2B, pegylated interferon alpha, consensus interferon, interferon alpha 2A, and lymphoblastiod interferon tau.

In a sixth embodiment of the tenth aspect the present disclosure provides a pharmaceutical composition comprising Form N-2 of



in combination with one or two additional compounds having anti-HCV activity wherein at least one of the additional compounds is selected from interleukin 2, interleukin 6, interleukin 12, a compound that enhances the development of a type 1 helper T cell response, interfering RNA, anti-sense RNA, Imiqimod, ribavirin, an inosine 5'-monophospate dehydrogenase inhibitor, amantadine, and rimantadine.

In an eleventh aspect the present disclosure provides a method of treating HCV infection in a mammal comprising administering to the mammal a therapeutically-effective amount of Form N-2 of



In a first embodiment of the eleventh aspect said Form N-2 has a purity of at least 90 weight percent. In a second embodiment of the eleventh aspect said Form N-2 has a purity of at least 95 weight percent. In a third embodiment of the eleventh aspect said Form N-2 has a purity of at least 99 weight percent. In a fourth embodiment of the eleventh aspect the mammal is a human.

Other embodiments of the present disclosure may comprise suitable combinations of two or more of embodiments and/or aspects disclosed herein.

Yet other embodiments and aspects of the disclosure will be apparent according to the description provided below.

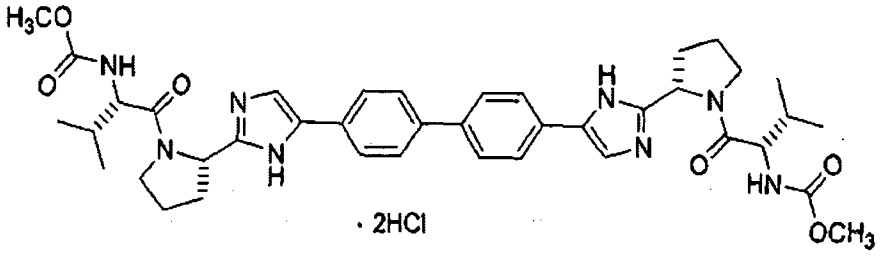
The compounds of the present disclosure also exist as tautomers; therefore the present disclosure also encompasses all tautomeric forms.

FIG. 1 illustrates experimental and simulated powdered X-Ray diffraction patterns (CuKα λ=1.54178 Å at T = room temperature) of the N-2 crystalline form of Compound (I).

FIG. 2 illustrates the differential scanning calorimetry pattern of the N-2 crystalline form of Compound (I).

FIG. 3 illustrates the solid state NMR spectrum of the N-2 crystalline form of Compound (I).

The disclosure relates to a crystalline form of Compound (I).



(I).

Definitions

As used herein "polymorph" refers to crystalline forms having the same chemical composition but different spatial arrangements of the molecules, atoms, and/or ions forming the crystal.

The term "pharmaceutically acceptable," as used herein, refers to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem complications commensurate with a reasonable beneift/risk ratio.

The term "substantially pure," as used herein refers to Form N-2 of Compound (I) which is great than about 90% pure. This means that the polymorph of Compound (I) does not contain more than about 10% of any other compound, and, in particular, does not contain more than about 10% of any other form of Compound (I).

The term "therapeutically effective amount," as used herein, is intended to include an amount of the crystalline forms of Compound (I) that is effective when administered alone or in combination to treat Hepatitis C. The crystalline forms of Compound (I) and pharmaceutical compositions thereof may be useful in treating Hepatitis C. If Compound (I) is used in combination with another medication, the combination of compounds described herein may result in a synergistic combination. Synergy, as described for example by Chou and Talalay, *Adv. Enzyme Regul.* **1984**, *22*, 27-55, occurs when the effect of the compounds when administered in combination is greater than the effect of the compounds when administered alone as single agents.

The term "treating" refers to: (i) preventing a disease, disorder or condition from occurring in a patient which may be predisposed to the disease, disorder and/or condition but has not yet been diagnosed as having it; (ii) inhibiting the disease, disorder or condition, i.e., arresting its development; and/or (iii) relieving the disease, disorder or condition, i.e., causing regression of the disease, disorder and/or condition.

In one embodiment the disclosure provides a crystalline form of Compound (I). This crystalline form of Compound (I) may be employed in pharmaceutical compositions which may optionally include one or more other components selected,

for example, from the group consisting of excipients, carriers, and one of other active pharmaceutical ingredients active chemical entities of different molecular structure.

In one embodiment the crystalline form has phase homogeneity indicated by less than 10 percent, in another embodiment the crystalline form has phase homogeneity indicated by less than 5 percent, and in another embodiment the crystalline form has phase homogeneity indicated by less than 2 percent of the total peak area in the experimentally measured PXRD pattern arising from the extra peaks that are absent from the simulated PXRD pattern. In another embodiment the crystalline form has phase homogeneity with less than 1 percent of the total peak area in the experimentally measured PXRD pattern arising from the extra peaks that are absent from the simulated PXRD pattern.

In one embodiment, a composition is provided consisting essentially of the crystalline form N-2 of Compound (I). The composition of this embodiment may comprise at least 90 weight percent of the crystalline form N-2 of Compound (I), based on the weight of Compound (I) in the composition. The remaining material comprises other form(s) of the compound and/or reaction impuritis and/or processing impurities arising from its preparation.

The presence of reaction impurities and/or processing impurities may be determined by analytical techniques known in the art, such as, for example, chromatography, nuclear magnetic resonance spectroscopy, mass spectrometry, or infrared spectroscopy.

General Preparation of Crystalline Materials:

Crystalline forms may be prepared by a variety of methods, including for example, crystallization or recrystallization from a suitable solvent, sublimation, growth from a melt, solid state transformation from another phase, crystallization from a supercritical fluid, and jet spraying. Techniques for crystallization or recrystallization of crystalline forms from a solvent mixture include, for example, evaporation of the solvent, decreasing the temperature of the solvent mixture, crystal seeding a supersaturated solvent mixture of the molecule and/or salt, freeze drying the solvent mixture, and addition of antisolvents (countersolvents) to the solvent mixture. High throughput crystallization techniques may be employed to prepare crystalline forms including polymorphs. Crystals of drugs, including polymorphs,

methods of preparation, and characterization of drug crystals are discussed in *Solid-State Chemistry of Drugs*, S.R. Byrn, R.R. Pfeiffer, and J.G. Stowell, 2nd Edition, SSCI, West Lafayette, Indiana (1999).

For crystallization techniques that employ solvent, the choice of solvent or solvents is typically dependent upon one or more factors, such as solubility of the compound, crystallization technique, and vapor pressure of the solvent. Combinations of solvents may be employed, for example, the compound may be solubilized into a first solvent to afford a solution, followed by the addition of an antisolvent to decrease the solubility of the compound in the solution and to afford the formation of crystals. An antisolvent is a solvent in which the compound has low solubility.

In one method to prepare crystals, a compound is suspended and/or stirred in a suitable solvent to afford a slurry, which may be heated to promote dissolution. The term "slurry", as used herein, means a saturated solution of the compound, which may also contain an additional amount of the compound to afford a heterogeneous mixture of the compound and a solvent at a given temperature.

Seed crystals may be added to any crystallization mixture to promote crystallization. Seeding may be employed to control growth of a particular polymorph or to control the particle size distribution of the crystalline product. Accordingly, calculation of the amount of seeds needed depends on the size of the seed available and the desired size of an average product particle as described, for example, in "Programmed Cooling of Batch Crystallizers," J.W. Mullin and J. Nyvlt, *Chemical Engineering Science*, **1971**, *26*, 369-377. In general, seeds of small size are needed to control effectively the growth of crystals in the batch. Seed of small size may be generated by sieving, milling, or micronizing of large crystals, or by micro-crystallization of solutions. Care should be taken that milling or micronizing of crystals does not result in any change in crystallinity of the desired crystal form (i.e., change to amorphous or to another polymorph).

A cooled crystallization mixture may be filtered under vacuum, and the isolated solids may be washed with a suitable solvent, such as cold recrystallization solvent, and dried under a nitrogen purge to afford the desired crystalline form. The isolated solids may be analyzed by a suitable spectroscopic or analytical technique, such as solid state nuclear magnetic resonance, differential scanning calorimetry, X-

Ray powder diffraction, or the like, to assure formation of the preferred crystalline form of the product. The resulting crystalline form is typically produced in an amount of greater than about 70 weight percent isolated yield, preferably greater than 90 weight percent isolated yield, based on the weight of the compound originally employed in the crystallization procedure. The product may be co-milled or passed through a mesh screen to delump the product, if necessary.

Crystalline forms may be prepared directly from the reaction medium of the final process for preparing Compound (I). This may be achieved, for example, by employing in the final process step a solvent or a mixture of solvents from which Compound (I) may be crystallized. Alternatively, crystalline forms may be obtained by distillation or solvent addition techniques. Suitable solvents for this purpose include, for example, the aforementioned non-polar solvents and polar solvents, including protic polar solvents such as alcohols, and aprotic polar solvents such as ketones.

The presence of more than one polymorph in a sample may be determined by techniques such as powder X-Ray diffraction (PXRD) or solid state nuclear magnetic resonance spectroscopy (SSNMR). For example, the presence of extra peaks in an experimentally measured PXRD pattern wehn compared with a simulated PXRD pattern may indicate more than one polymorph in the sample. The simulated PXRD may be calculated from single crystal X-Ray data. see Smith, D.K., "*A FORTRAN Program for Calculating X-Ray Powder Diffraction Patterns,*" Lawrence Radiation Laboratory, Livermore, California, UCRL-7196 (April 1963).

Characterization:

Form N-2 of Compound (I) can be characterized using various techniques, the operation of which are well known to those of ordinary skill in the art. Examples of characterization methods include, but are not limited to, single crystal X-Ray diffraction, powder X-Ray diffraction (PXRD), simulated powder X-Ray patterns (Yin, S.; Scaringe, R. P.; DiMarco, J.; Galella, M. and Gougoutas, J. Z., *American Pharmaceutical Review*, **2003**, *6*, 2, 80), differential scanning calorimetry (DSC), solid-state ^{13}C NMR (Earl, W.L. and Van der Hart, D. L., *J. Magn. Reson.*, **1982**, *48*, 35-54), Raman spectroscopy, infrared spectroscopy, moisture sorption isotherms, thermal gravimetric analysis (TGA), and hot stage techniques.

The forms may be characterized and distinguished using single crystal X-Ray diffraction, which is based on unit cell measurements of a single crystal of form N-2. A detailed description of unit cells is provided in Stout & Jensen, X-Ray Structure Determination: A Practical Guide, Macmillan Co., New York (1968), Chapter 3, which is herein incorporated by reference. Alternatively, the unique arrangement of atoms in spatial relation within the crystalline lattice may be characterized according to the observed fractional atomic coordinates. Another means of characterizing the crystalline structure is by powder X-Ray diffraction analysis in which the diffraction profile is compared to a simulated profile representing pure powder material, both run at the same analytical temperature, and measurements for the subject form characterized as a series of 2θ values.

One of ordinary skill in the art will appreciate that an X-Ray diffraction pattern may be obtained with a measurement of error that is dependent upon the measurement conditions employed. In particular, it is generally known that intensities in an X-Ray diffraction pattern may fluctuate depending upon measurement conditions employed. It should be further understood that relative intensities may also vary depending upon experimental conditions, and, accordingly, the exact order of intensity should not be taken into account. Additionally, a measurement error of diffraction angle for a conventional X-Ray diffraction pattern is typically about 5 percent or less, and such degree of measurement error should be taken into account as pertaining to the aforementioned diffraction angles. Consequently, it is to be understood that the crystal forms of the present disclosure are not limited to the crystal forms that provide X-Ray diffraction patterns completely identical to the X-Ray diffraction patterns depicted in the accompanying Figures disclosed herein. Any crystal form that provides and X-Ray diffraction pattern, DSC thermogram, or SSNMR spectrum substantiallyidentical to those disclosed in the accompanying Figures fall within the scope of the present disclosure. The ability to ascertain substantial identities of X-Ray diffraction patters is within the purview of one of ordinary skill in the art.

Utility:

The N-2 form of Compound (I), alone or in combination with other compounds, can be used to treat HCV infection.

The present disclosure also provides compositions comprising a therapeutically effective amount of the N-2 form of Compound (I) and at least one pharmaceutically acceptable carrier.

The active ingredient, i.e., form N-2 of Compound (I), in such compositions typically comprises from 0.1 weight percent to 99.9 percent by weight of the composition, and often comprises from about 5 to 95 weight percent. In some cases, the pH of the formulation may be adjusted with pharmaceutically acceptable modifiers (such as calcium carbonate and magnesium oxide) to enhance the stability of the formulated compound or its delivery form. Formulations of the polymorph of the present disclosure may also contain additives for enhancement of absorption and bioavailability.

The pharmaceutical compositions of this disclosure may be administered orally, parenterally or via an implanted reservoir. The term parenteral as used herein includes subcutaneous, intracutaneous, intravenous, intramuscular,intra-articular, intrasynovial, intrasternal, intrathecal, and intralesional injection or infusion techniques.

The pharmaceutical compositions may be in the form of a sterile injectable preparation, for example, as a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to techniques known in the art using suitable dispersing or wetting agents and suspending agents. The details concerning the preparation of such compounds are known to those skilled in the art.

When orally administered, the pharmaceutical compositions of this disclosure may be administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, and aqueous suspensions and solutions. In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, can also be added. For oral administration in a capsule form, useful carriers/diluents include lactose, high and low molecular weight polyethylene glycol, and dried corn starch. When aqueous suspensions are administered orally, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavoring and/or coloring agents may be added.

Other suitable carriers for the above noted compositions can be found in standard pharmaceutical texts, e.g. in "Remington's Pharmaceutical Sciences", 19th

ed., Mack Publishing Company, Easton, Penn., 1995. Further details concerning the design and preparation of suitable delivery forms of the pharmaceutical compositions of the disclosure are known to those skilled in the art.

Dosage levels of between about 0.05 and about 100 milligram per kilogram ("mg/kg") body weight per day, more specifically between about 0.1 and about 50 mg/kg body weight per day of the compounds of the disclosure are typical in a monotherapy for the prevention and/or treatment of HCV mediated disease. Typically, the pharmaceutical compositions of this disclosure will be administered from about 1 to about 3 times per day or alternatively, as a continuous infusion. Such administration can be used as a chronic or acute therapy. The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration.

As the skilled artisan will appreciate, lower or higher doses than those recited above may be required. Specific dosage and treatment regimens for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health status, gender, diet, time of administration, the duration of treatment, rate of excretion, drug combination, the severity and course of the infection, the patient's disposition to the infection and the judgment of the treating physician. In one embodiment, unit dosage formulations are those containing a daily dose or sub-dose, as herein above recited, or an appropriate fraction thereof, of an active ingredient. Generally, treatment is initiated with small dosages substantially less than the optimum dose of the peptide. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. In general, the compound is most desirably administered at a concentration level that will generally afford antivirally effective results without causing any harmful or deleterious side effects.

When the compositions of this disclosure comprise a combination of the polymorph of the disclosure and one or more additional therapeutic or prophylactic agents, both the compound and the additional agent are usually present at dosage levels of between about 10 and 100 percent, and more preferably between about 10 and 80 percent of the dosage normally administered in a monotherapy regimen.

Administration of the one or more additional agents may occur prior to, after, or simultaneously with the polymorph of the present disclosure.

When the polymorph is formulated together with a pharmaceutically acceptable carrier, the resulting composition may be administered *in vivo* to mammals, such as man, to inhibit NS5A or to treat or prevent HCV virus infection. Such treatment may also be achieved using the polymorph of this disclosure in combination with agents which include, but are not limited to: Immunomodulatory agents, such as interferons; other antiviral agents such as ribavirin, amantadine; other inhibitors of NS5A; inhibitors of other targets in the HCV life cycle such as helicase, protease, polymerase, metalloprotease, or internal ribosome entry site; or combinations thereof. The additional agents may be combined with the polymorph of this disclosure to create a single dosage form. Alternatively these additional agents may be separately administered to a mammal as part of a multiple dosage form.

Table 1 below lists some illustrative examples of compounds that can be administered with the compounds of this disclosure. The compounds of the disclosure can be administered with other anti-HCV activity compounds in combination therapy, either jointly or separately, or by combining the compounds into a composition.

Table 1

Brand Name	*Physiological Class*	*Type of Inhibitor or Target*	*Source Company*
NIM811		Cyclophilin Inhibitor	Novartis
Zadaxin		Immunomodulator	Sciclone
Suvus		Methylene blue	Bioenvision
Actilon (CPG10101)		TLR9 agonist	Coley
Batabulin (T67)	Anticancer	β-tubulin inhibitor	Tularik Inc., South San Francisco, CA

Brand Name	*Physiological Class*	*Type of Inhibitor or Target*	*Source Company*
ISIS 14803	Antiviral	antisense	ISIS Pharmaceuticals Inc, Carlsbad, CA/Elan Phamaceuticals Inc., New York, NY
Summetrel	Antiviral	antiviral	Endo Pharmaceuticals Holdings Inc., Chadds Ford, PA
GS-9132 (ACH-806)	Antiviral	HCV Inhibitor	Achillion / Gilead
Pyrazolopyrimidine compounds and salts From WO-2005047288 26 May 2005	Antiviral	HCV Inhibitors	Arrow Therapeutics Ltd.
Levovirin	Antiviral	IMPDH inhibitor	Ribapharm Inc., Costa Mesa, CA
Merimepodib (VX-497)	Antiviral	IMPDH inhibitor	Vertex Pharmaceuticals Inc., Cambridge, MA
XTL-6865 (XTL-002)	Antiviral	monoclonal antibody	XTL Biopharmaceuticals Ltd., Rehovot, Isreal

Brand Name	*Physiological Class*	*Type of Inhibitor or Target*	*Source Company*
Telaprevir (VX-950, LY-570310)	Antiviral	NS3 serine protease inhibitor	Vertex Pharmaceuticals Inc., Cambridge, MA/ Eli Lilly and Co. Inc., Indianapolis, IN
HCV-796	Antiviral	NS5B Replicase Inhibitor	Wyeth / Viropharma
NM-283	Antiviral	NS5B Replicase Inhibitor	Idenix / Novartis
GL-59728	Antiviral	NS5B Replicase Inhibitor	Gene Labs / Novartis
GL-60667	Antiviral	NS5B Replicase Inhibitor	Gene Labs / Novartis
2'C MeA	Antiviral	NS5B Replicase Inhibitor	Gilead
PSI 6130	Antiviral	NS5B Replicase Inhibitor	Roche
R1626	Antiviral	NS5B Replicase Inhibitor	Roche
2'C Methyl adenosine	Antiviral	NS5B Replicase Inhibitor	Merck
JTK-003	Antiviral	RdRp inhibitor	Japan Tobacco Inc., Tokyo, Japan
Levovirin	Antiviral	ribavirin	ICN Pharmaceuticals, Costa Mesa, CA

Brand Name	*Physiological Class*	*Type of Inhibitor or Target*	*Source Company*
Ribavirin	Antiviral	ribavirin	Schering-Plough Corporation, Kenilworth, NJ
Viramidine	Antiviral	Ribavirin Prodrug	Ribapharm Inc., Costa Mesa, CA
Heptazyme	Antiviral	ribozyme	Ribozyme Pharmaceuticals Inc., Boulder, CO
BILN-2061	Antiviral	serine protease inhibitor	Boehringer Ingelheim Pharma KG, Ingelheim, Germany
SCH 503034	Antiviral	serine protease inhibitor	Schering Plough
Zadazim	Immune modulator	Immune modulator	SciClone Pharmaceuticals Inc., San Mateo, CA
Ceplene	Immunomodulator	immune modulator	Maxim Pharmaceuticals Inc., San Diego, CA
CellCept	Immunosuppressant	HCV IgG immunosuppressant	F. Hoffmann-La Roche LTD, Basel, Switzerland

Brand Name	*Physiological Class*	*Type of Inhibitor or Target*	*Source Company*
Civacir	Immunosuppressant	HCV IgG immunosuppressant	Nabi Biopharmaceuticals Inc., Boca Raton, FL
Albuferon - α	Interferon	albumin IFN-α2b	Human Genome Sciences Inc., Rockville, MD
Infergen A	Interferon	IFN alfacon-1	InterMune Pharmaceuticals Inc., Brisbane, CA
Omega IFN	Interferon	IFN-ω	Intarcia Therapeutics
IFN-β and EMZ701	Interferon	IFN-β and EMZ701	Transition Therapeutics Inc., Ontario, Canada
Rebif	Interferon	IFN-β1a	Serono, Geneva, Switzerland
Roferon A	Interferon	IFN-α2a	F. Hoffmann-La Roche LTD, Basel, Switzerland
Intron A	Interferon	IFN-α2b	Schering-Plough Corporation, Kenilworth, NJ

Brand Name	*Physiological Class*	*Type of Inhibitor or Target*	*Source Company*
Intron A and Zadaxin	Interferon	IFN-α2b/α1-thymosin	RegeneRx Biopharmiceuticals Inc., Bethesda, MD/ SciClone Pharmaceuticals Inc, San Mateo, CA
Rebetron	Interferon	IFN-α2b/ribavirin	Schering-Plough Corporation, Kenilworth, NJ
Actimmune	Interferon	INF-γ	InterMune Inc., Brisbane, CA
Interferon-β	Interferon	Interferon-β-1a	Serono
Multiferon	Interferon	Long lasting IFN	Viragen/Valentis
Wellferon	Interferon	lymphoblastoid IFN-αn1	GlaxoSmithKline plc, Uxbridge, UK
Omniferon	Interferon	natural IFN-α	Viragen Inc., Plantation, FL
Pegasys	Interferon	PEGylated IFN-α2a	F. Hoffmann-La Roche LTD, Basel, Switzerland
Pegasys and Ceplene	Interferon	PEGylated IFN-α2a/ immune modulator	Maxim Pharmaceuticals Inc., San Diego, CA

Brand Name	*Physiological Class*	*Type of Inhibitor or Target*	*Source Company*
Pegasys and Ribavirin	Interferon	PEGylated IFN-α2a/ribavirin	F. Hoffmann-La Roche LTD, Basel, Switzerland
PEG-Intron	Interferon	PEGylated IFN-α2b	Schering-Plough Corporation, Kenilworth, NJ
PEG-Intron / Ribavirin	Interferon	PEGylated IFN-α2b/ribavirin	Schering-Plough Corporation, Kenilworth, NJ
IP-501	Liver protection	antifibrotic	Indevus Pharmaceuticals Inc., Lexington, MA
IDN-6556	Liver protection	caspase inhibitor	Idun Pharmaceuticals Inc., San Diego, CA
ITMN-191 (R-7227)	Antiviral	serine protease inhibitor	InterMune Pharmaceuticals Inc., Brisbane, CA
GL-59728	Antiviral	NS5B Replicase Inhibitor	Genelabs
ANA-971	Antiviral	TLR-7 agonist	Anadys

Another aspect of this disclosure provides methods of inhibiting HCV NS5A activity in patients by administering the polymorph of the present disclosure.

In one embodiment, these methods are useful in decreasing HCV NS5A activity in the patient. If the pharmaceutical composition comprises only the polymorph of this disclosure as the active component, such methods may additionally comprise the step of administering to said patient an agent selected from an immunomodulatory agent, an antiviral agent, an HCV NS5A inhibitor, or an inhibitor of other targets in the HCV life cycle such as, for example, helicase, polymerase, protease, or metalloprotease. Such additional agent may be administered to the patient prior to, concurrently with, or following the administration of the compounds of this disclosure.

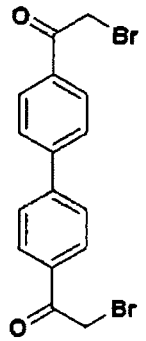
In another embodiment, these methods are useful for inhibiting viral replication in a patient. Such methods can be useful in treating or preventing HCV disease.

The polymorph of the disclosure may also be used as a laboratory reagent. The polymorph may be instrumental in providing research tools for designing of viral replication assays, validation of animal assay systems and structural biology studies to further enhance knowledge of the HCV disease mechanisms.

The polymorph of this disclosure may also be used to treat or prevent viral contamination of materials and therefore reduce the risk of viral infection of laboratory or medical personnel or patients who come in contact with such materials, e.g., blood, tissue, surgical instruments and garments, laboratory instruments and garments, and blood collection or transfusion apparatuses and materials.

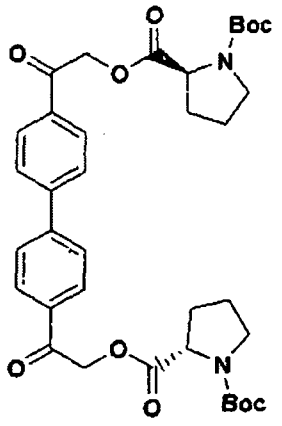
The following non-limiting examples are illustrative of the disclosure.

EXAMPLES



Preparation of Compound 2

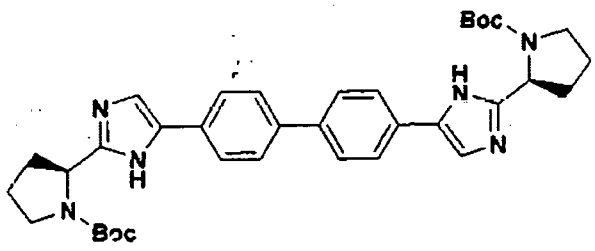
A 1 L, 3-neck round bottom flask, fitted with a nitrogen line, overhead stirrer and thermocouple, was charged with 20 g (83.9 mmol, 1 equiv) 1,1'-(biphenyl-4,4'-diyl)diethanone, 200 mL CH_2Cl_2 and 8.7 mL (27.1g, 169.3 mmol, 2.02 quiv) bromine. The mixture was allowed to stir under nitrogen for about 20 hours under ambient conditions. The resulting slurry was charged with 200 mL CH_2Cl_2 and concentrated down to about 150 mL *via* vacuum distillation. The slurry was then solvent exchanged into THF to a target volume of 200 mL *via* vacuum distillation. The slurry was cooled to 20-25 °C over 1 hour and allowed to stir at 20-25 °C for an additional hour. The off-white crystalline solids were filtered and washed with 150 mL CH_2Cl_2. The product was dried under vacuum at 60 °C to yield 27.4 g (69.2 mmol, 82%) of the desired product: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95-7.85 (m, 4H), 7.60-7.50 (m, 4H), 4.26 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.0, 145.1, 133.8, 129.9, 127.9, 30.8; IR (KBr, cm-1) 3007, 2950, 1691, 1599, 1199; Anal calcd for $C_{16}H_{12}Br_2O_2$: C, 48.52; H, 3.05; Br, 40.34. Found: C, 48.53; H, 3.03; Br, 40.53. HRMS calcd for $C_{16}H_{13}Br_2O_2$ (M + H; DCI$^+$): 394.9282. Found: 394.9292. mp 224-226 °C.



Preparation of Compound 3

A 500 mL jacketed flask, fitted with a nitrogen line, thermocouple and overhead stirrer, was charged with 20 g (50.5 mmol, 1 equiv) of Compound 2, 22.8 g (105.9 moles, 2.10 equiv) 1-(*tert*-butoxycarbonyl)-L-proline and 200 mL acetonitrile. The slurry was cooled to 20 °C followed by the addition of 18.2 mL (13.5 g, 104.4 mmol, 2.07 equiv) DIPEA. The slurry was warmed to 25 °C and allowed to stir for 3

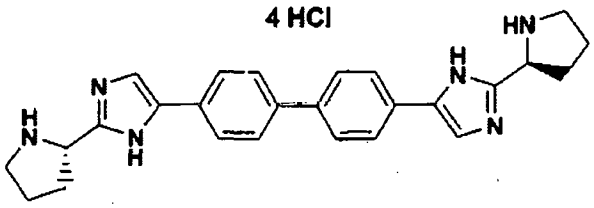
hours. The resulting clear, organic solution was washed with 3 x 100 mL 13 wt% aqueous NaCl. The rich acetonitrile solution was solvent exchanged into toluene (target volume = 215 mL) by vacuum distillation until there was less than 0.5 vol% acetonitrile.



Preparation of Compound 4

The toluene solution of Compound 3 was charged with 78 g (1.011 moles, 20 equiv) ammonium acetate and heated to 95-100 °C. The mixture was allowed to stir at 95-100 °C for 15 hours. After reaction completion, the mixture was cooled to 70-80 °C and charged with 7 mL acetic acid, 40 mL n-butanol, and 80 mL of 5 vol% aqueous acetic acid. The resulting biphasic solution was split while maintaining a temperature > 50 °C. The rich organic phase was charged with 80 mL of 5 vol% aqueous acetic acid, 30 mL acetic acid and 20 mL n-butanol while maintaining a temperature > 50 °C. The resulting biphasic solution was split while maintaining a temperature > 50 °C and the rich organic phase was washed with an additional 80 mL of 5 vol% aqueous acetic acid. The rich organic phase was then solvent exchanged into toluene to a target volume of 215 mL by vacuum distillation. While maintaining a temperature > 60 °C, 64 mL methanol was charged. The resulting slurry was heated to 70-75 °C and aged for 1 hour. The slurry was cooled to 20-25 °C over 1 hour and aged at that temperature for an additional hour. The slurry was filtered and the cake was washed with 200 mL 10:3 toluene:methanol. The product was dried under vacuum at 70 °C, resulting in 19.8 g (31.7 mmol, 63%) of the desired product: ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.00-11.00 (s, 2H), 7.90-7.75 (m, 4H), 7.75-7.60 (m, 4H), 7.60-7.30 (s, 2H), 4.92-4.72 (m, 2H), 3.65-3.49 (m, 2H), 3.49-3.28 (m, 2H), 2.39-2.1 (m, 2H), 2.10-1.87 (m, 6H), 1.60-1.33 (s, 8H), 1.33-1.07 (s, 10H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 154.1, 153.8, 137.5, 126.6, 125.0, 78.9, 78.5, 55.6, 55.0, 47.0, 46.7, 33.7, 32.2, 28.5, 28.2, 24.2, 23.5; IR (KBr, cm-1) 2975, 2876, 1663, 1407,

1156, 1125; HRMS calcd for $C_{36}H_{45}N_6O_4$ (M + H; ESI^+): 625.3502. Found: 625.3502. mp 190-195 °C (decomposed).

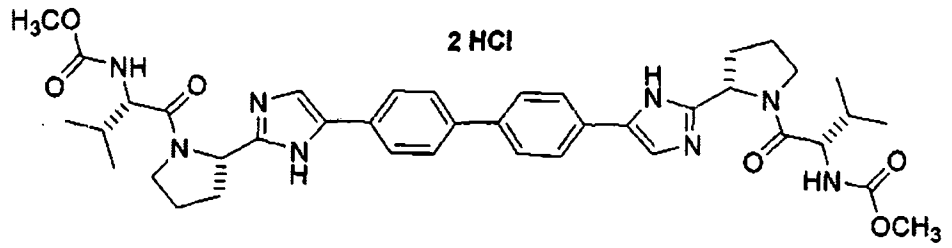


Preparation of Compound 5

To a 250 mL reactor equipped with a nitrogen line and overhead stirrer, 25.0 g of Compound 4 (40.01 mmol, 1 equiv) was charged followed by 250 mL methanol and 32.85 mL (400.1 mmol, 10 equiv) 6M aqueous HCl. The temperature was increased to 50 °C and agitated at 50 °C for 5 hours. The resulting slurry was cooled to 20-25 °C and held with agitation for about 18 hours. Filtration of the slurry afforded a solid which was washed successively with 100 mL 90% methanol/water (V/V) and 2 x 100 mL of methanol. The wet cake was dried in a vacuum oven at 50 °C overnight to give 18.12 g (31.8 mmol, 79.4%) of the desired product.

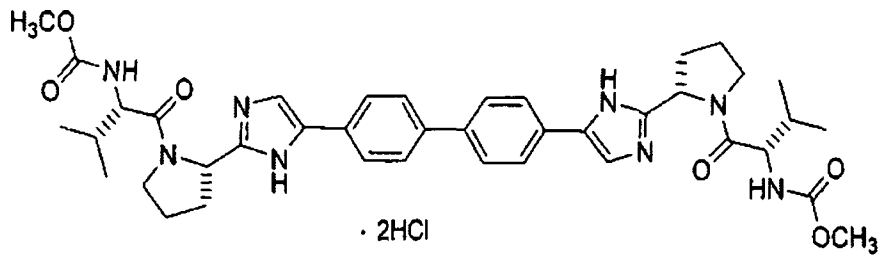
Recrystallization of Compound 5

To a 250 mL reactor equipped with a nitrogen line and an overhead stirrer, 17.8g of Compound 5 from above was charged followed by 72 mL methanol. The resulting slurry was agitated at 50 °C for 4 hours, cooled to 20-25 °C and held with agitation at 20-25 °C for 1 hour. Filtration of the slurry afforded a crystalline solid which was washed with 60 mL methanol. The resulting wet cake was dried in a vacuum oven at 50 °C for 4 days to yield 14.7 g (25.7 mmol, 82.6%) of the purified product: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.5-10.25 (br, 2H), 10.1-9.75 (br, 2H), 8.19 (s, 2H), 7.05 (d, J = 8.4, 4H), 7.92 (d, J = 8.5, 4H), 5.06 (m, 2H), 3.5-3.35 (m, 4H), 2.6-2.3 (m, 4H), 2.25-2.15 (m, 2H), 2.18-1.96 (m, 2H); ^{13}C NMR (100 MHz, DMSO- d_6) δ 156.6, 142.5, 139.3, 128.1, 127.5, 126.1, 116.9, 53.2, 45.8, 29.8, 24.3; IR (KBr, cm^{-1}) 3429, 2627, 1636, 1567, 1493, 1428, 1028. Anal calcd for $C_{26}H_{32}N_6Cl_4$: C, 54.75; H, 5.65; Cl, 24.86; Adjusted for 1.9% water: C, 53.71; H, 5.76; N, 14.46; Cl, 24.39. Found: C, 53.74; H, 5.72; N, 14.50; Cl, 24.49; KF = 1.9. mp 240 °C (decomposed).



Preparation of Compound (I)

A 1 L jacketed flask equipped with a nitrogen line and an overhead stirrer was sequentially charged with 100 mL acetonitrile, 13.69 g (89.4 mmol, 2.5 equiv) hydroxybenzotriazole hydrate, 15.07 g (86 mmol, 2.4 equiv) *N*-(methoxycarbonyl)-L-valine, 16.46 g (85.9 mmol, 2.4 equiv) 1-(3-dimethyaminopropyl)-3-ethylcarbodiimide hydrochloride and an additional 100 mL acetonitrile. The resulting solution was agitated at 20 °C for 1 hour and charged with 20.4 g (35.8 mmol, 1 equiv) of purified Compound 5. The slurry was cooled to about 0 °C and 18.47 g (142.9 mmol, 4 equiv) diisopropylethylamine was added over 30 minutes while maintaining a temperature below 10 °C. The solution was slowly heated to 15 °C over 3 hours and held at 15 °C for 12 hours. The resulting solution was charged with 120 mL 13 wt% aqueous NaCl and heated to 50 °C for 1 hour. After cooling to 20 °C, 100 mL of isopropyl acetate was added. The biphasic solution was filtered through a 0.45 μm filter and the mixture split. The rich organic phase was washed with 2 x 240 mL of a 0.5 N NaOH solution containing 13 wt% NaCl followed by 120 mL 13 wt% aqueous NaCl. The mixture was then solvent exchanged into isopropyl acetate by vacuum distillation with a target volume of 400 mL. The resulting hazy solution was cooled to 20 °C and filtered through a 0.45 μm filter. The clear solution was then solvent exchanged into ethanol by vacuum distillation with a target volume of 140 mL. While maintaining a temperature of 50 °C, 66.4 mL (82.3 mmol, 2.3 equiv) of 1.24M HCl in ethanol was added. The mixture was then charged with 33 mg (0.04 mmol, 0.001 equiv) of seed crystals of Compound (I) (see preparation below) and the resulting slurry was stirred at 50 °C for 3 hours. The mixture was cooled to 20 °C over 1 hour and aged at that temperature for an additional 22 hours. The slurry was filtered and the wet cake was washed with 100 mL of 2:1 acetone:ethanol. The solids were dried in a vacuum oven at 70 °C to give 22.15 g (27.3 mmol, 76.3%) of the desired product.



Carbon Treatment and Recrystallization of Compound (I)

A solution of Compound (I) was prepared by dissolving 3.17 g of Compound (I) from above in 22 mL methanol. The solution was passed through a 47mm Cuno Zeta Carbon® 53SP filter at ~5 psig at a flow rate of ~58mL/min. The carbon filter was rinsed with 32 mL of methanol. The solution was concentrated down to 16 mL by vacuum distillation. While maintaining a temperature of 40-50 °C, 15.9 mL acetone and 5 mg of seed crystals of Compound (I) (see procedure below) were added. The resulting slurry was then charged with 32 mL acetone over 30 minutes. The slurry was held at 50 °C for 2 hours, cooled to 20 °C over about 1 hour and held at 20 °C for about 20 hours. The solids were filtered, washed with 16 mL 2:1 acetone:methanol and dried in a vacuum oven at 60 °C to give 2.14 g (67.5%) of purified Compound (I): ^{1}H NMR (400 MHz, DMSO-d_6, 80 °C): 8.02 (d, J=8.34 Hz, 4 H), 7.97 (s, 2 H), 7.86 (d, J=8.34 Hz, 4 H), 6.75 (s, 2 H), 5.27 (t, J=6.44 Hz, 2 H), 4.17 (t, J=6.95 Hz, 2 H), 3.97 - 4.11 (m, 2 H), 3.74 - 3.90 (m, 2 H), 3.57 (s, 6 H), 2.32 - 2.46 (m, 2 H), 2.09 - 2.31 (m, 6 H), 1.91 - 2.07 (m, 2 H), 0.88 (d, J=6.57 Hz, 6 H), 0.79 (d, J=6.32 Hz, 6 H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 170.9, 156.9, 149.3, 139.1, 131.7, 127.1, 126.5, 125.9, 115.0, 57.9, 52.8, 51.5, 47.2, 31.1, 28.9, 24.9, 19.6, 17.7; IR (neat, cm^{-1}): 3385, 2971, 2873, 2669, 1731, 1650. Anal. Calcd for $C_{40}H_{52}N_8O_6Cl_2$: C, 59.18; H, 6.45; N, 13.80; Cl, 8.73. Found C, 59.98; H, 6.80; N, 13.68; Cl, 8.77. mp 267 °C (decomposed).

Preparation of Seed Crystals of Compound (I)

A 250 mL round-bottom flask was charged with 6.0g (10.5 mmol, 1 equiv) Compound 5, 3.87g (22.1 mmol, 2.1 equiv) N-(methoxycarbonyl)-L-valine, 4.45g (23.2 mmol, 2.2 equiv) 1-(3-dimethyaminopropyl)-3-ethylcarbodiimide hydrochloride, 0.289 g (2.14 mmol, 0.2 equiv) 1-hydroxybenzotriazole, and 30 mL acetonitrile. The resulting slurry was then charged with 7.33 mL (42.03 mmol, 4

equiv) diisopropylethylamine and allowed to stir at 24-30 °C for about 18 hours. The mixture was charged with 6 mL of water and heated to 50 °C for about 5 hours. The mixture was cooled and charged with 32 mL ethyl acetate and 30 mL water. The layers were separated and the rich organic layer was washed with 30 mL of 10 wt% aqueous $NaHCO_3$, 30 mL water, and 20 mL of 10 wt% aqueous NaCl. The rich organic layer was then dried over $MgSO_4$, filtered, and concentrated down to a residue. The crude material was then purified via flash chromatography (silica gel, 0-10% methanol in dichloromethane) to provide the free base of Compound (I).

The free-base of Compound (I) (0.03g) was dissolved in 1 mL isopropanol at 20 °C. Anhydrous HCl (70 µL, dissolved in ethanol, approximately 1.25M concentration) was added and the reaction mixture was stirred. To the solution was added methyl *tert*-butyl ether (1 mL) and the resulting slurry was stirred vigorously at 40 °C to 50 °C for 12 hours. The crystal slurry was cooled to 20 °C and filtered. The wet cake was air-dried at 20 °C. A white crystalline solid (Form N-2 of Compound (I)) was obtained.

Form N-2 was analyzed using one or more of the testing methods described below.

1 Single Crystal X-Ray Measurements

A Bruker APEX2 Kappa CCD diffractometer equipped with a rotating anode generator of Cu Kα radiation, (λ = 1.54178 Å) was used to collect diffraction data at the room temperature. Indexing and processing of the measured intensity data were carried out with the APEX2 software package/program suite (APEX2 Data collection and processing user interface: APEX2 User Manual, v1.27; BRUKER AXS, INc., 5465 East Cheryl Parkway, Madison, WI 53711 USA). The final unit cell parameters were determined using the entire data set.

The structure was solved by direct methods and refined by the full-matrix least-squares techniques, using the SHELXTL software package (Sheldrick, GM. 1997, SHELXTL. Structure Determination Programs. Version 5.10, Bruker AXS, Madison, Wisconsin, USA.). The function minimized in the refinements was $\Sigma w(|F_o| - |F_c|)^2$. R is defined as $\Sigma ||F_o| - |F_c||/\Sigma |F_o|$ while $R_w = [\Sigma_w(|F_o| - |F_c|)^2/\Sigma_w |Fo|^2]^{1/2}$,

where w is an appropriate weighting function based on errors in the observed intensities. Difference Fourier maps were examined at all stages of refinement. All non-hydrogen atoms were refined with anisotropic thermal displacement parameters. The hydrogen atoms associated with hydrogen bonding were located in the final difference Fourier maps while the positions of the other hydrogen atoms were calculated from an idealized geometry with standard bond lengths and angles. They were assigned isotropic temperature factors and included in structure factor calculations with fixed parameters.

The crystal data of the N-2 form is shown in Table 2. The fractional atomic coordinates are listed in Table 3. It should be understood by one of ordinary skill in the art that slight variations in the coordinates are possible and are considered to be within the scope the present disclosure.

Table 2. Crystal Data of Form N-2

Temperature	room temperature
Wavelength	1.54178 Å
Crystal system, space group	Triclinic, P1
Unit cell dimensions	a = 7.5680(2) Å alpha = 74.132(2) °
	b = 9.5848(3) Å beta = 84.132(2) °
	c = 16.2864(5) Å gamma = 70.646(2) °
Volume	1072.06(5) $Å^3$
Z, Calculated density	1, 1.257 Mg/m^3

Table 3. Atomic coordinates

Atom	*X*	*Y*	*Z*	*Atom*	*X*	*Y*	*Z*
C7	0.0807	-0.0688	0.0165	H3	0.0264	0.2281	-0.0035
C16	-0.5489	0.4635	-0.1121	H17	-0.7884	0.4046	-0.0848
C4	-0.0807	0.0688	-0.0165	H2	-0.2192	0.4393	-0.0575
C18	-0.7034	0.6975	-0.1863	H5	-0.2549	-0.0380	-0.0365
C13	0.5516	-0.4628	0.1105	H6	-0.5015	0.1728	-0.0892
C15	0.7037	-0.6988	0.1841	H9	0.5090	-0.1737	0.0755
C3	-0.0789	0.2157	-0.0218	H14	0.7875	-0.4013	0.0906

Atom	*X*	*Y*	*Z*	*Atom*	*X*	*Y*	*Z*
C10	0.3885	-0.3317	0.0771	H12	-0.0376	-0.2264	0.0165
C1	-0.3895	0.3303	-0.0781	H11	0.2109	-0.4403	0.0683
C17	-0.7335	0.4794	-0.1115	H8	0.2590	0.0389	0.0270
C2	-0.2275	0.3428	-0.0531	H19	0.8664	-0.8827	0.2693
C5	-0.2458	0.0584	-0.0412	H20A	0.6721	-0.9411	0.1489
C6	-0.3950	0.1847	-0.0720	H20B	0.8848	-1.0218	0.1745
C9	0.3978	-0.1858	0.0641	H22A	0.4299	-0.9831	0.2863
C14	0.7330	-0.4774	0.1143	H22B	0.5433	-1.0623	0.3720
C12	0.0728	-0.2143	0.0290	H24	0.4288	-0.8972	0.4553
C11	0.2233	-0.3439	0.0597	H29A	0.3610	-0.6896	0.7199
C8	0.2471	-0.0573	0.0347	H29B	0.5410	-0.6388	0.7042
C19	0.7480	-0.8565	0.2404	H29C	0.5552	-0.8060	0.7046
C20	0.7591	-0.9804	0.1959	H26A	0.0099	-0.5669	0.3086
C22	0.5494	-1.0075	0.3126	H26B	0.2158	-0.5619	0.2923
C24	0.3932	-0.7895	0.4232	H26C	0.1027	-0.5160	0.3723
C28	0.4299	-0.7573	0.5628	H25	0.2074	-0.8105	0.3478
C29	0.4783	-0.7007	0.6895	H21A	0.6629	-1.1660	0.2427
C26	0.1249	-0.5830	0.3353	H21B	0.8099	-1.1619	0.3036
C25	0.1972	-0.7461	0.3866	H27A	0.0368	-0.7163	0.4938
C21	0.7052	-1.0999	0.2661	H27B	0.1093	-0.8874	0.4894
C27	0.0588	-0.7834	0.4569	H27C	-0.0572	-0.7699	0.4319
C23	0.5435	-0.7711	0.3553	H30	-0.6271	0.8706	-0.2714
C30	-0.7440	0.8547	-0.2454	H31A	-0.9249	0.9498	-0.1547
C34	-0.8171	0.7743	-0.3628	H31B	-0.7674	1.0278	-0.1856
C31	-0.8522	0.9853	-0.2037	H33A	-1.1460	0.9828	-0.2916
C33	-1.0373	1.0092	-0.3191	H33B	-1.0659	1.0635	-0.3783
C32	-0.9782	1.1019	-0.2736	H32A	-1.0859	1.1679	-0.2499
C38	-0.8340	0.7734	-0.5748	H32B	-0.9111	1.1645	-0.3120
C36	-1.1117	0.7288	-0.3922	H36	-1.1758	0.7856	-0.3502
C39	-0.6953	0.7302	-0.7067	H39A	-0.7874	0.7037	-0.7301
C37	-1.0485	0.5605	-0.3464	H39B	-0.5733	0.6820	-0.7276
C35	-0.9477	0.7893	-0.4312	H39C	-0.7221	0.8392	-0.7235
N1	0.5385	-0.6067	0.1537	H37A	-1.1562	0.5276	-0.3279

Atom	*X*	*Y*	*Z*	*Atom*	*X*	*Y*	*Z*
N4	-0.5358	0.6044	-0.1590	H37B	-0.9757	0.5444	-0.2977
N2	0.8232	-0.6215	0.1585	H37C	-0.9736	0.5027	-0.3846
N3	-0.8254	0.6252	-0.1572	H35	-0.9995	0.8976	-0.4608
N6	-0.8719	0.8722	-0.3123	H1	0.4378	-0.6316	0.1597
N5	0.5974	-0.8687	0.3055	H4	-0.4338	0.6276	-0.1688
N8	-0.8375	0.7087	-0.4913	H2A	0.9413	-0.6576	0.1685
N7	0.3941	-0.6991	0.4812	H3A	-0.9442	0.6631	-0.1654
O4	-0.6651	0.6742	-0.3518	H8A	-0.7710	0.6146	-0.4726
O1	0.6094	-0.6663	0.3446	H7	0.3699	-0.6020	0.4611
O2	0.4413	-0.8890	0.6028	H40A	-1.1909	0.7164	-0.5066
O3	0.4448	-0.6524	0.5991	H40B	-1.3113	0.8675	-0.4819
O5	-0.9383	0.8955	-0.6125	H40C	-1.3481	0.7128	-0.4362
O6	-0.7001	0.6782	-0.6138				
C40	-1.2538	0.7592	-0.4606				
Cl1	-0.2486	0.7587	-0.1475				
Cl2	0.2421	-0.7524	0.1377				

2. *Powder X-Ray Diffraction*

About 200mg were packed into a Philips powder X-ray diffraction (PXRD) sample holder. The sample was transferred to a Philips MPD unit (45 KV, 40mA, Cu Kα). Data were collected at room temperature in the 2 to 32 2θ range (continuous scanning mode, scanning rate 0.03 degrees/sec., auto divergence and anti scatter slits, receiving slit: 0.2 mm, sample spinner: ON).

The results of the PXRD pattern and a simulated pattern calculated from the single crystal data are shown in FIG. 1.

Table 4 lists the characteristic PXRD peaks that describe Form N-2 of Compound (I).

Table 4. Characteristic diffraction peak positions (degrees 2θ ± 0.1) at room temperature, based on a high quality pattern collected with a diffractometer (cuKα) with a spinning capillary with 2θ calibrated with a NIST other suitable standard.

Form N-2
10.3
12.4
12.8
13.3
13.6
15.5
20.3
21.2
22.4
22.7
23.7

3. *Differential Scanning Calorimetry*

Differential scanning calorimetry (DSC) experiments were performed in a TA Instruments ™ model Q2000, Q1000 or 2920. The sample (about 2-6mg) was weighed in an aluminum pan and recorded accurately to a hundredth of a milligram, and transferred to the DSC. The instrument was purged with nitrogen gas adt 50 mL/min. Data were collected between room temperature and 300 °C at 10 °C/min heating rate. The plot was made with the endothermic peaks pointing down.

The results are shown in FIG. 2.

4. *Solid-State NMR (SSNMR)*

All solid-state C-13 NMR measurements were made with a Bruker DSX-400, 400 MHz NMR spectromter. High resolution spectra were obtained using high-power proton decoupling and the TPPM pulse sequence and ramp amplitude cross-polarization (RAMP-CP) with magic-angle spinning (MAS) at approximately 12 kHz (A.E. Bennett et al. *J. Chem. Phys.* **1995**, *103*, 6951). (G. Metz, X. Wu, and S.O. Smith, *J. Magn. Reson. A.*, **1994**, *110*, 219-227). Approximately 70 mg of sample, packed into a canister-design zirconia rotor was used for each experiment. Chemical shifts (δ) were referenced to external adamantane with the high frequency resonance

being set to 38.56 ppm (W.L. Earl and D.L. VanderHart, *J. Magn. Reson.*, **1982**, *48*, 35-54).

The SSNMR spectrum is shown in FIG. 3.

Table 5 lists the characteristic SSNMR peaks that describe Form N-2 of Compound (I).

Table 5: SSNMR peak positions of Form N-2 of Compound (I). Peak positions δ (in ppm) relative to TMS scale.

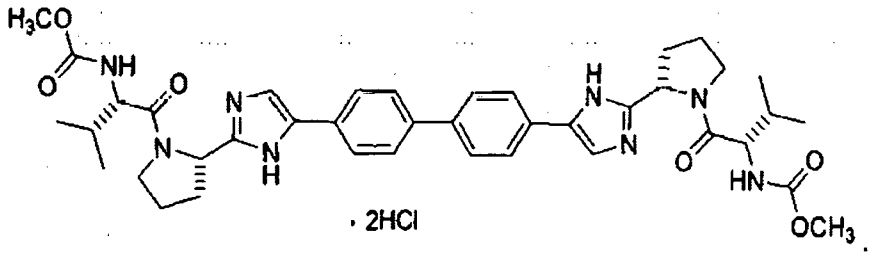
Form N-2
14.8
15.3
19.6
20.4
25.1
25.6
28.4
29.3
29.3
30.1
32.3
46.8
51.6
54.3
55.2
57.5
57.8
58.2
111.7
113.1
125.4
127.4
128.5
132.6

133.7
138.8
150.5
151.9
156.7
169.9

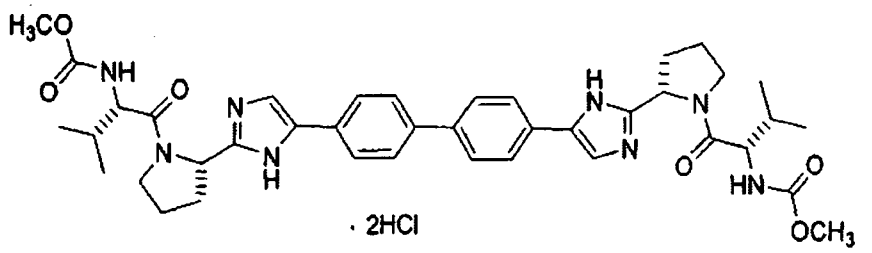
CLAIMS

What is claimed is:

1. Form N-2 of



2. Form N-2 of



characterized by the following unit cell parameters:

Cell dimensions: a = 7.5680 Å

b= 9.5848 Å

c = 16.2864 Å

α = 74.132 degrees

β = 84.132 degrees

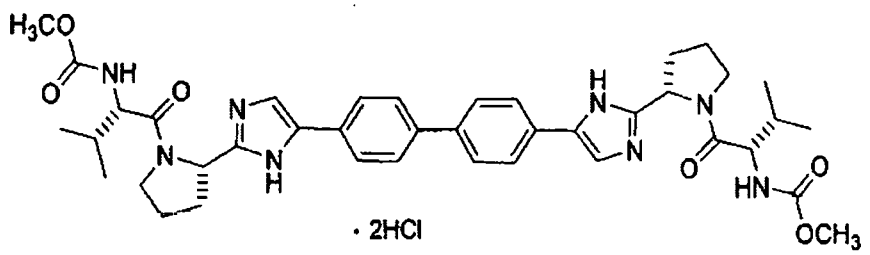
γ = 70.646 degrees

Space group P1

Molecules/unit cell 1

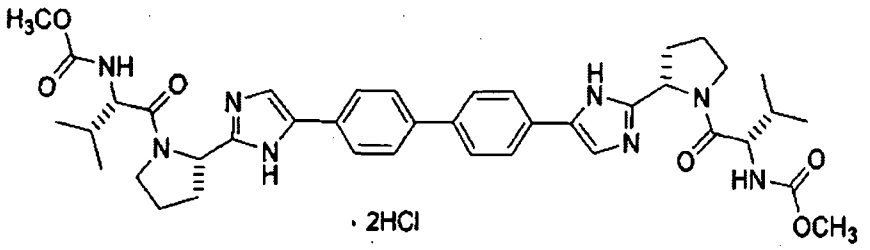
wherein measurement of said crystalline form is at a temperature between about 20 °C to about 25 °C.

3. Form N-2 of



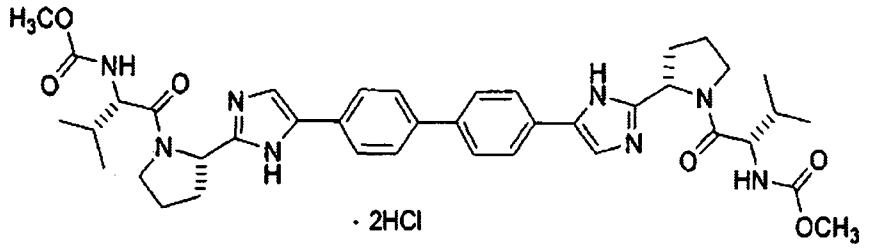
characterized by fractional atomic coordinates within the unit cell as listed in Table 3.

4. Form N-2 of



with characteristic peaks in the powder X-Ray diffraction pattern at values of two theta of 10.3 ± 0.1, 12.4 ± 0.1, 12.8 ± 0.1, 13.3 ± 0.1, 13.6 ± 0.1, 15.5 ± 0.1, 20.3 ± 0.1, 21.2 ± 0.1, 22.4 ± 0.1, 22.7 ± 0.1, and 23.7 ± 0.1 at a temperature between about 20°C and about 25 °C.

5. Form N-2 of



characterized by one or more of the following:

a) a unit cell with parameters substantially equal to the following:

Cell dimensions: a = 7.5680 Å

b= 9.5848 Å

c = 16.2864 Å

α = 74.132 degrees

β = 84.132 degrees

γ = 70.646 degrees

Space group P1

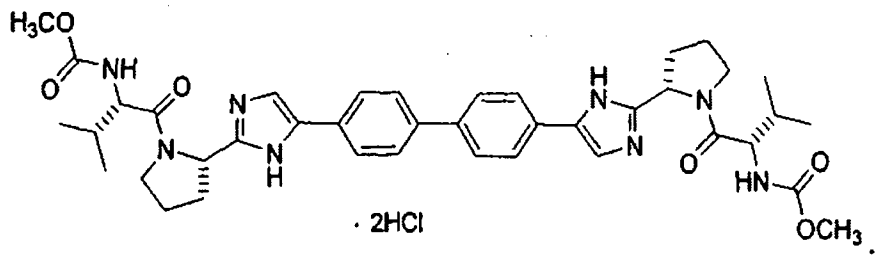
Molecules/unit cell 1

wherein measurement of said crystalline form is at a temperature between about 20 °C to about 25 °C;

b) characteristic peaks in the powder X-Ray diffraction pattern at values of two theta of 10.3 ± 0.1, 12.4 ± 0.1, 12.8 ± 0.1, 13.3 ± 0.1, 13.6 ± 0.1, 15.5 ± 0.1, 20.3 ± 0.1, 21.2 ± 0.1, 22.4 ± 0.1, 22.7 ± 0.1, and 23.7 ± 0.1 at a temperature between about 20°C and about 25 °C; and/or

c) a melt with decomposition endotherm with onset typically in the range of 225-245 °C.

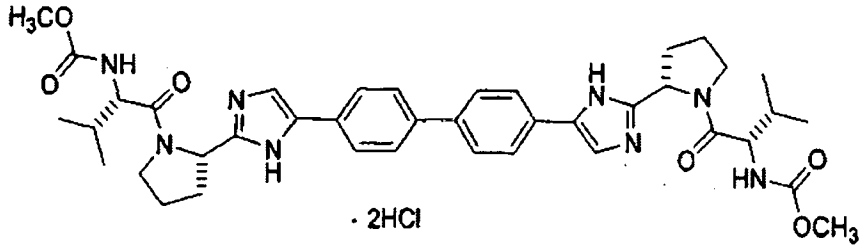
6. Substantially pure Form N-2 of



7. The form of Claim 6 wherein said Form N-2 has a purity of at least 95 weight percent.

8. The form of Claim 6 wherein said Form N-2 has a purity of at least 99 weight percent.

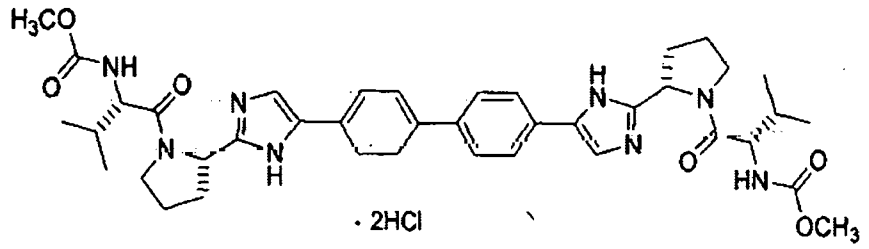
9. Substantially pure Form N-2 of



with characteristic peaks in the powder X-Ray diffraction pattern at values of two theta of 10.3 ± 0.1, 12.4 ± 0.1, 12.8 ± 0.1, 13.3 ± 0.1, 13.6 ± 0.1, 15.5 ± 0.1, 20.3 ±

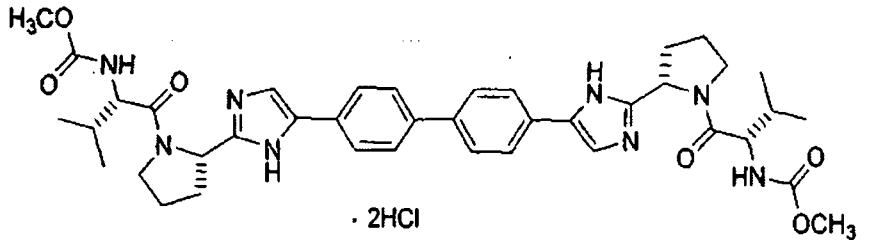
0.1, 21.2 ± 0.1, 22.4 ± 0.1, 22.7 ± 0.1, and 23.7 ± 0.1 at a temperature between about 20°C and about 25 °C.

10. A pharmaceutical composition comprising Form N-2 of



and a pharmaceutically acceptable carrier or diluent.

11. A pharmaceutical composition comprising substantially pure Form N-2 of

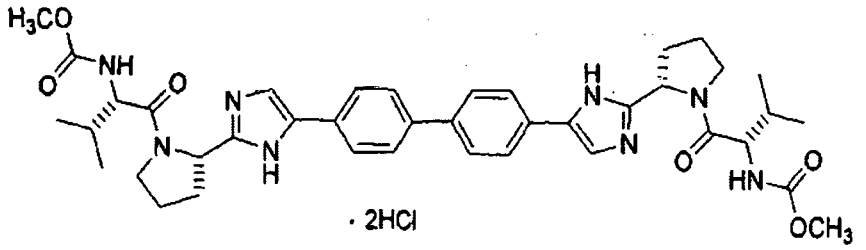


and a pharmaceutically acceptable carrier or diluent.

12. The pharmaceutical composition of Claim 11 wherein said Form N-2 has a purity of at least 95 weight percent.

13. The pharmaceutical composition of Claim 11 wherein said Form N-2 has a purity of at least 99 weight percent.

14. A pharmaceutical composition comprising Form N-2 of



in combination with one or two additional compounds having anti-HCV activity.

15. The pharmaceutical composition of Claim 14 wherein said Form N-2 has a purity of at least 90 weight percent.

16. The pharmaceutical composition of Claim 14 wherein said Form N-2 has a purity of at least 95 weight percent.

17. The pharmaceutical composition of Claim 14 wherein said Form N-2 has a purity of at least 99 weight percent.

18. The composition of Claim 14 wherein at least one of the additional compounds having anti-HCV activity is an interferon or ribavirin.

19. The composition of Claim 18 wherein the interferon is selected from interferon alpha 2B, pegylated interferon alpha, consensus interferon, interferon alpha 2A, and lymphoblastiod interferon tau.

20. The composition of Claim 14 wherein at least one of the additional compounds is selected from interleukin 2, interleukin 6, interleukin 12, a compound that enhances the development of a type 1 helper T cell response, interfering RNA, anti-sense RNA, Imiqimod, ribavirin, an inosine 5'-monophospate dehydrogenase inhibitor, amantadine, and rimantadine.

Dated this 05/02/2010

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OF REMFRY & SAGAR
ATTORNEY FOR THE APPLICANT[S]

WO 2009/020828 PCT/US2008/071734

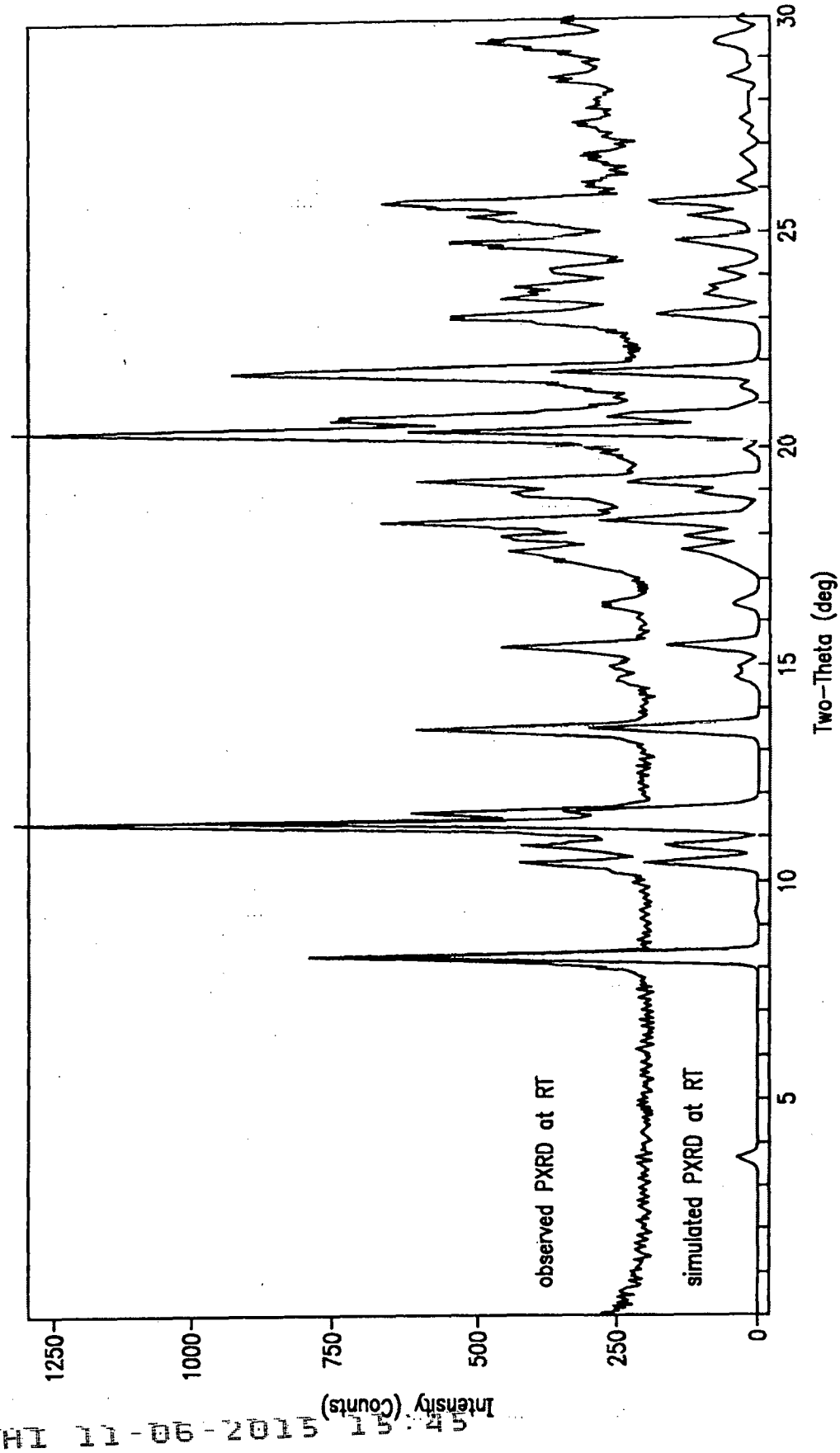

FIG. 1

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ORIGINAL

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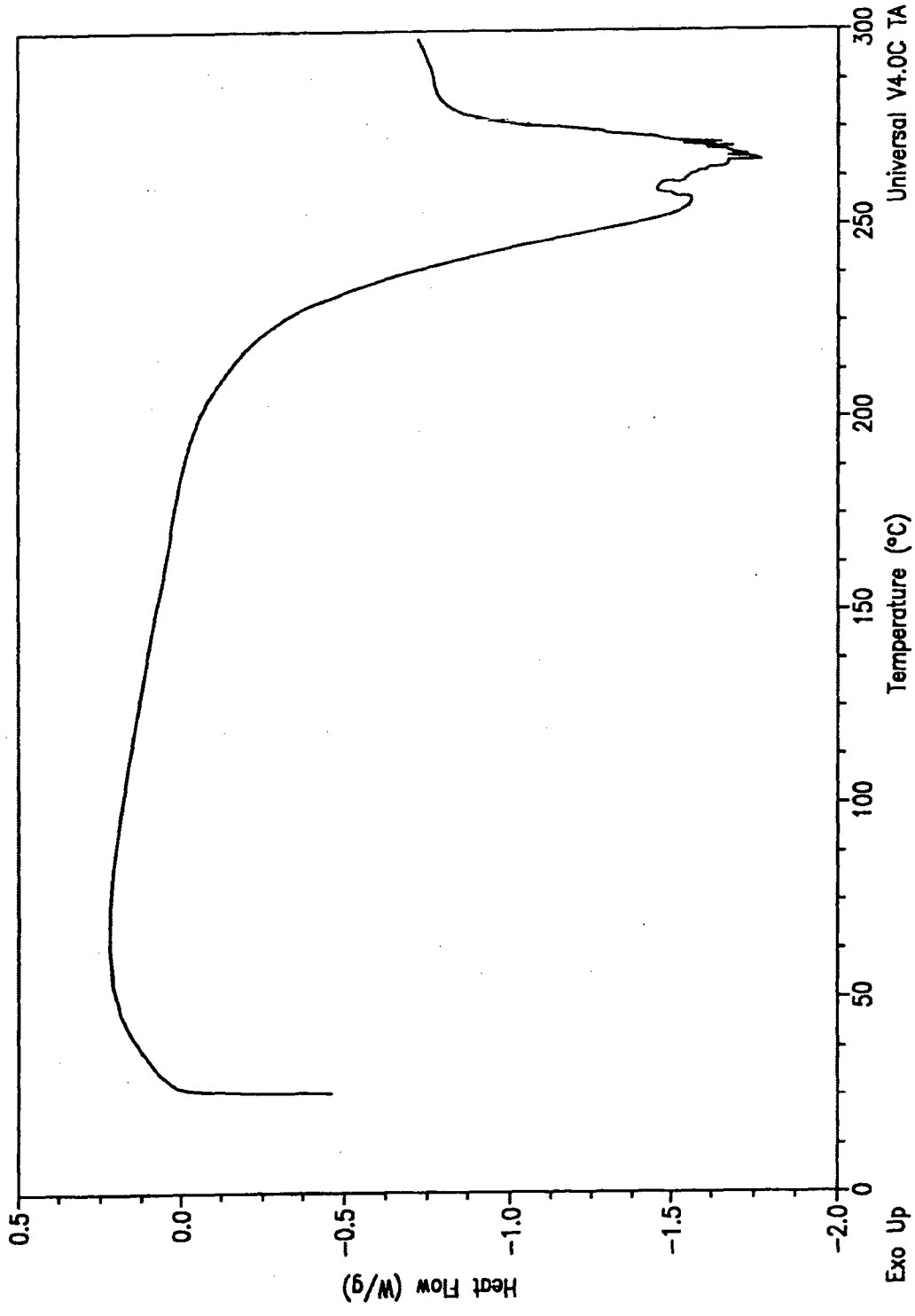

FIG. 2

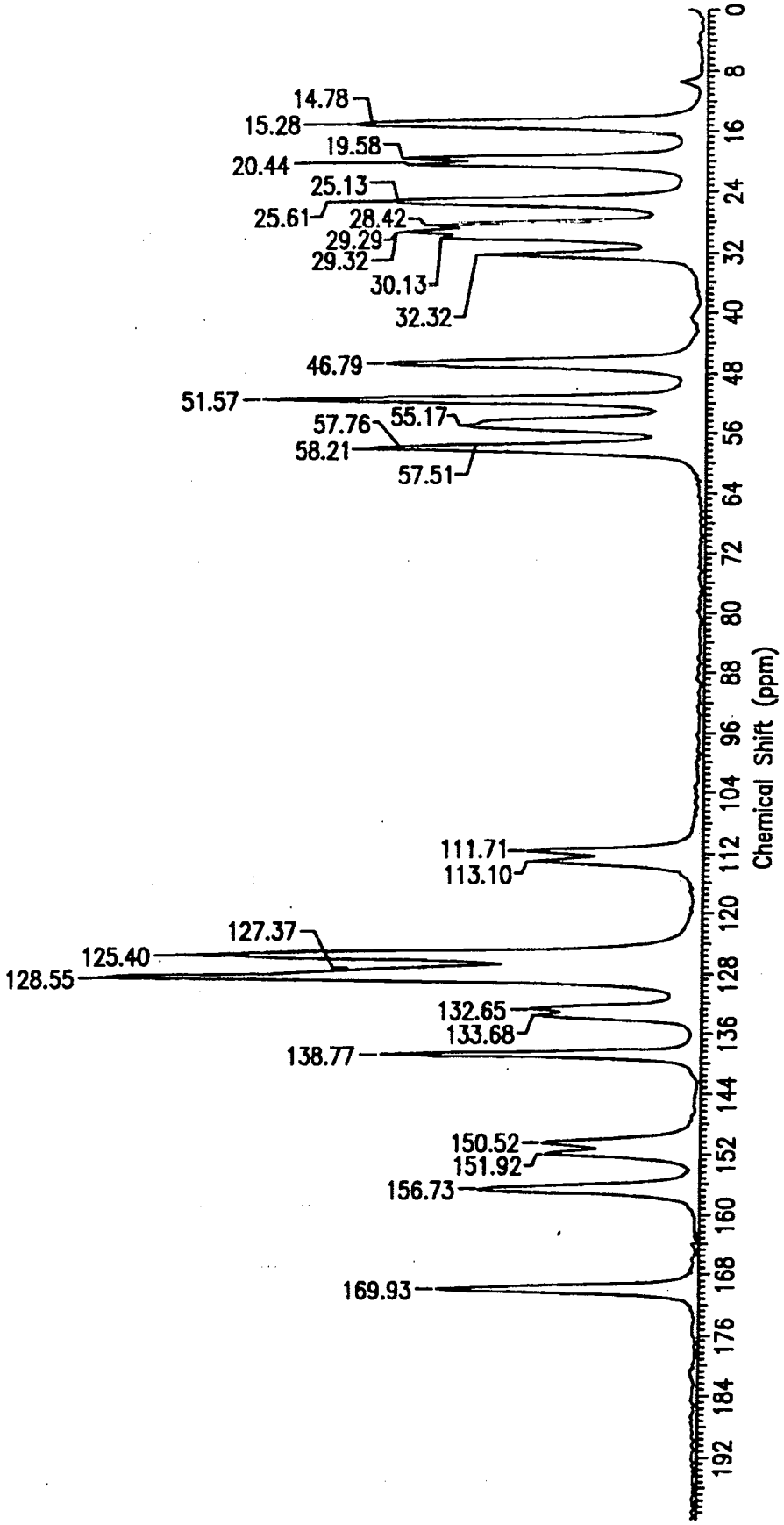

FIG. 3

IN THE MATTER OF

Indian Patent Application 853/DELNP/2009

In the name of

BRISTOL-MYERS SQUIBB COMPANY

AND IN THE MATTER OF

A pre-grant representation by

DALVIR SINGH

D5 – US Patent Publication 20040152073

US 20040152073A1

(19) United States

(12) Patent Application Publication (10) Pub. No.: US 2004/0152073 A1

Herget et al. (43) Pub. Date: Aug. 5, 2004

(54) THERAPEUTIC TARGETS FOR TREATMENT OF HCV INFECTIONS, METHODS OF TREATING HCV INFECTIONS AND COMPOUNDS USEFUL THEREFOR

(76) Inventors: **Thomas Herget**, Planegg (DE); **Matthew Cotten**, Munchen (DE); **Sabine Obert**, Munchen (DE); **Bert Klebl**, Munchen (DE)

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(21) Appl. No.: **10/723,719**

(22) Filed: **Nov. 26, 2003**

Related U.S. Application Data

(63) Continuation-in-part of application No. 10/342,054, filed on Jan. 14, 2003, which is a continuation-in-part of application No. PCT/EP02/04167, filed on Apr. 15, 2002.

(60) Provisional application No. 60/283,345, filed on Apr. 13, 2001. Provisional application No. 60/430,367, filed on Dec. 3, 2002.

(30) **Foreign Application Priority Data**

Nov. 29, 2002 (DE)..... DE 102 55 861.2

Publication Classification

(51) **Int. Cl.**[7] **C07H 21/04**; C12Q 1/28; C12Q 1/70; G01N 33/53

(52) **U.S. Cl.** **435/5**; 435/7.1; 435/28; 536/23.2; 536/23.5

(57) **ABSTRACT**

The present invention relates to the human cellular protein glutathione peroxidase-gastrointestinal as a target for medical intervention against Hepatitis C virus (HCV) infections. Furthermore, the present invention relates to a method for the detection of compounds useful for prophylaxis and/or treatment of Hepatitis C virus infections and a method for detecting Hepatitis C virus infections in an individual or in cells. Also compositions, compounds, nucleic acid molecules (such as aptamers), mono- or polyclonal antibodies are disclosed which are effective for the treatment of HCV infections, and methods for prophylaxis and/or treatment of Hepatitis C virus infections or for the regulation of Hepatitis C virus production are disclosed.

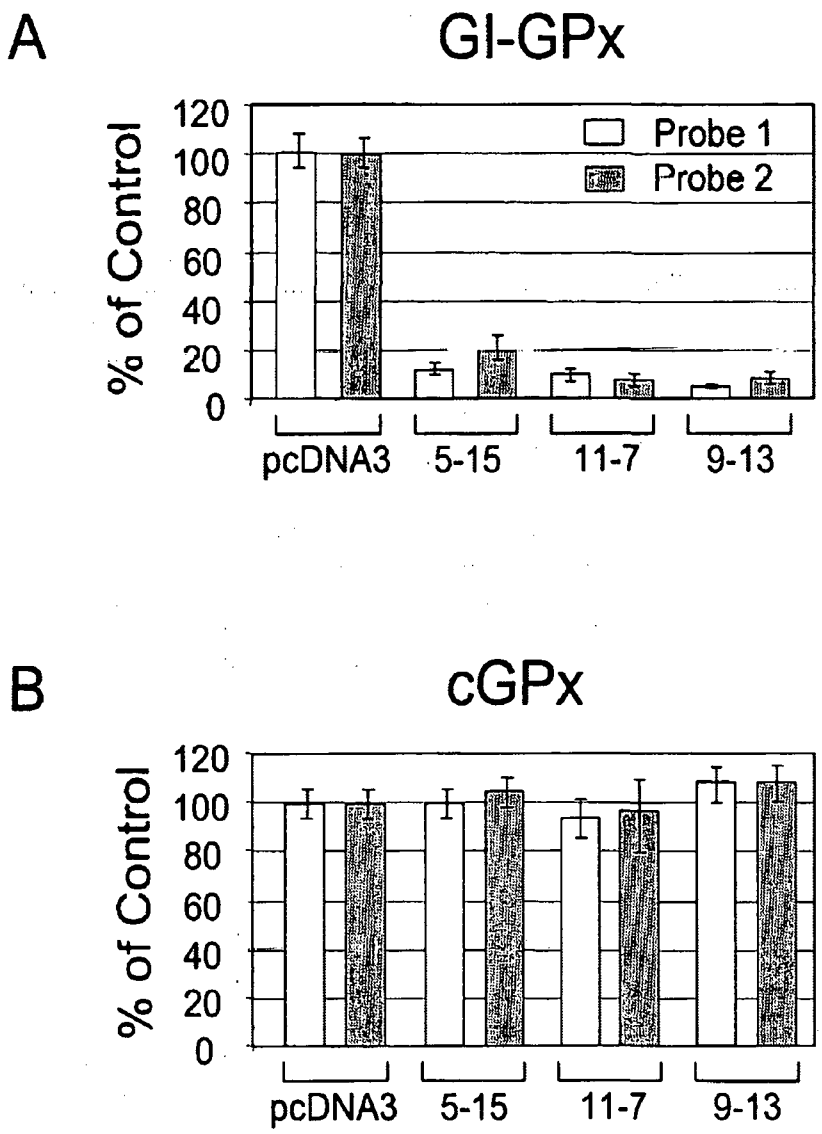

Fig. 1

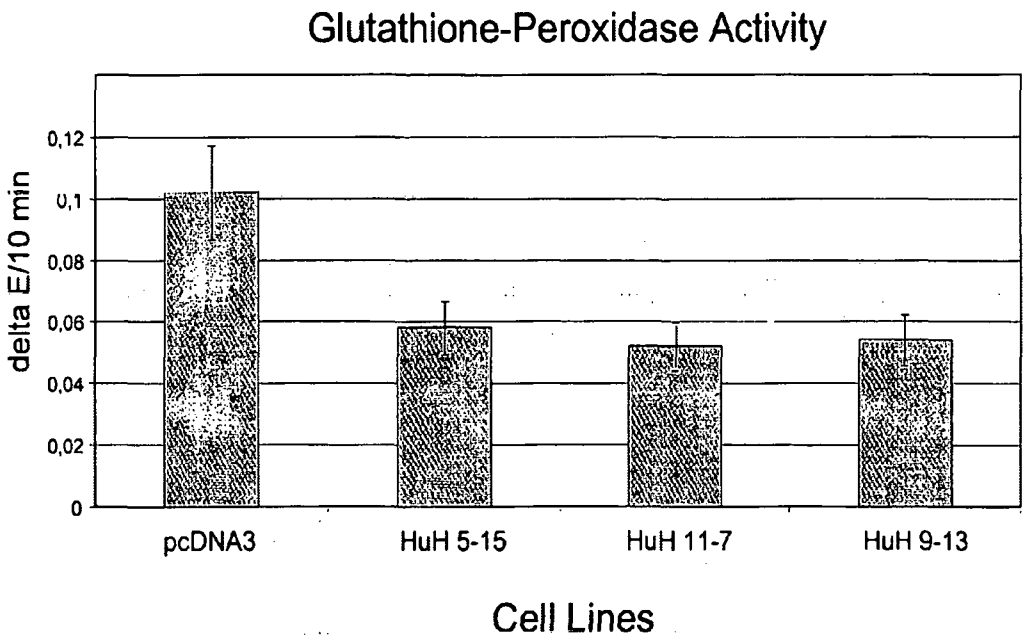

Fig. 2

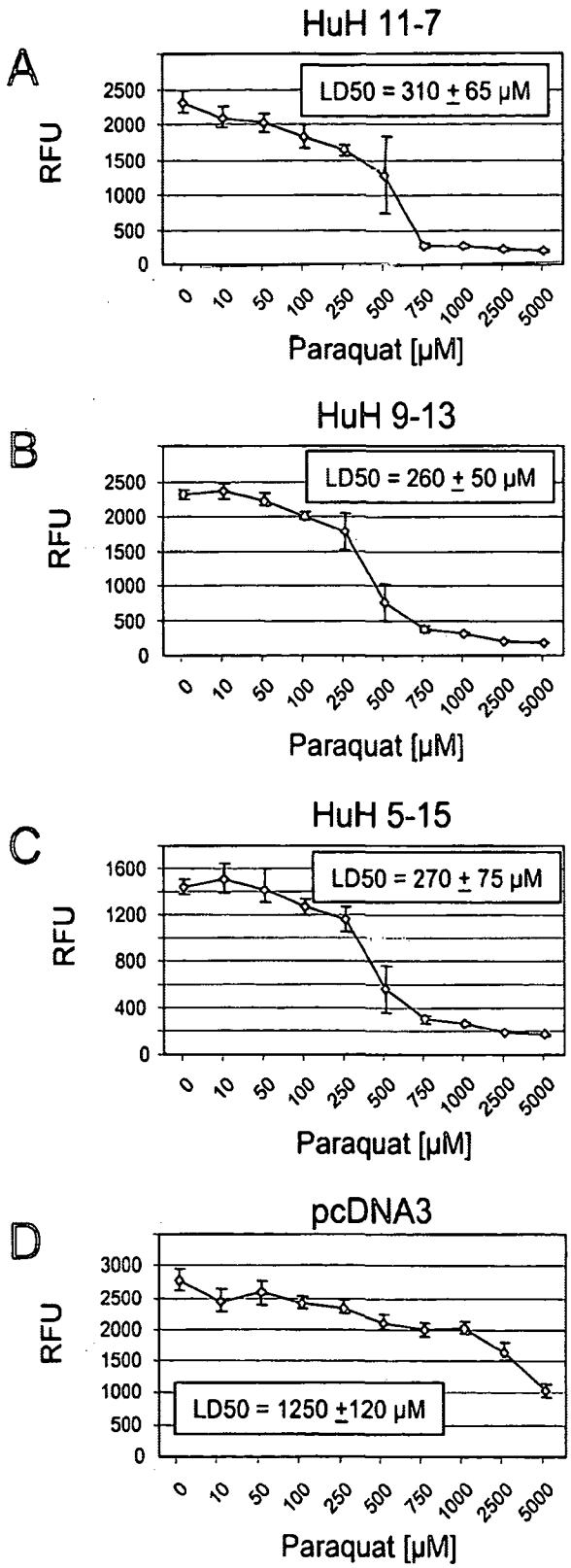

Fig. 3

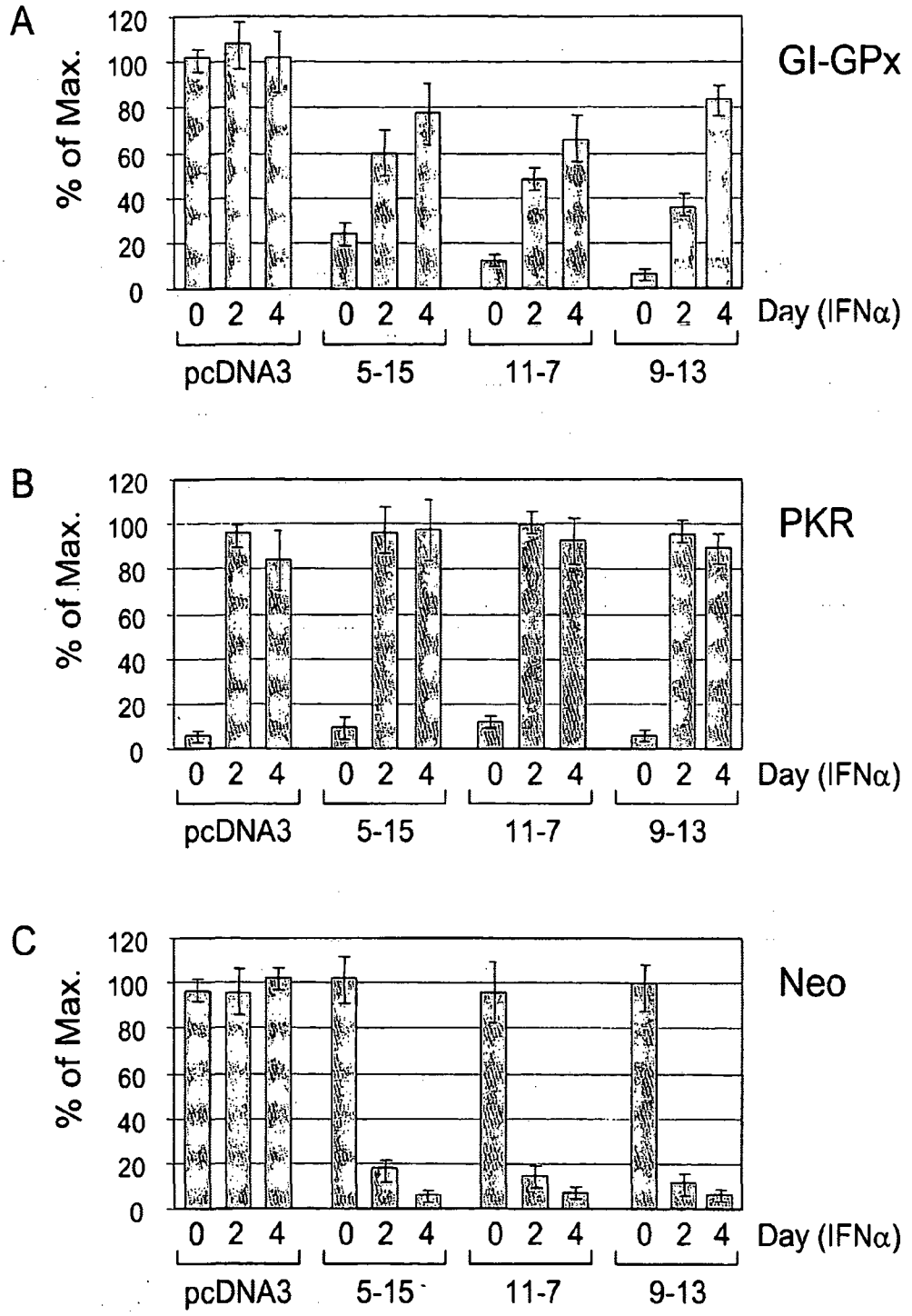

Fig. 4

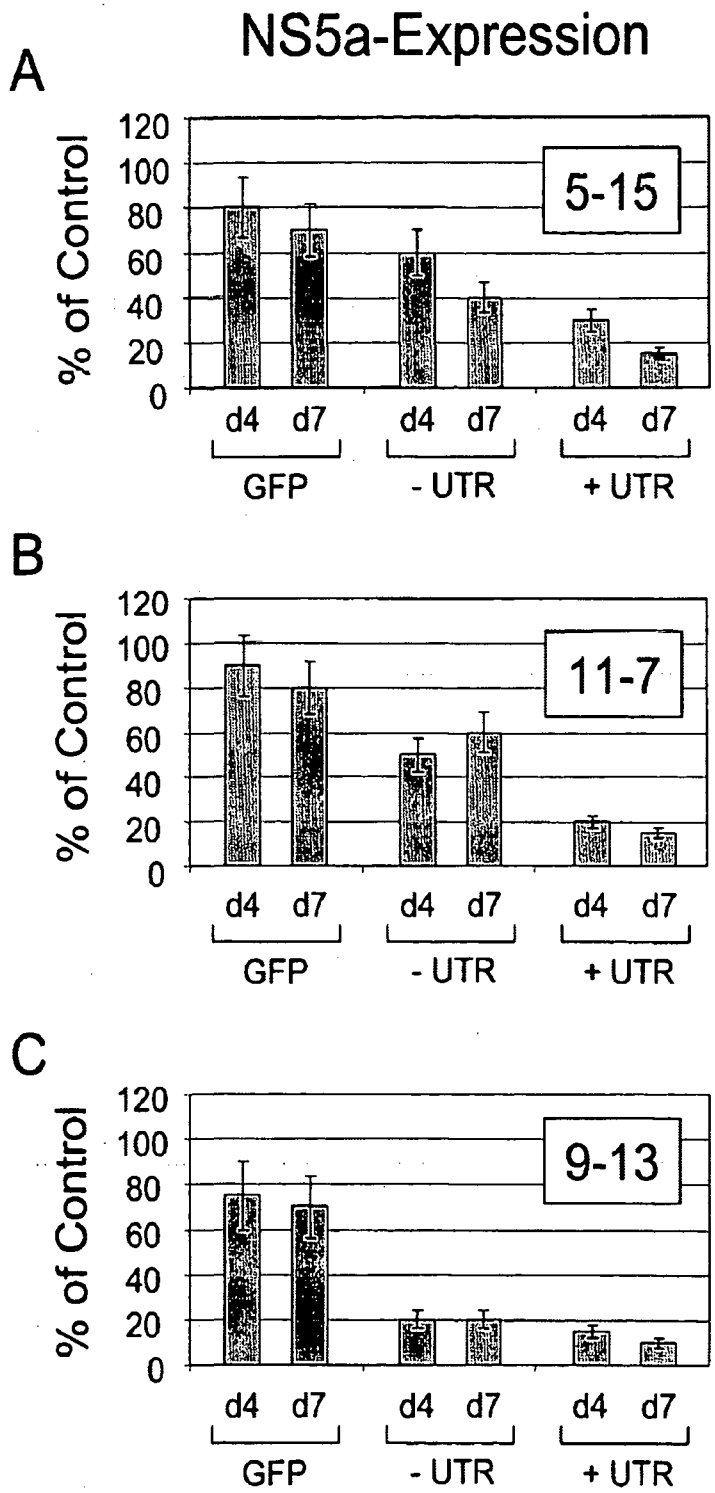

Fig. 5

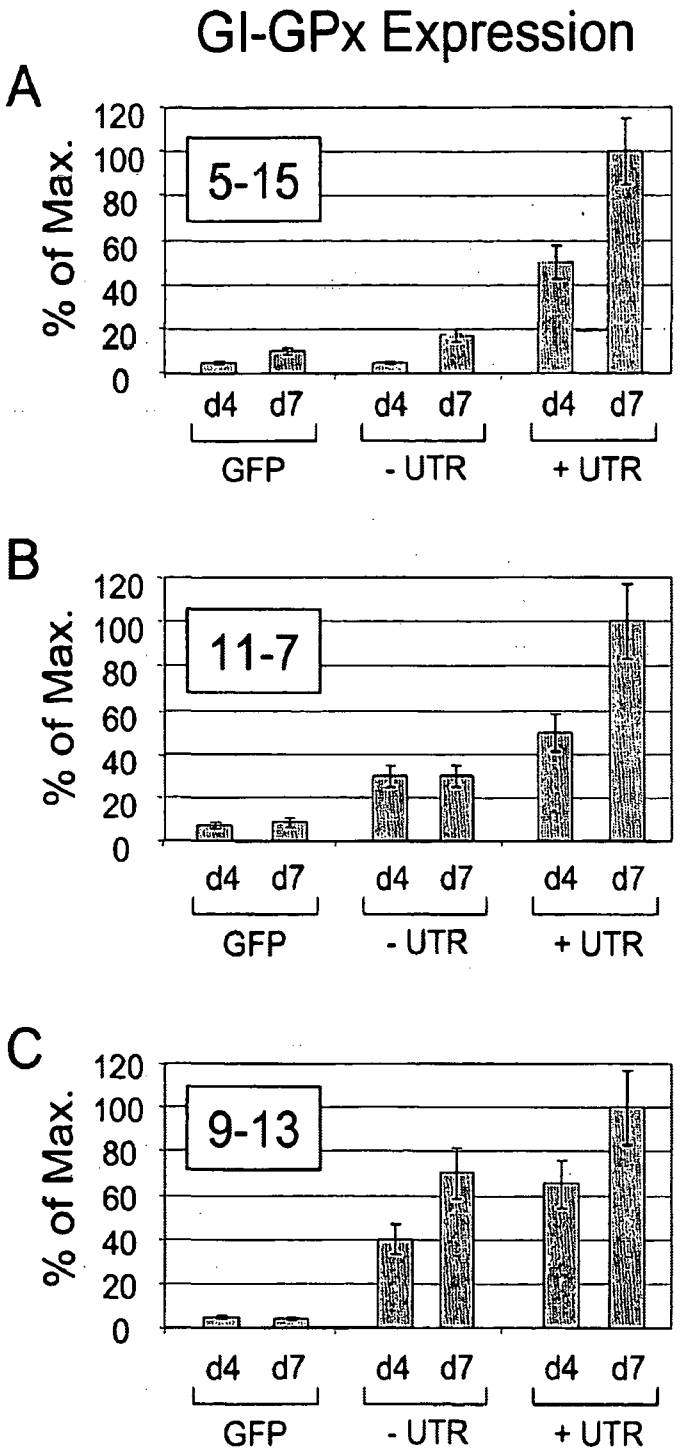

Fig. 6

THERAPEUTIC TARGETS FOR TREATMENT OF HCV INFECTIONS, METHODS OF TREATING HCV INFECTIONS AND COMPOUNDS USEFUL THEREFOR

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] The present application is a continuation-in-part of copending U.S. application Ser. No. 10/342,054, filed Jan. 14, 2003, which is a continuation-in-part of international application PCT/EP02/04167, filed Apr. 15, 2002 and designating the U.S., which claims priority to U.S. provisional application No. 60/283,345, filed Apr. 13, 2001. The present application also claims priority to German patent application No. DE 102 55 861.2, filed Nov. 29, 2002 and to U.S. provisional application No. 60/430,367, filed Dec. 3, 2002.

FIELD OF THE INVENTION

[0002] The present invention relates to the human cellular protein glutathione peroxidase-gastrointestinal (or gastrointestinal glutathione peroxidase, abbreviated GI-GPx) as a potential target for medical intervention against Hepatitis C virus (HCV) infections. Furthermore, the present invention relates to a method for the detection of compounds useful for prophylaxis and/or treatment of Hepatitis C virus infections and a method for detecting Hepatitis C virus infections in an individual or in cells. Also mono- or polyclonal antibodies are disclosed that are effective for the treatment of HCV infections together with methods for treating Hepatitis C virus infections or for the regulation of Hepatitis C virus production wherein genes or said antibodies may be used.

[0003] The present invention also relates to chemical compounds and substances which are effective against Hepatitis C virus (HCV) infections. In particular, compositions comprising said compounds and/or substances, use of the compounds and/or substances for the preparation of compositions useful for the prophylaxis and/or treatment of HCV infections, as well as methods for preventing and/or treating HCV infections.

BACKGROUND OF THE INVENTION

[0004] Hepatitis C Virus (HCV) infection is a major cause of chronic hepatitis, cirrhosis and hepatocellular carcinoma. The World Health Organization estimates that approximately 3% of the world population, or 170 million people, have been infected with the Hepatitis C virus. In the United States, an estimated 3.9 million Americans have been infected with HCV (CDC fact sheet September 2000). Over 80% of HCV-infected individuals develop chronic hepatitis, which is associated with disease states ranging from asymptomatic carrier states to repeated inflammation of the liver and serious chronic liver disease. Over the course of 20 years, more than 20% of chronic HCV-patients are expected to be at risk to develop cirrhosis or progress to hepatocellular carcinoma. Liver failure from chronic hepatitis C is the leading indicator for liver transplantation. Excluding transplantation, the CDC estimates that medical and work-loss cost for HCV annually are around $600 million.

[0005] HCV is transmitted primarily by blood and blood products. Due to routine screening of the blood supplies from mid-1992, new transfusion-related cases are exceedingly rare and have been surpassed by injection drug use as the highest risk factor for acquiring the virus. There is also a sexual, however inefficient, route of transmission, and a 6% rate of transmission from infected mothers to their children, which is higher in case of HIV co-infection. In a certain percentage of infections, the mode of transmission remains unknown. In spite of the significant decline in incidence in the 1990's, the number of deaths (estimated deaths annually at the moment: 8000 to 10,000 in U.S.) and of severe disease due to HCV is anticipated to triple in the next 10 to 20 years. (Sources: CDC fact sheets, accessed Dec. 12, 2000; Houghton, "Hepatitis C Viruses", in *Fields Virology*, B. N. Fields, D. M. Knipe, P. M. Howley, eds. (Lippencott-Raven Pub., Philadelphia, (1996); Rosen and Gretch, *Molecular Medicine Today*, 5: 393 (September 1999); *Science*, 285: 26 (July 1999): News Focus: The scientific challenge of Hepatitis C; Wong et al., *Am J Public Health*, 90: 1562 (October 2000), estimating future hepatitis C morbidity, mortality, and costs in the United States.)

[0006] According to the announcement from the EASL (European Association for the Study of the Liver) International Consensus Conference on Hepatitis C (Feb. 26-28, 1999, Paris, France), combination therapy of alpha interferon and ribavirin is the recommended treatment for naive patients. Monotherapy with interferon has also been approved by the FDA, but the sustained response rate (i.e., HCV RNA remains undetectable in the serum for more than 6 months after end of therapy) is only 15 to 20%, in contrast to 35 to 45% with combination therapy. Interferons (Intron A, Schering-Plough; Roferon A, Hoffmann-LaRoche; Wellferon, Glaxo Wellcome; Infergen, Amgen) are injected subcutaneously three times a week, ribavirin (Rebetol, Schering-Plough) is an oral drug given twice a day. Recommended treatment duration is 6 to 12 months, depending on HCV genotype. Experimental forms of slow-release pegylated interferons (Pegasys, Hoffmann-LaRoche; PEG-Intron, Schering-Plough) have shown improvements in response rates (42 to 82% in combination with ribavirin) and application (once-weekly injection) in recent clinical studies (Hepatology 32:4, Pt 2 of 2. October 2000; NEJM 343, 1673. December 2000; NEJM 343, 1666. December 2000). Common side effects of interferon therapy include: e.g., fatigue, muscle aches, head aches, nausea, fever, weight loss, irritability, depression, bone marrow suppression, reversible hair loss. The most common side effects of ribavirin are anemia, fatigue and irritability, itching, skin rash, nasal stuffiness, sinusitis, cough. More serious side effects of mono-and combination therapy occur in less than two percent of patients (NIDDK information: Chronic Hepatitis C: Current Disease Management; accessed Sep. 12, 1999). Some of the contraindications to interferon are psychosis or severe depression; neutropenia and/or thrombocytopenia; organ transplantation except liver; symptomatic heart disease; decompensated cirrhosis; uncontrolled seizures. Contraindications to ribavirin are end-stage renal failure; anemia; hemoglobinopathies; severe heart disease; pregnancy; no reliable method of contraception (consensus statement EASL). Moreover, treatment of Hepatitis C virus infection with interferon-alpha is effective in only a minority of individuals. This suggests that the virus may be resistant to interferon.

[0007] Moreover, although the combination therapy of interferon and ribavirin induces a sustained virologic response in up to 50 to 60% of cases, a significant number

of patients do not respond to the combination therapy. (See, Hoofnagle J H, di Bisceglie A M, *N. Engl. J Med.* 1 336(5): 347-356 (1997)).

[0008] Other experimental treatments include: the administration of Maxamine (histamine dihydrochloride, Maxim Pharmaceuticals), which will be combined with Interferon in phase III studies; VX-497 (Vertex Pharmaceuticals), an IMP dehydrogenase inhibitor, as a less toxic ribavirin substitute in phase II; and amantadine (Endo Labs), an approved influenza drug, as the third component in triple therapy (phase II). Inhibitors for HCV enzymes such as protease inhibitors, RNA polymerase inhibitors, helicase inhibitors as well as ribozymes and antisense RNAs are under preclinical development (Boehringer Ingelheim, Ribozyme Pharmaceuticals, Vertex Pharmaceuticals, Schering-Plough, Hoffmann-LaRoche, Immusol, Merck, etc.). No vaccine is available for prevention or therapeutic use, but several companies are trying to develop conventional or DNA vaccines or immunostimulatory agents (e.g., Chiron, Merck/Vical, Epimmune, NABI, Innogenetics).

[0009] In addition, antibodies against HCV virion have been developed and entered into clinical trials recently (Trimera Co., Israel).

[0010] In summary, the available treatment for chronic Hepatitis C is expensive, effective only in a certain percentage of patients, and commonly leads to adverse side effects.

[0011] What is needed, therefore, is an alternate and effective approach to inhibiting HCV replication and for treating HCV infections in patients, particularly in patients who fail to respond to current therapies involving interferon.

SUMMARY OF THE INVENTION

[0012] The present invention is based upon the surprising discovery that the human cellular protein gastrointestinal glutathione peroxidase (P18283) is specifically downregulated as a result of HCV replication in HCV infected host cells. The antiviral therapeutic and/or prophylactic research approach described herein focuses on discovering the cellular signal transduction pathways involved in viral infections. Identification of the signal transduction molecules that are key to viral infection provides for, among other things, novel diagnostic methods, for example, assays and compositions useful therefor, novel targets for antiviral therapeutics, a novel class of antiviral therapeutics, and new screening methods (e.g., assays), and materials to discover new antiviral agents.

[0013] In one aspect, the present invention is directed to a method for detecting compounds useful for the prophylaxis and/or treatment of Hepatitis C virus infections comprising the steps of contacting a test compound with human cellular protein gastronintestinal glutathione peroxidase and detecting gastrointestinal glutathione peroxidase activity.

[0014] In another aspect, the present invention is directed to a method for detecting Hepatitis C virus infections in an individual comprising:

[0015] a) providing a sample from said individual; and

[0016] b) detecting activity in the sample of gastrointestinal glutathione peroxidase.

[0017] In another aspect, the present invention is directed to a method for detecting Hepatitis C virus infections in cells, cell cultures, or cell lysates, comprising:

[0018] a) providing the cells, cell cultures, or cell lysates; and

[0019] b) detecting activity in said cells, cell cultures, or cell lysates of human cellular protein gastrointestinal glutathione peroxidase.

[0020] In another aspect, the present invention is directed to a method for preventing and/or treating Hepatitis C virus infection and/or diseases associated with HCV infection comprising the step of administering a pharmaceutically effective amount of an agent which inhibits at least partially the activity of GI-GPx or which inhibits at least partially the production of GI-GPx.

[0021] In another aspect, the present invention is directed to a method for regulating the production of Hepatitis C virus in an individual, cells, cell culture, or cell lysates comprising the step of administering a pharmaceutically effective amount of an agent wherein said agent inhibits at least partially the activity of human cellular protein gastrointestinal glutathione peroxidase or wherein said agent at least partially inhibits the production of human cellular protein gastrointestinal glutathione peroxidase.

[0022] Accordingly, as disclosed in the present application, agents with an inhibitory activity for gastrointestinal glutathione peroxidase include, but are not limited to, monoclonal or polyclonal antibodies that bind to GI-GPx.

[0023] In yet another aspect, the present invention is directed to methods for preventing and/or treating Hepatitis C virus infection and/or diseases associated with HCV infection in an individual comprising the step of administering a pharmaceutically effective amount of an agent which activates at least partially the activity of human cellular protein gastrointestinal glutathione peroxidase or which activates or stimulates at least partially the production of human cellular protein gastrointestinal glutathione peroxidase.

[0024] In another aspect, the present invention is directed to a method for regulating the production of Hepatitis C virus in an individual, cells, cell culture, or cell lysates, comprising the step of administering a pharmaceutically effective amount of an agent wherein said agent activates at least partially the activity of human cellular protein gastrointestinal glutathione peroxidase or wherein said agent at least partially activates or stimulates the production of the human cellular protein gastrointestinal glutathione peroxidase.

[0025] In still another aspect, the present invention is directed to a method for regulating the expression of the human cellular protein gastrointestinal glutathione peroxidase in an individual, cells, cell culture, or cell lysates, comprising the step of administering a pharmaceutically effective amount of an agent wherein said agent inhibits at least partially the transcription of DNA and/or the translation of RNA encoding the human cellular protein gastrointestinal glutathione peroxidase.

[0026] Accordingly, as disclosed in the present application, agents which inhibit the transcription of DNA and/or the translation of RNA include, but are not limited to,

oligonucleotides that bind the DNA and/or RNA coding for GI-GPx. Such oligonucleotides may be aptamers or antisense nucleic acid molecules.

[0027] The present invention is also directed to a method for regulating the expression of the human cellular protein gastrointestinal glutathione peroxidase in an individual, cell, cell culture, or cell lysate, comprising the step of administering a pharmaceutically effective amount of an agent wherein said agent activates at least partially the transcription of DNA and/or the translation of RNA encoding human cellular protein gastrointestinal glutathione peroxidase.

[0028] In addition, the present invention is directed to a method for regulating the activity of the human cellular protein gastrointestinal glutathione peroxidase in an individual, cell, cell culture, or cell lysate, comprising the step of administering a pharmaceutically effective amount of an agent wherein said agent interacts with the human cellular protein gastrointestinal glutathione peroxidase.

[0029] In another aspect, the present invention is directed to a method for the selective killing of HCV infected cells in an individual, cells, cell culture, or cell lysate, comprising the step of administering a pharmaceutically effective amount of a radical initiator which is capable of generating artificial oxidative stress conditions within the cells.

[0030] In yet another aspect, the present invention is directed to a method for preventing and/or treating HCV infections in an individual by at least partially compensating for the down-regulation of GI-GPx comprising the step of administering a pharmaceutically effective amount of at least one antioxidant which is capable of supporting the function of GI-GPx present within the cells.

[0031] In still another aspect, the present invention is directed to a method for at least partially compensating for the down-regulation of GI-GPx in an individual, cells, cell culture, or cell lysates, comprising the step of administering a pharmaceutically effective amount of at least one antioxidant which is capable of supporting the function of GI-GPx present within the cells.

[0032] The present invention is also directed to a composition useful for the prophylaxis and/or treatment of Hepatitis C virus and/or diseases associated with HCV infection in an individual, said composition comprising at least one agent capable of inhibiting activity of human cellular protein gastrointestinal glutathione peroxidase or capable of decreasing the expression of human cellular protein gastrointestinal glutathione peroxidase.

[0033] The present invention is also directed to a composition useful for the regulation of GI-GPx activity in an individual, cells, cell culture, or cell lysates, said composition comprising at least one agent capable of inhibiting activity of human cellular protein gastrointestinal glutathione peroxidase or capable of decreasing the expression of human cellular protein gastrointestinal glutathione peroxidase.

[0034] In another aspect, the present invention is directed to a composition useful for the prophylaxis and/or treatment of Hepatitis C virus and/or diseases associated with HCV infection in an individual, said composition comprising at least one agent capable of increasing the activity of human cellular protein gastrointestinal glutathione peroxidase or capable of activating or stimulating the expression of human cellular protein gastrointestinal glutathione peroxidase.

[0035] The present invention is also directed to a composition useful for the regulation of GI-GPx activity in an individual, cells, cell culture, or cell lysates, said composition comprising at least one agent capable of increasing the activity of human cellular protein gastrointestinal glutathione peroxidase or capable of activating or stimulating the expression of human cellular protein gastrointestinal glutathione peroxidase.

[0036] Accordingly, as disclosed in the present application, specific chemical substances and compounds that can be used alone or in combination to upregulate and/or activate the human cellular protein gastrointestinal glutathione peroxidase include, but are not limited to, selenium, selenium salts, Vitamin D_3, and retinoids. Particularly preferred retinoids include all forms of retinoic acid, including, but not limited to, 9-cis retinoic acid, salts of 9-cis retinoic acid, C_1-C_{10} alkyl esters of 9-cis retinoic acid, salts of C_1-C_{10} alkyl esters of 9-cis retinoic acid, C_1-C_{10} alkyl amides of 9-cis retinoic acid, salts of C_1-C_{10} alkyl amides of 9-cis retinoic acid, 13-cis retinoic acid, salts of 13-cis retinoic acid, C_1-C_{10} alkyl esters of 13-cis retinoic acid, salts of C_1-C_{10} alkyl esters of 13-cis retinoic acid, C_1-C_{10} alkyl amides of 13-cis retinoic acid, salts of C_1-C_{10} alkyl amides of 13-cis retinoic acid, retinol, retinoic acid adlehyde, etretinate, N-(4-hydroxyphenyl) retinamide (4-HPR), 6-[3-(1-adamantyl)-4-hydroxyphenyl]-2-naphthalene carboxylic acid (CD437; AHPN), all-trans-retinoic acid, C_1-C_{10} esters and amides of all-trans-retinoic acid, paraquat, 4-[E-2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)-1-propenyl]benzoic acid, 4-hydroxyphenylretinamide, and 4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)carboxamido]benzoic acid. Additionally, alpha interferon and/or ribavirin may be included to maximize the antiviral effect.

[0037] Because retinoic acid and other retinoids are well known, persons skilled in the art will be aware of various other retinoids which may be useful in practicing the methods of the present invention. For example, additional retinoids suitable for use in the present invention are disclosed in U.S. Pat. No. 6,274,747; U.S. Pat. No. 6,326,397; and U.S. Pat. No. 6,403,554, incorporated herein by reference.

[0038] In order to develop new pharmaceutically active compounds, a potential target for medical intervention has to be identified. Thus, processes for finding pharmaceutically effective compounds include target identification. Target identification is basically the identification of a particular biological component, namely a protein and its association with particular disease states or regulatory systems. A protein identified in a search for a pharmaceutically active chemical compound (drug) that can affect a disease or its symptoms is called a "target". Said target is involved in the regulation or control of biological systems and its function can be interfered with by a drug.

[0039] It is an object of the present invention to provide novel targets for medical intervention, prophylaxis and/or treatment of Hepatitis C virus infections in mammals, including humans, cells, cell cultures, or cell lysates together with methods for detecting HCV infections in individuals, cells, cell cultures and cell lysates, and methods for detecting compounds useful for prophylaxis and/or treatment of

HCV infections. It is another object of the present invention to provide compounds, compositions and methods which are effective in the prophylaxis and/or treatment of Hepatitis C virus infections, but which lack the negative side-effects described above. A further object of the invention is to provide alternative, effective therapeutic treatments for HCV-infected patients, particularly patients who fail to respond to current anti-HCV combinatorial therapies, for example, patients who fail to successfully respond to interferon and ribavirin treatment. The object of the present invention is accomplished according to the teachings herein and the methods defined in the following independent claims. Further advantageous features, aspects and details of the invention are evident from the description, the examples, and the dependent claims of the present application.

[0040] Definitions

[0041] The word "disease" is used herein to refer to an acquired condition or genetic condition. A disease can alter the normal biological system of the body, causing an over- or under-abundance of chemical compounds (chemical imbalance). The regulatory systems for these chemical compounds involve the use by the body of certain proteins to detect imbalances or cause the body to produce neutralizing compounds in an attempt to restore the chemical balance.

[0042] The word "body" is used herein to refer to any biological system, e.g., human, animal, cells, cell culture, or cell lysates.

[0043] The term "associated diseases" refers to, for instance, opportunistic infections, liver cirrhosis, liver cancer, hepatocellular carcinoma, or any other diseases that can come along with HCV infection.

[0044] As used herein, the term "inhibitor" refers to any compound capable of downregulating, decreasing, inactivating, suppressing or otherwise regulating the amount and/or activity of GI-GPx or its expression. Generally, GI-GPx inhibitors may be proteins, oligopeptides and polypeptides, nucleic acids such as RNAi's, genes, small chemical molecules, or other chemical moieties. Small chemical molecules are, for instance, organic compounds with molecular weight typically below 500 g/mol and preferably also with less than 10 heteroatoms.

[0045] As used herein, the term "activator" refers to any chemical compound capable of upregulating, activating, stimulating, or increasing the amount and/or activity of GI-GPx or its expression. Generally, said agents may be proteins, oligo- and polypeptides, nucleic acids, genes, small chemical molecules, or other chemical moieties. An example for an activator of glutathione peroxidase is, e.g., selenium and retinoic acid (see, Brigelius-Flohé, 1999, *Free Radicals in Biology and Medicine*, 27: 951-965; Chu et al., 1999, *Journal of Nutrition*, 129: 1846-1854).

[0046] The term "agent" is used herein as a synonym for regulator, inhibitor, and/or activator. Thus, the term "agent" refers to any chemical or biological compound capable of downregulating or upregulating, decreasing or increasing, suppressing or stimulating, inactivating or activating, or otherwise regulating or effecting the amount and/or activity of GI-GPx and/or the expression of GI-GPx.

[0047] One special kind of said agents are aptamers which function as regulators of the activity of a wide range of cellular molecules such as GI-GPx. Aptamers are nucleic acid molecules selected in vitro to bind small molecules, peptides, or proteins with high affinity and specificity. Aptamers not only exhibit highly specific molecular recognition properties but are also able to modulate the function of their cognate targets in a highly specific manner by agonistic or antagonistic mechanisms. The most familiar examples of aptamers are DNA aptamers or RNA aptamers.

[0048] In addition to their role in transmitting genetic information from DNA to proteins, RNA molecules participate actively in many cell processes. Examples are found in translation (rRNA, tRNA, tmRNA), intracellular protein targeting (SRP), nuclear splicing of pre-mRNA (snRNPs), mRNA editing (gRNA), and X-chromosome inactivation (Xist RNA). Each of these RNA molecules acts as a functional product in its own right, without coding any protein. Because RNA molecules can fold into unique shapes with distinct structural features, some RNAs bind to specific proteins or small molecules (as in the ATP-binding aptamer), while others catalyze particular chemical reactions. Thus, RNA aptamers can be used to interact with GI-GPx and thereby modulate, regulate, activate, or inhibit the activity and biological function of said peroxidase.

[0049] As used herein, the term "regulating expression and/or activity" generally refers to any process that functions to control or modulate the quantity or activity (functionality) of a cellular component. Static regulation maintains expression and/or activity at some given level. Upregulation refers to a relative increase in expression and/or activity. Accordingly, downregulation refers to a relative decrease in expression and/or activity. Downregulation is synonymous with inhibition of a given cellular component's activity.

BRIEF DESCRIPTION OF THE DRAWINGS

[0050] **FIG. 1:**

[0051] Replicon cells express less GI-GPx mRNA than control HuH7 cells:

[0052] HuH7 control cells (pcDNA3) and the HuH7 replicon cell lines 5-15, 11-7 and 9-13 were plated in 10-cm culture dishes (5×10^5 cells/58 cm^2) and harvested after three days when cells were actively progressing through the cell cycle. Total RNA was isolated and 10 μg separated in a 1.2% agarose gel and used for Northern blot analysis.

[0053] Graph A: Blots were hybridized with radioactively labeled oligonucleotides (Probe 1: open bar and Probe 2: filled bar) complementary to the mRNA coding for human gastrointestinal glutathione peroxidase (GI-GPx). Membrane was exposed to Kodak x-ray films for one day at −80° C. with intensifier screens. The films were scanned and the density of the mRNA coding for GI-GPx calculated. The value for the control cells (pcDNA3) was set as 100% and compared with the values of the three replicon cell lines (±SEM), as indicated.

[0054] Graph B: Blots were stripped and re-hybridized with two oligonucleotides (Probe 1: open bars and Probe 2: filled bars) recognizing the classic glutathione peroxidase (cGPx) mRNA. Membrane was exposed to Kodak x-ray films for two days at −80° C. with intensifier screens. The film was densitrometrically scanned, the intensities of the cGP mRNA of the control cell line pcDNA3 (set as 100%)

compared with the replicon cell lines, as indicated. The data shown are the results of three independent experiments.

[0055] **FIG. 2**:

[0056] Cellular activity of glutathione peroxidase is reduced in replicon cell lines:

[0057] Cultures were plated and harvested as described in the examples section below. 180 μg protein of cytosolic extract were used for estimation of glutathione peroxidase activity as described infra. The mean change (±SEM) of extinction at 340 nm reflecting glutathione peroxidase activity for each cell line is illustrated.

[0058] **FIG. 3**:

[0059] Replicon cells are susceptible towards oxidative stress:

[0060] Cells were plated in 96-well microtiter plates (5×10^3 cells/0.35 cm^2) and after three days treated for 24 hours with the concentration of paraquat depicted. Cell viability was measured utilizing an Alamar-Blue assay and is reflected by relative fluorescence units (RFU) at 405 nm. The LD_{50} values (±SEM) of three independent experiments are shown for each cell line.

[0061] **FIG. 4**:

[0062] Effect of interferon on GI-GPx-, PKR- and genomic HCV-RNA levels:

[0063] The HuH7 pcDNA3 control cells and the replicon cell lines 5-15, 11-7 and 9-13 were plated as described in legend to **FIG. 1** and after three days (Day 0) treated for two (Day 2) and four days (Day 4) with 1000U/ml interferon α (IFN-α). Then, cultures were harvested and RNA was prepared. 10 μg of total RNA were used for Northern blot analysis. For detection of GI-GPx (A) Probe 1 was used (see **FIG. 1**). The membranes were stripped and successively hybridized with probes for PKR (B) and neomycin phosphotransferase (Neo)(C).

[0064] Exposure time for all blots was two days at −80° C. with intensifier screen. The autoradiograms were densitrometrically scanned and the values compared with the maximal value obtained with each probe in the respective experiment. The values depicted (±SEM) are obtained from three independent experiments.

[0065] **FIG. 5** and **FIG. 6**:

[0066] Overexpression of GI-GPx in replicon cells causes downregulation of HCV:

[0067] The replicon cell lines 5-15, 11-7 and 9-13 were plated at a density of 10^5 cells per well of a 6-well plate and infected with 10^3 Adenovirus particles/cell containing either the green fluorescent protein (GFP) as negative control, the GI-GPx cDNA without the 3'UTR (−UTR) and with the 3'UTR containing the SECIS (+UTR), as indicated.

[0068] After four (d4) and seven days (d7) post-infection, cultures were harvested and 10 μg protein separated on a 12.5% polyacrylamide gel. Western blot analysis was performed using an NS5a antibody (**FIG. 5**). Expression of the transduced GI-GPx cDNA was monitored with a GI-GPx-specific antiserum (**FIG. 6**).

[0069] The x-ray films were densitometrically scanned and the NS5a values compared with untransfected control cells (set as 100%) (**FIG. 5**) and the GI-GPx values compared with the maximum expression of the transduced GI-GPx cDNA obtained seven days post infection (set as 100%) (**FIG. 6**).

[0070] A considerable over-expression of the GI-GPx protein was observed, when cells were infected with the GI-GPx +3'UTR virus and slight over-expression of GI-GPx was observed with the GI-GPx −3'UTR virus (**FIG. 6**).

[0071] The data show a drastic down-regulation of the HCV protein NS5a in all replicon cell lines infected with the GI-GPx+3'UTR virus (**FIG. 5**).

[0072] Loading efficiency and integrity of proteins was controlled with a tubulin antibody (data not shown). The values depicted (±SEM) are obtained from three independent experiments.

DETAILED DESCRIPTION OF THE INVENTION

[0073] Recent research has revealed how cells communicate with each other to coordinate the growth and maintenance of the multitude of tissues within the human body. A key element of this communication network is the transmission of a signal from the exterior of a cell to its nucleus, which results in the activation or suppression of specific genes. This process is called signal transduction.

[0074] Signal transduction at the cellular level refers to the movement of signals from outside the cell to inside. The movement of signals can be simple, like that associated with receptor molecules of the acetylcholine class: receptors that constitute channels which, upon ligand interaction, allow signals to be passed in the form of small ion movement, either into or out of the cell. These ion movements result in changes in the electrical potential of the cells that, in turn, propagates the signal along the cell. More complex signal transduction involves the coupling of ligand-receptor interactions to many intracellular events. These events include phosphorylations by tyrosine kinases and/or serine/threonine kinases. Protein phosphorylations change enzyme activities and protein conformations. The eventual outcome is an alteration in cellular activity and changes in the program of genes expressed within the responding cells.

[0075] Signal transducting receptors are of three general classes:

[0076] 1. Receptors that Penetrate the Plasma Membrane and Have Intrinsic Enzymatic Activity:

[0077] Receptors that have intrinsic enzymatic activities include those that are tyrosine kinases (e.g., PDGF, insulin, EGF and FGF receptors), tyrosine phosphatases (e.g., CD45 protein of T cells and macrophages), guanylate cyclases (e.g. natriuretic peptide receptors) and serine/threonine kinases (e.g. activin and TGF-beta receptors). Receptors with intrinsic tyrosine kinase activity are capable of autophosphorylation as well as phosphorylation of other substrates.

[0078] Additionally, several families of receptors lack intrinsic enzyme activity, yet are coupled to intracellular tyrosine kinases by direct protein-protein interactions. This class of receptors includes all of the cytokine receptors (e.g., the interleukin-2 receptor) as well as the CD4 and CD8 cell surface glycoproteins of T cells and the T cell antigen receptor.

[0079] 2. Receptors that are Coupled, Inside the Cell, to GTP-Binding and Hydrolyzing Proteins (Termed G-Proteins):

[0080] Receptors of the class that interact with G-proteins all have a structure that is characterized by seven transmembrane-spanning domains. These receptors are termed serpentine receptors. Examples of this class are the adrenergic receptors, odorant receptors, and certain hormone receptors (e.g., glucagon, angiotensin, vasopressin, and bradykinin).

[0081] 3. Receptors that are Found Intracellularly and that Upon Ligand Binding Migrate to the Nucleus where the Ligand-Receptor Complex Directly Affects Gene Transcription:

[0082] The steroid/thyroid hormone receptor superfamily (e.g., glucocorticoid, vitamin D, retinoic acid, and thyroid hormone receptors) is a class of proteins that reside in the cytoplasm and bind the lipophilic steroid/thyroid hormones. These hormones are capable of freely penetrating the hydrophobic plasma membrane. Upon binding ligand the hormone-receptor complex translocates to the nucleus and bind to specific DNA sequences resulting in altered transcription rates of the associated gene.

[0083] When the message reaches the nucleus via one or several of the pathways described above, it initiates the modulation of specific genes, resulting in the production of RNA and finally proteins that carry out a specific biological function. Disturbed activity of signal transduction molecules may lead to the malfunctioning of cells and disease processes.

[0084] The antiviral therapeutic and/or prophylactic research approach described herein focused on discovering the cellular signal transduction pathways involved in Hepatitis C viral infections. Identification of the signal transduction molecules that are key to HCV infection and persistence provides for, inter alia, novel targets for HCV antiviral therapeutics, novel classes of HCV antiviral therapeutics, and new screening methods (e.g., assays), and materials to discover new antiviral agents, and novel HCV diagnostic methods.

[0085] It is now revealed for the first time that the human cellular protein gastrointestinal glutathione peroxidase (GI-GPx) is specifically downregulated in a body as a result of HCV infection. This human cellular protein gastrointestinal glutathione peroxidase has been identified as a novel diagnostic and therapeutic target for HCV infection.

[0086] Glutathione Peroxidase:

[0087] Four distinct species of glutathione peroxidase have been identified in mammals to date, the classical cellular enzyme, the phospholipid hydroperoxide metabolizing enzyme, the gastroinestinal tract enzyme, and the extracellular plasma enzyme. Their primary structures are poorly related. It has been shown that they are encoded by different genes and have different enzymatic properties. The physiological role of the human plasma enzyme remains still unclear due to the low levels of reduced glutathione in human plasma and the low reactivity of this enzyme.

[0088] The human cellular protein glutathione peroxidase-gastrointestinal (GI-GPx) is also known as gastrointestinal glutathione peroxidase, glutathione peroxidase-related protein 2 (GPRP) or glutathione hydrogen peroxide oxidoreductase. It has been assigned to the Accession Number P18283 and the EC Number 1.11.1.9.

[0089] GI-GPx catalyzes the reduction of various organic hydroperoxides, as well as hydrogen peroxide, with glutathione (GSH) as hydrogen donor ($2GSH+H_2O_2 \rightarrow GS\text{-}GS+2H_2O$). It has a molecular weight of 84,000 and 4 subunits per mol of enzyme. The enzyme is useful for enzymatic determination of lipid hydroperoxide.

[0090] GI-GPx belongs to the family of selenoproteins and plays an important role in the defense mechanisms of mammals, birds and fish against oxidative damage by catalyzing the reduction of a variety of hydroperoxides, using glutathione as the reducing substrate. It has been suggested that this enzyme functions as a mechanism of protecting the cellular membrane system against peroxidative damage and that selenium as an essential trace element, may play an important role in this suggested function of the enzyme. It is known that both vitamin E and selenium (Se) act as antioxidants also in a common mechanism of oxidative stress as an underlying cause of genetic changes.

[0091] Selenium functions within mammalian systems primarily in the form of selenoproteins. Selenoproteins contain selenium as selenocysteine and perform a variety of physiological roles. Seventeen selenoproteins have been identified: cellular or classical glutathione peroxidase; plasma (or extracellular) glutathione peroxidase; phospholipid hydroperoxide glutathione peroxidase; gastrointestinal glutathione peroxidase; selenoprotein P; types 1, 2, and 3 iodothyronine deiodinase; selenoprotein W; thioredoxin reductase; and selenophosphate synthetase. Of these, cellular and plasma glutathione peroxidase are the functional parameters used for the assessment of selenium status (Holben and Smith, 1999, *J. Am. Diet. Assoc.*, 99:836-843).

[0092] In addition to vitamin E (DL-α-tocopherol), vitamin C (L-ascorbic acid), co-enzyme Q10, zinc, and selenium, many other antioxidants such as N-acetyl-L-cycteine, N-acetyl-S-farnesyl-L-cysteine, Bilirubin, caffeic acid, CAPE, catechin, ceruloplasmin, Coelenterazine, copper diisopropylsalicylate, deferoxamine mesylate, R-(-)-deprenyl, DMNQ, DTPA dianhydride, Ebselen, ellagic acid, (-)-epigallocatechin, L-ergothioneine, EUK-8, Ferritin, glutathione, glutathione monoethylester, α-lipoic acid, Luteolin, Manoalide, MCI-186, MnTBAP, MnTMPyP, morin hydrate, NCO-700, NDGA, p-Nitroblue, propyl gallate, Resveratrol, rutin, silymarin, L-stepholidine, taxifolin, tetrandrine, tocopherol acetate, tocotrienol, Trolox®, U-74389G, U-83836E, and uric acid (all available from Calbiochem, San Diego, Calif., U.S.A.) can be applied within the disclosed methods for preventing and/or treating HCV infections by compensating at least partially for the down-regulation of GI-GPx.

[0093] Additional antioxidants may be selected from the group of carboxylic acids such as citric acid and phenolic compounds such as BHA (butylated hydroxyanisole), BHT (butylated hydroxytoluene), propyl gallate, TBHQ (tert-butyl hydroquinone), tocopherols, lecithin, gums and resin guiac, THBP (trihydroxybutyrophenone), thiodipropionic acid and dilauryl thiodipropionate, and glycines.

[0094] Oxidative damage is mainly caused by free radicals, particularly reactive oxygen intermediates, derived from normal cellular respiration and oxidative burst pro-

duced when phagocytic cells destroy bacteria or virus-infected cells. In order to cope with the constant generation of potentially damaging oxygen radicals, eukaryotic organisms have evolved many defense mechanisms. These include the above-mentioned antioxidants which act as free radical scavengers and which may interact with GI-GPx and/or may activate, stimulate, and/or increase the expression and/or production of GI-GPx. This advantageous effect of the antioxidants on the amount of GI-GPx generated in the cells competes with the HCV-induced down-regulation of GI-GPx and supports the cells in their fight against the Hepatitis C viruses.

[0095] HCV Infection Studies:

[0096] The only reliable experimental HCV infection studies have been performed with chimpanzees. So far, there is no simple cell culture infection system available for HCV. Although a number of reports have been published describing in vitro propagation attempts of HCV in primary cells and cell lines, questions remain concerning reproducibility, low levels of expression and properly controlled detection methods (reviewed in *J. Gen Virol.*, 81: 1631; *Antiviral Chemistry and Chemotherapy*, 10: 99). For this reason, has been extremely difficult to study how HCV infects cells and to test anti-viral drugs in a model system (the only animals that can be infected are humans and chimpanzees). A major step in devising a culture system for HCV was established by the replicon cell lines (see, Lohmann et al., *Replication of subgenomic hepatitis C virus RNAs in a hepatoma cell line, Science*, 285: 110-113 (1999)). Replication of subgenomic HCV RNAs in cultured hepatocytes were obtained for the first time. These subgenomic replicons are composed of only the part of the HCV genome that encodes the non-structural proteins but are competent to be replicated in cells and to synthesize viral proteins. The replicons described in the scientific article of Lohmann et al., supra, and used in making the discoveries disclosed herein allows studies of HCV replication, pathogenesis and evolution in cell culture. They may also allow for cell-based testing of certain types of anti-viral drugs.

[0097] Thus, the replicon system described by Lohmann et al., supra, reproduces a crucial part of the HCV replication cycle which is used as a system for simulating HCV infection. Lohmann et al. produced bicistronic recombinant RNAs, so-called "replicons", which carry the neomycin-phosphotransferase (NPT) gene as well as a version of the HCV genome where the sequences for the structural HCV proteins were deleted. After transfection of the subgenomic HCV RNA molecules into the human hepatoma cell line HuH7, cells supporting efficient RNA-dependent RNA replication of the HCV replicons were selected based on co-amplification of the NPT gene and resulting resistance to the antibiotic G-418. Integration of coding information into the cellular genome was an exclusion criteria for functional replicons. Several lines were established from G-418 resistant clones with autonomously replicating HCV RNAs detectable by Northern Blotting. Minus-strand RNA replication intermediates were detected by Northern Blotting or metabolic radio-labeling, and the production of nonstructural HCV proteins was demonstrated by immuno-precipitation after metabolic labeling or Western Blotting.

[0098] Possible influences and/or dependencies of HCV's RNA-dependent RNA replication and nonstructural proteins on host cell transcription are accessible to analysis with the Clontech cDNA arrays used in the inventive methods described herein. HuH-pcDNA3 cells are HuH7 cells resistant to G-418 by integration of a NPT gene-carrying plasmid (pcDNA3, Invitrogen) and serve as a negative control. Three replicon lines were analyzed for changes in cellular RNA expression patterns compared to the control line:

[0099] HuH-9-13: a cell line with persistant replicon I377/NS3-3'/wt, described by Lohmann et al., supra,

[0100] HuH-5-15: a cell line with persistant replicon I389/NS3-3'/wt, described by Lohmann et al., supra,

[0101] HuH-11-7: a cell line with persistant replicon I377/NS2-3'/wt, described by Lohmann et al., supra.

[0102] These HCV replicon cells serve as a system for simulation of HCV infected cell systems, especially for simulating HCV infected mammals, including humans. Interference of HCV with the cellular signaling events is reflected in differential gene expression when compared to cellular signaling in control cells. Results from this novel signal transduction microarray analysis revealed significant downregulation of GI-GPx. Radioactively-labeled complex cDNA probes from HCV Replicon cells HuH-9-13, HuH-5-15, and HuH-11-7 were hybridized to cDNA arrays and compared to hybridizations with cDNA probes from HuH-pcDNA control cells which did not contain HCV Replicons.

[0103] Based on the surprising results reported herein, one aspect of the present invention is directed to a screening method for detecting compounds useful for the prophylaxis and/or treatment of Hepatitis C virus infections. Specifically, this method involves contacting a test compound with GI-GPx and detecting the GI-GPx activity. Such methods are advantageously carried out using cell-based techniques, where GI-GPx activity (e.g., GI-GPx transcription) can be measured (e.g., by Northern blotting, see Example 14, infa). Test compounds that enhance the activity of GI-GPx are identified as compounds for treating HCV infections. Alternatively, inhibitors of GI-GPx activity may be identified in this manner and may be used to promote the selective killing of HCV infected cells, in which GI-GPx is already down-regulated.

[0104] Another aspect of the present invention is directed to specific chemical substances and compounds, which, alone or in combination, are useful for the prophylaxis and/or treatment of Hepatitis C virus infections. Specifically, these chemical substances and compounds comprise selenium, selenium salts, Vitamin D_3, and retinoids. Particularly preferred retinoids include all forms of retinoic acid, including, but not limited to, 9-9-cis retinoic acid, salts of 9-cis retinoic acid, C_1-C_{10} alkyl esters of 9-cis retinoic acid, salts of C_1-C_{10} alkyl esters of 9-cis retinoic acid, C_1-C_{10} alkyl amides of 9-cis retinoic acid, salts of C_1-C_{10} alkyl amides of 9-cis retinoic acid, 13-cis retinoic acid, salts of 13-cis retinoic acid, C_1-C_{10} alkyl esters of 13-cis retinoic acid, salts of C_1-C_{10} alkyl esters of 13-cis retinoic acid, C_1-C_{10} alkyl amides of 13-cis retinoic acid, salts of C_1-C_{10} alkyl amides of 13-cis retinoic acid, retinol, retinoic acid adlehyde, etretinate, N-(4-hydroxyphenyl) retinamide (4-HPR), 6-[3-(1-adamantyl)-4-hydroxyphenyl]-2-naphthalene carboxylic acid (CD437; AHPN), all-trans-retinoic acid, C_1-C_{10} esters and amides of all-trans-retinoic acid, paraquat, 4-[E-2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)-1-pro-

penyl]benzoic acid, 4-hydroxyphenylretinamide, and 4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)carboxamido]benzoic acid.

[0105] An additional aspect of the present invention is directed to the use of a combination of compounds for the prophylaxis and/or treatment of Hepatitis C virus infection. Such combinations preferably include, but are not limited to, one or more selenium compounds, especially selenium and selenium salts, in combination with one or more retinoid compounds, especially retinoic acid, including all-trans-retinoic acid, 9-cis retinoic acid and/or 13-cis retinoic acid. Also contemplated are combination therapies which include alpha interferon and/or ribavirin in combination with selenium compounds and retinoids. Particularly preferred combination therapeutics include alpha interferon in combination with selenium or selenium salt(s) also in combination with retinoic acid (most preferably all-trans-retinoic acid, 9-cis retinoic acid and/or 13-cis retinoic acid).

[0106] Another aspect of the present invention is directed to a diagnostic method, for example, an assay for detecting Hepatitis C virus infections in an individual or in cells. This method involves providing a sample from the individual or providing cells and detecting activity of GI-GPx.

[0107] Suitable samples for such methods include, for instance, blood, biopsies, cells, cell cultures, or cell lysates of liver or of any other tissue infected with HCV.

[0108] Accordingly, one aspect of the present invention is directed to novel compounds useful in the above-identified methods. Therefore, the present invention relates to monoclonal or polyclonal antibodies that bind to GI-GPx.

[0109] In addition, the present invention discloses a method for treating Hepatitis C virus infection in an individual comprising the step of administering a pharmaceutically effective amount of an agent which inhibits at least partially the activity of GI-GPx or which inhibits at least partially the production of GI-GPx in the cells.

[0110] Furthermore, the present invention discloses a method for treating Hepatitis C virus infection in an individual comprising the step of administering a pharmaceutically effective amount of at least one of the specific chemical compounds and substances referred to above, which upregulates at least partially the activity of GI-GPx or which upregulates at least partially the production of GI-GPx in the cells.

[0111] A similar aspect of the present invention is directed to a method for preventing and/or treating Hepatitis C virus infection and/or diseases associated with HCV infection in an individual comprising the step of administering a pharmaceutically effective amount of an agent which inhibits at least partially the activity of GI-GPx or which inhibits at least partially the production of GI-GPx.

[0112] Another aspect of the present invention is directed to a method for preventing and/or treating Hepatitis C virus infection and/or diseases associated with HCV infection in an individual, comprising the step of administering a pharmaceutically effective amount of at least one of the specific chemical compounds and substances referred to above, which upregulates at least partially the activity of GI-GPx or which upregulates at least partially the production of GI-GPx.

[0113] Another object of the present invention is to provide a method for regulating the production of Hepatitis C virus in an individual or in cells, cell cultures, or cell lysates comprising the step of administering a pharmaceutically effective amount of an agent wherein said agent inhibits at least partially the activity of GI-GPx or wherein said agent at least partially inhibits the production GI-GPx in the cells. The above-mentioned monoclonal or polyclonal antibodies directed against GI-GPx may be used as pharmaceutically active agents within said methods.

[0114] Another aspect of the present invention is to provide a method for regulating the production of Hepatitis C virus in an individual or in cells, cell cultures, or cell lysates comprising the step of administering a pharmaceutically effective amount of at least one of the specific chemical compounds and substances referred to above, which at least partially upregulate the activity GI-GPx or which at least partially upregulate the production of GI-GPx in the cells.

[0115] In addition to the above-mentioned methods the present invention is also directed to a method for preventing and/or treating Hepatitis C virus infection and/or diseases associated with HCV infection in an individual comprising the step of administering a pharmaceutically effective amount of an agent which activates at least partially GI-GPx or which activates or stimulates the production of GI-GPx in the cells of the individual.

[0116] In addition to the above-mentioned methods the present invention is also directed to a method for preventing and/or treating Hepatitis C virus infection and/or diseases associated with HCV infection in an individual comprising the step of administering a pharmaceutically effective amount of at least one of the specific chemical compounds and substances referred to above, which activates at least partially GI-GPx or which activates or stimulates the production of GI-GPx in the individual.

[0117] Another inventive aspect of the present invention is related to a method for preventing and/or treating Hepatitis C virus infection and/or diseases associated with HCV infection in an individual comprising the step of administering a pharmaceutically effective amount of an agent which activates at least partially the activity of GI-GPx or which activates or stimulates at least partially the production of GI-GPx.

[0118] In addition, the present invention is related to a method for regulating the effects of Hepatitis C virus infection and/or diseases associated with HCV infection in cells, cell cultures, or cell lysates comprising the step of administering a pharmaceutically effective amount of at least one of the specific chemical compounds and substances referred to above, which activates at least partially the activity of GI-GPx or which activate or stimulate at least partially the production of GI-GPx.

[0119] The function of GI-GPx is to detoxify peroxides in cells and prevent the cells from oxidative damage. As demonstrated in **FIG. 3**, subjecting HCV infected cells to oxidative stress conditions, preferably induced by paraquat or radicals generated from peroxides, leads to a decreased resistance of HCV infected cells in comparison to uninfected cells against toxicity of radicals. Thus, generating artificial oxidative stress conditions allows selective killing of HCV-infected cells.

[0120] Examples for useful radical forming compounds (radical initiators) are bipyridyls such as paraquat, 2,2'-bipyridyl and 4,4'-bipyridyl derivatives, bis-6-(2,2'-bipyridyl)-pyrimidines, tris-(2,2'-bipyridyl)-ruthenium, peroxides such as dibenzoylperoxide, diacetylperoxide, hydrogen peroxide, di-tert-butylperoxide, or diaza compounds such as diazaisobutyronitril.

[0121] Another aspect of the present invention is directed to a novel therapeutic composition useful for the prophylaxis and/or treatment of an individual afflicted with Hepatitis C virus and/or associated diseases comprising at least one agent capable of inactivating or inhibiting the activity of GI-GPx or of decreasing or inhibiting the production and/or expression of GI-GPx.

[0122] Yet another aspect of the present invention is directed to a novel therapeutic composition useful for the prophylaxis and/or treatment of an individual afflicted with Hepatitis C virus and/or associated diseases comprising at least one of the specific chemical substances and compounds, alone or in combination, selected from the group consisting of selenium, selenium salts, Vitamin D_3, and retinoids. Particularly preferred retinoids include all forms of retinoic acid, including, but not limited to, 9-cis retinoic acid, salts of 9-cis retinoic acid, C_1-C_{10} alkyl esters of 9-cis retinoic acid, salts of C_1-C_{10} alkyl esters of 9-cis retinoic acid, C_1-C_{10} alkyl amides of 9-cis retinoic acid, salts of C_1-C_{10} alkyl amides of 9-cis retinoic acid, 13-cis retinoic acid, salts of 13-cis retinoic acid, C_1-C_{10} alkyl esters of 13-cis retinoic acid, salts of C_1-C_{10} alkyl esters of 13-cis retinoic acid, C_1-C_{10} alkyl amides of 13-cis retinoic acid, salts of C_1-C_{10} alkyl amides of 13-cis retinoic acid, retinol, retinoic acid adlehyde, etretinate, N-(4-hydroxyphenyl) retinamide (4-HPR), 6-[3-(1-adamantyl)-4-hydroxyphenyl]-2-naphthalene carboxylic acid (CD437; AHPN), all-trans-retinoic acid, C_1-C_{10} esters and amides of all-trans-retinoic acid, paraquat, 4-[E-2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)-1-propenyl]benzoic acid, 4-hydroxyphenylretinamide, and 4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)carboxamido]benzoic acid.

[0123] A preferred selenium salt is sodium selenite. Moreover, according to a further preferred aspect of the present invention, the composition may contain a certain amount of all-trans-retinoic acid.

[0124] Further embodiments of the present invention are represented by methods for regulating the production of Hepatitis C virus in an individual or in cells, cell cultures, or cell lysates comprising the step of administering to an individual or the cells, a pharmaceutically effective amount of an agent wherein said agent activates or increases at least partially the activity of said human cellular protein gastrointestinal glutathione peroxidase or wherein said agent at least partially activates or stimulates the production of said human cellular protein gastrointestinal glutathione peroxidase.

[0125] Agents useful for this method include, but are not limited to, specific chemical substances and compounds, alone or in combination, selected from the group consisting of selenium, selenium salts, Vitamin D_3, and retinoids. Particularly preferred retinoids include all forms of retinoic acid, including, but not limited to, 9-cis retinoic acid, salts of 9-cis retinoic acid, C_1-C_{10} alkyl esters of 9-cis retinoic acid, salts of C_1-C_{10} alkyl esters of 9-cis retinoic acid, C_1-C_{10} alkyl amides of 9-cis retinoic acid, salts of C_1-C_{10} alkyl amides of 9-cis retinoic acid, 13-cis retinoic acid, salts of 13-cis retinoic acid, C_1-C_{10} alkyl esters of 13-cis retinoic acid, salts of C_1-C_{10} alkyl esters of 13-cis retinoic acid, C_1-C_{10} alkyl amides of 13-cis retinoic acid, salts of C_1-C_{10} alkyl amides of 13-cis retinoic acid, retinol, retinoic acid adlehyde, etretinate, N-(4-hydroxyphenyl) retinamide (4-HPR), 6-[3-(1-adamantyl)-4-hydroxyphenyl]-2-naphthalene carboxylic acid (CD437; AHPN), all-trans-retinoic acid, C_1-C_{10} esters and amides of all-trans-retinoic acid, paraquat, 4-[E-2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)-1-propenyl]benzoic acid, 4-hydroxyphenylretinamide, and 4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)carboxamido]benzoic acid, wherein said substances or compounds activate or increase at least partially the activity of said human cellular protein gastrointestinal glutathione peroxidase or wherein said substances or compounds at least partially activate or stimulate the production of said human cellular protein gastrointestinal glutathione peroxidase.

[0126] Further aspects of the present invention relate to methods either for regulating the expression of the human cellular protein gastrointestinal glutathione peroxidase in an individual or in cells, cell culture, or cell lysates comprising the step of administering to either to the individual or the cells, cell culture or cell lysates, a pharmaceutically effective amount of an agent wherein said agent stimulates or increases at least partially the transcription of DNA and/or the translation of RNA encoding GI-GPx.

[0127] According to the above-mentioned method another aspect of the present invention is directed to novel therapeutic compositions useful within said methods for prophylaxis and/or treatment of an individual afflicted with Hepatitis C virus and/or associated diseases. Said compositions comprise at least one agent capable of increasing the activity of GI-GPx or of activating or stimulating the production and/or expression of GI-GPx.

[0128] Agents useful in said compositions include, but are not limited to at least one of the specific chemical substances and compounds, alone or in combination, selected from the group consisting of selenium, selenium salts, Vitamin D_3, and retinoids. Particularly preferred retinoids include all forms of retinoic acid, including, but not limited to, 9-cis retinoic acid, salts of 9-cis retinoic acid, C_1-C_{10} alkyl esters of 9-cis retinoic acid, salts of C_1-C_{10} alkyl esters of 9-cis retinoic acid, C_1-C_{10} alkyl amides of 9-cis retinoic acid, salts of C_1-C_{10} alkyl amides of 9-cis retinoic acid, 13-cis retinoic acid, salts of 13-cis retinoic acid, C_1-C_{10} alkyl esters of 13-cis retinoic acid, salts of C_1-C_{10} alkyl esters of 13-cis retinoic acid, C_1-C_{10} alkyl amides of 13-cis retinoic acid, salts of C_1-C_{10} alkyl amides of 13-cis retinoic acid, retinol, retinoic acid adlehyde, etretinate, N-(4-hydroxyphenyl) retinamide (4-HPR), 6-[3-(1-adamantyl)-4-hydroxyphenyl]-2-naphthalene carboxylic acid (CD437; AHPN), all-trans-retinoic acid, C_1-C_{10} esters and amides of all-trans-retinoic acid, paraquat, 4-[E-2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)-1-propenyl]benzoic acid, 4-hydroxyphenylretinamide, and 4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)carboxamido]benzoic acid, wherein said substances and compounds are capable of increasing the activity of GI-GPx or of activating or stimulating the production and/or expression of GI-GPx.

[0129] Said pharmaceutical compositions may further comprise pharmaceutically acceptable carriers, excipients, and/or diluents.

[0130] Further aspects of the present invention relate to methods either for regulating the expression of the human cellular protein gastrointestinal glutathione peroxidase in an individual or in cells, cell cultures, or cell lysates comprising the step of administering to either the individual or the cells, cell cultures, or cell lysates a pharmaceutically effective amount of an agent wherein said agent inhibits or decreases at least partially the transcription of DNA and/or the translation of RNA encoding said human cellular protein gastrointestinal glutathione peroxidase.

[0131] Therapeutics, pharmaceutically active agents or inhibitors, respectively, may be administered to cells from an individual in vitro, or may involve in vivo administration to the individual. The term "individual" preferably refers to mammals and most preferably to humans. Routes of administration of pharmaceutical preparations to an individual may include oral and parenteral, including dermal, intradermal, intragastral, intracutan, intravasal, intravenous, intramuscular, intraperitoneal, intranasal, intravaginal, intrabuccal, percutaneous, rectal, subcutaneous, sublingual, topical or transdermal application, but are not limited to these ways of administration. For instance, preferred preparations according to the invention will be in a form which is suitable for oral administration. These orally administratable forms, for example, include pills, tablets, film tablets, coated tablets, capsules, powders and deposits. Administration to an individual may be in a single dose or in repeated administrations, and may be in any of a variety of physiologically acceptable salt forms, and/or with an acceptable pharmaceutical carrier, binder, lubricant, excipient, diluent and/or adjuvant. Pharmaceutically acceptable salt forms and standard pharmaceutical formulation techniques are well known to persons skilled in the art.

[0132] As used herein, a "pharmaceutical effective amount" of a GI-GPx activator or GI-GPx inhibitor is an amount effective to achieve the desired physiological result, either in cells, cell cultures, or cell lysates treated in vitro or in a mammalian subject such as a human patient treated in vivo. Specifically, a pharmaceutically effective amount is an amount sufficient to inhibit, for some period of time, one or more of the clinically defined pathological processes associated with the viral infection. The effective amount may vary depending on the specific GI-GPx inhibitor or activator selected, and is also dependent on a variety of factors and conditions related to the subject to be treated and the severity of the infection. For example, if the inhibitor or activator is to be administered in vivo, factors such as the age, weight and health of the patient as well as dose response curves and toxicity data obtained in pre-clinical animal work would be among those considered. If the inhibitor or activator is to be contacted with the cells, cell cultures, or cell lysates in vitro, one would also design a variety of pre-clinical in vitro studies to assess such parameters as uptake, half-life, dose, toxicity, etc. The determination of a pharmaceutically effective amount for a given agent is well within the ability of those skilled in the art.

[0133] By way of illustration, a contemplated therapy according to the invention would entail administration of 1-100 mg/m^2/day of an oral retinoid such as all-trans-retinoic acid, preferably 20-50 mg/m^2/day, preferably administered in 1-4 doses/day (more preferably 1-3 doses daily, most preferably 2 doses daily). Advantageously, this retinoid administration is combined with interferon therapy, e.g., pegylated alpha interferon administered, e.g., 135-180 μg per week by subcutaneous injection. In a preferred aspect of this invention, a selenium compound such as a selenium salt may be added to this combination therapy (e.g., one 30-50 μg capsule daily).

[0134] It is also apparent to a person skilled in the art that detection includes any method known in the art useful to indicate the presence, absence, or amount of a detection target. Such methods may include, but are not limited to, any molecular or cellular techniques, used singularly or in combination, including, but not limited to: hybridization and/or binding techniques, including blotting techniques and immunoassays; labeling techniques (chemiluminescent, calorimetric, fluorescent, radioisotopic); spectroscopic techniques; separations technology, including precipitations, electrophoresis, chromatography, centrifugation, ultrafiltration, cell sorting; and enzymatic manipulations (e.g. digestion).

[0135] The present disclosure also teaches for the first time the downregulation of GI-GPx specifically involved in the viral infection of Hepatitis C virus. Thus, the present invention is also directed to a method useful for detecting novel compounds useful for prophylaxis and/or treatment of HCV infections.

[0136] The present disclosure teaches for the first time the upregulation of GI-GPx specifically involved in the viral infection of Hepatitis C virus using specific chemical compounds and substances, or combinations thereof, selected from the group consisting of selenium, selenium salts, Vitamin D_3, and retinoids. Particularly preferred retinoids include all forms of retinoic acid, including, but not limited to, 9-cis retinoic acid, salts of 9-cis retinoic acid, C_1-C_{10} alkyl esters of 9-cis retinoic acid, salts of C_1-C_{10} alkyl esters of 9-cis retinoic acid, C_1-C_{10} alkyl amides of 9-cis retinoic acid, salts of C_1-C_{10} alkyl amides of 9-cis retinoic acid, 13-cis retinoic acid, salts of 13-cis retinoic acid, C_1-C_{10} alkyl esters of 13-cis retinoic acid, salts of C_1-C_{10} alkyl esters of 13-cis retinoic acid, C_1-C_{10} alkyl amides of 13-cis retinoic acid, salts of C_1-C_{10} alkyl amides of 13-cis retinoic acid, retinol, retinoic acid adlehyde, etretinate, N-(4-hydroxyphenyl) retinamide (4-HPR), 6-[3-(1-adamantyl)-4-hydroxyphenyl]-2-naphthalene carboxylic acid (CD437; AHPN), all-trans-retinoic acid, C_1-C_{10} esters and amides of all-trans-retinoic acid, paraquat, 4-[E-2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)-1-propenyl]benzoic acid, 4-hydroxyphenylretinamide, and 4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthaleuyl)carboxamido]benzoic acid.

[0137] The present invention provides methods to identify compounds useful for prophylaxis and/or treatment of HCV infections by screening a test compound, or a library of test compounds, for its ability to inhibit or activate GI-GPx, identified herein as characteristically downregulated during HCV growth and RNA replication inside a cell or individual. A variety of assay protocols and detection techniques are well known in the art and easily adapted for this purpose by a skilled practitioner. Such methods include, but are not

limited to, high throughput assays (e.g., microarray technology, phage display technology), and in vitro and in vivo cellular and tissue assays.

[0138] In a related aspect, the present invention provides, in view of the important role of GI-GPx in the HCV infection and/or replication process, an assay component especially useful for detecting HCV in an individual, in cells, cell cultures, or cell lysates. Preferably the assay component comprises oligonucleotides immobilized on a solid support capable of detecting GI-GPx activity. Preferably the solid support would contain oligonucleotides of sufficient quality and quantity to detect all of the above-mentioned human cellular proteins (e.g., a nucleic acid microarray).

[0139] Similarly, it is an object of the present invention to provide an assay component especially useful for screening compounds for the prophylaxis and/or treatment of HCV infections. One preferred assay component comprises oligonucleotides that encode GI-GPx immobilized on a solid support.

[0140] The polypeptide product of gene expression may be assayed to determine the amount of expression as well. Methods for assaying for a protein include, but are not limited to, Western Blotting, immuno-precipitation, radio-immuno-assay, immuno-histochemistry and peptide immobilization in an ordered array. It is understood, however, that any method for specifically and quantitatively measuring a specific protein or mRNA product can be used.

[0141] The present invention further incorporates by reference in their entirety techniques well known in the field of microarray construction and analysis. These techniques include, but are not limited to, techniques described in the following patents and patent applications describing array of biopolymeric compounds and methods for their fabrication:

[0142] U.S. Pat. Nos. 5,242,974; 5,384,261; 5,405,783; 5,412,087; 5,424,186; 5,429,807; 5,436,327; 5,445,934; 5,472,672; 5,527,681; 5,529,756; 5,545,531; 5,554,501; 5,556,752; 5,561,071; 5,559,895; 5,624,711; 5,639,603; 5,658,734; 5,807,522; and 6,087,102; international patent publications WO 93/17126; WO 95/11995; and WO 95/35505; European patent publications EP 742 287 and EP 799 897.

[0143] Suitable techniques also include, but are not limited to, techniques described in the following patents and patent application describing methods of using arrays in various applications:

[0144] U.S. Pat. Nos. 5,143,854; 5,288,644; 5,324,633; 5,432,049; 5,470,710; 5,492,806; 5,503,980; 5,510,270; 5,525,464; 5,547,839; 5,580,732; 5,661,028; 5,994,076; 6,033,860; 6,040,138; 6,040,140; international patent publications WO 95/21265; WO 96/31622; WO 97/10365; and WO 97/27317; European patent publications EP 373 203 and EP 785 280.

[0145] It will be readily apparent to those skilled in the art that other suitable modifications and adaptations of the compositions and methods of the invention described herein are evident and may be made and used without departing from the scope of the invention or the embodiments disclosed herein. Having now described the present invention in detail, the same will be more clearly understood by reference to the following examples, which are included for purposes of illustration only and are not intended to be limiting of the invention.

EXAMPLES

[0146] 1. Human cDNA-Arrays on Membranes

[0147] Atlas™ Human Stress Array (Catalog #: 7747-1) from Clontech (Clontech Laboratories, Palo Alto, Calif. 94303, USA) were used. This array includes 234 human cDNAs immobilized in duplicate dots (10 ng of cDNA per dot) on a nylon membrane.

[0148] 2. Cellular HCV RNA Replication System

[0149] HuH-pcDNA3, HuH-9-13, HuH-5-15 and HuH-11-7 cells were grown in DMEM (Dulbecco's Modified Eagle's Medium) supplemented with 10% FCS (fetal calf serum), 2 mM Glutamine, Penicillin (100 IU/ml) /Streptomycin (100 μg/ml) and 1× nonessential amino acids in the presence of 1 mg/ml G-418. Cells were routinely passaged three times a week at a dilution of 1:3 or 1:2.

[0150] 3. Lysis of Cells, and Isolation of Total RNA

[0151] HuH-pcDNA3, HuH-9-13, HuH-5-15 and HuH-11-7 cells were seeded at 5×10^5 cells per 10 cm plate in medium without G-148. The medium was changed 3 days after plating and cells were harvested 5 days after plating by lysing the cells directly on the plate with 4 ml of Tri-reagent (Molecular Research Center, Inc., USA). The lysates were stored at room temperature for 5 minutes and then centrifuged at 12000×g for 15 minutes at 4° C. The supernatant was mixed with 0.1 ml of 1-bromo-3-chloropropane per 1 ml of Tri-reagent and vigorously shaken. The suspension was stored for 5 minutes at room temperature and then centrifuged at 12000×g for 15 minutes at 4° C. The colorless upper phase was transferred into new tubes, mixed with 5 μl of polyacryl-carrier (Molecular Research Center Inc., USA) and with 0.5 ml of isopropanol per 1 ml of Tri-reagent and vigorously shaken. The samples were stored at room temperature for 5 minutes and then centrifuged at 12000×g for 8 minutes at 4° C. The supernatant was removed and the RNA pellet washed twice with 1 ml of 75% ethanol. The pellet was dried and resuspended in 25 μl of RNase-free buffer per initial 1 ml lysate.

[0152] 4. Preparation of Radioactively Labeled cDNA Probes from RNA

[0153] In order to obtain radioactively labeled cDNA probe, RNA was transcribed into a cDNA-probe in the presence of radioactively labeled dATP. Six μg of total RNA was labeled with 100 μCi [^{33}P]-dATP (Amersham, UK) according to the protocol provided by Clontech. Subsequently, the reaction was stopped by adding 5 μl 0.5M EDTA (ethylene diamine tetraacetate) and 25 μl 0.6M NaOH and incubation for 30 minutes at 68° C.

[0154] Unincorporated nucleotides were removed from the labeling reaction using ProbeQuant G-50 columns (Amersham, UK). The column was vigorously shaken and centrifuged for 1 minute at 735×g in an appropriate reaction tube after bottom closure and lid were removed. The column was placed into a new reaction tube, the probe was applied onto the center of a column material and the column was centrifuged for 2 minutes at 735×g. The flow-through was transferred into new reaction tubes and filled up to a volume

of 100 μl with 10 mM Tris, pH 7.4, 1 mM EDTA. The probe was precipitated by centrifugation for 15 minutes at 12000×g after 4 μl of 5M NaCl, 1 μl poly-acryl-carrier (Molecular Research Centre, Inc., USA) and 250 μl ethanol were added. The supernatant was discarded and the pellet dried before starting with the hybridization.

[0155] 5. Hybridization of Radioactively Labeled cDNA-Probes to cDNA-Arrays

[0156] The pellet was resuspended in 10 μl C_0t-1 DNA (1 μg/μl, Roche Diagnostics, Germany), 10 μl yeast tRNA (1 μg/μl Sigma, USA) and 10 μl polyA (1 μg/μl); Roche Diagnostics, Germany). Herring sperm DNA was added to a final concentration of 100 μg/ml and the volume was filled up to 100 μl with 5 μl 10% SDS (Sodiumdodecylsulfate), 25 μl 20×SSC (3 M NaCl, 300 mM Sodium Citrate, pH 7.0) and bidistilled H_2O. The mix was put on 95° C. for 5 minutes, centrifuged for 30 seconds at 10000×g and vigorously shaken for 60 minutes at 65° C. A 1 μl aliquot of the probe was used to measure the incorporation of radioactive dATP with a scintillation counter. Probes with at least a total of 20×10^6 cpm were used. The arrays were prehybridized for at least 3 hours at 65° C. in hybridization solution in a roller bottle oven. After prehybridization the radioactively labeled probe was added into the hybridization solution and hybridization was continued for 20 hours. The probe was discarded and replaced with wash solution A (2×SSC). The arrays were washed twice in wash solution A at room temperature in the roller oven. Afterwards, wash solution A was replaced by wash solution B (2×SSC, 0.5% SDS) preheated to 65° C. and arrays were washed twice for 30 minutes at 65° C. Then, wash solution B was replaced by wash solution C (0.5×SSC, 0.5% SDS) preheated to 65° C. and arrays were washed twice for 30 minutes at 65° C. The moist arrays were wrapped in airtight bags and exposed for 8 to 72 hours on erased phospho-imager screens (Fujifilm, Japan).

[0157] 6. Analysis of cDNA-Arrays

[0158] The exposed phospho-imager screens were scanned with a resolution of 100 μm and 16 bits per pixel using a BAS-1800 (Fujifilm, Japan). Files were imported into the computer program ArrayVision (Imaging Research, Canada). Using the program's features, the hybridization signals of each target cDNA were converted into numbers. The strength of the hybridization signals reflected the quantity of RNA molecules present in the probe. Differentially expressed genes were selected according to the ratio of their signal strength after normalization to the overall intensity of the arrays.

[0159] 7. Results

[0160] Comparing the expression pattern of signal transduction mRNAs in HCV Replicon cells HuH-9-13, HuH-5-15, and HuH-11-7 and HuH-pcDNA control cells which do not contain HCV replicons using cDNA-arrays on membranes, the human gastrointestinal glutathione peroxidase (P18283) gene was identified as anti-HCV target. The mRNA levels were down-regulated to 2.8% in HuH-9-13, to 8.3% in HuH-5-15 and to 6.1% in HuH-11-7 cells compared to non-infected HuH-pcDNA control cells.

[0161] 8. Northern Blotting

[0162] Ten (10) μg total RNA of each cell line was separated in a 1.2% agarose-formaldehyde gel, transferred on nylon membrane (Amersham) and hybridized with two different oligo-desoxyribonucleotides. Their sequences were derived from the coding (5'-TGGTTGGG AAGGTGCG-GCTGTAGC GTC GGAAGGGC-3'; SEQ ID NO:1) and 3'-untranslated (5'-CCTCTCAGACACCACCCAT-GAGGGTTTAGGAAGGTGCCAT-3'; SEQ ID NO:2) region of the human gastrointestinal glutathione peroxidase (P18283) gene. Labeling was performed by 3'-end tailing with ^{32}P-dCTP and terminal transferase (Roche Diagnostics GmbH, Mannheim, Germany). Northern Blotting membranes were hybridized with the labeled oligonucleotides overnight at 65° C. and unspecifically bound probe washed away.

[0163] After final washing (1×SSC, 1% SDS at 60° C. for 30 min.), bound probe was detected by autoradiography for 12 hrs at −70° C. using an x-ray film (Fuji) and quantified with a phospho-imager.

[0164] 9. Confirmation of Expression Pattern by Northern Blotting

[0165] Northern blot analysis was performed with two oligonucleotide probes derived from the human gastrointestinal glutathione peroxidase cDNA. Hybridization resulted in detection of one RNA of about 1 kb in HuH-pcDNA3 cells, but no or only weak detection of this band in HCV-replicon carrying cells. Therefore, analysis of the Northern Blotting signals confirmed precisely the down-regulation previously observed in the filter array hybridization (cf. section 6., supra; **FIG. 1**).

[0166] 10. Glutathione Peroxidase Activity is Reduced in Replicon Cell Lines

[0167] Measuring the glutathione peroxidase activity utilizing tert-butyl hydroperoxide as substrate, revealed that the replicon cells exhibited reduced glutathione peroxidase activity (see **FIG. 2**).

[0168] Methods:

[0169] For measuring cellular glutathione peroxidase activity, the description of the kit's manufacturer (Calbiochem) was followed. Briefly, cells were washed with ice-cold PBS (phosphate buffered saline), harvested with a rubber policeman in 5 mM EDTA, 1 mM DTT (dithiothreitol) and 50 mM Tris-HCl (Tris-(hydroxymethyl)-aminomethane-hydrochloride), pH 7.5 and lysed by three cycles of freezing and thawing. After spinning for 15 min at 10,000×g (4° C.) protein concentration of the supernatant was determined with the BCA reagents (Pierce, Bruchsal, Germany). 180 μg protein were used per assay.

[0170] Tert-butyl hydroperoxide was used as substrate and GI-GPx activity was estimated indirectly. Oxidized glutathione, produced upon reduction of the peroxide by GI-GPx, is recycled to its reduced state by glutathione reductase by oxidation of $NADPH+H^+$ to $NADP^+$. The oxidation of NADPH is accompanied by a decrease in absorbance at 340 nm (A_{340}), which provides a spectrophotometric means of monitoring GI-GPx activity. Thus, the rate of decrease in the A_{340} (delta E in **FIG. 2**) is directly proportional to the GI-GPx activity in the sample.

[0171] 11. Sensitivity of Replicon Cells Towards Paraquat

[0172] Treating mock transfected and replicon cells with increasing amounts of paraquat, a compound which pro-

duces radicals intracellularly, showed enhanced susceptibility of replicon cells against this drug.

[0173] Paraquat impaired the viability of replicon cells more severely than of pcDNA3 control cells (**FIG. 3**). The estimated LD_{50} values for paraquat calculated from three independent experiments were 260±50 μM for HuH 9-13, 270±75 μM for HuH 5-15, 310±65 μM for HuH 11-7 and 1250±120 μM for HuH pcDNA3 (cf **FIG. 3**).

[0174] Methods:

[0175] Replicon cell lines and control cells were incubated for 24 hours with various concentrations of paraquat (methylviologen), and viability of the cultures was measured using the Alamar Blue assay.

[0176] For quantification of the degree of cell death in cell culture we employed the viability assay based on the reduction of tetrazolium salt to formazan by mitochondrial dehydrogenase activity. The assay was performed in 96-well microtiter plates (Greiner, Frickenhausen, Germany) as described previously (T. Herget et al., 1998, *J. Neurochem.*, 70: 47-58) but Alamar Blue (Roche Molecular Biochemicals, Germany) was used instead of MTT. The light absorbance at 405 nm of the medium including all factors but without cells was determined and subtracted from the absorption readings with cells. Eight wells per sample point were analyzed and each experiment was repeated independently at least three times.

[0177] 12. Inverse Regulation of HCV Replication and GI-GPx Expression

[0178] Replicon cells were incubated with alpha interferon (IFN-α) for two and four days. Northern blot analyses were performed with 10 μg total RNA. The IFN-α treatment (1000 U/ml) caused a time- and dose-dependent down-regulation of the HCV-replicon RNA and the HCV protein NS5a. An inverse correlated expression was observed for GI-GPx, i.e., GI-GPx was up-regulated within four days of interferon treatment. Interferon had no effect on the expression of GI-GPx in mock transfected HuH7 cells (cf **FIG. 4**).

[0179] 13. Ectopic Expression of GI-GPx in Replicon Cell Lines

[0180] The cDNA coding for the GI-GPx was cloned by RT-PCR from HuH7 cells. Transient expression of the GI-GPx protein in HEK293 cells caused an increase of glutathione peroxidase activity demonstrating its functionality. The construct was recombined into the genome of Adenovirus. Adenovirus carrying the GI-GPx cDNA was produced and used for transduction of the GI-GPx cDNA into HuH7 and replicon cells. Western blot analyses performed 4 and 7 days after transfection showed a drastic down-regulation of the HCV protein NS5a. Such a down-regulation was not observed when 'empty' or the GFP (green fluorescent protein) gene-containing Adeno virus was used in parallel (cf. **FIGS. 5 and 6**).

[0181] Methods:

[0182] The adenoviruses used here were all E1, E3 defective derivatives of adenovirus type 5 (W. C. Russell, 2000, *J. Gen. Virol.*, 81: 2573-2604). The coding region for GI-GPx (0.7 kb) was amplified by PCR using an upstream primer containing an HindIII recognition site (5'-GCG CAAGCTTATGGCTTTCATTGCCAAGTCCTTC-3', start codon underlined italics; SEQ ID NO:3) and a downstream primer containing an XbaI site (5'-GTTCATCTAGATATG-GCAAC TTTAAGGAGGCGCTTG-3'; SEQ ID NO:4) but without stop-codon to allow expression of fusion proteins with HIS- and VSV-tag. The 3'-UTR (0.3 kb) of the GI-GPx mRNA, containing a SECIS (selenocysteine inserting sequence), was amplified using the up-stream primer 5'-GCC CTCGAGATGTGAACTGCTCAACACACAG-3' (SEQ ID NO:5) with an XhoI recognition site and the down-stream primer 5'-CCACGCGGCCGCTTTATTG-GTCTCTTCTAGCAGAGT GGC-3' (SEQ ID NO: 6) covering the polyadenylation site (AAUAAA) and containing a NotI restriction site for cloning. RNA isolated from HuH7 cells were reverse transcribed and used as template for PCR. The cDNA coding for human GI-GPx was cloned into the transfer plasmid (pPM7) between the CMV (cytomegalovirus) immediately early promoter/enhancer and the rabbit beta-globin intron/polyadenylation signal. This expression cassette was inserted into a bacterial plasmid borne-adenovirus genome using recombination in bacteria (C. Chartier et al., 1996, *J. Virol.*, 70: 4805-4810). A cloned version of the novel genome was identified, the viral genome was released from the plasmid by restriction enzyme digestion and virus replication was initiated by transfecting the genome into HEK 293 cells using a modified PEI transfection method (A.-I. Michou et al., 1999, *J. Virol.*, 73: 1399-1410). Virus was amplified in modified HEK 293 cells (F. L. Graham et al., 1977, *J. Gen. Virol.*, 36: 59-74) and purified from cell lysates using CsCl density gradient centrifugation as described (M. Cotten et al., "Adenovirus polylysine DNA conjugates," in *Current Protocols in Human Genetics* (John Wiley and Sons, Inc.; New York 1996), pp. 12.3.1-12.3.33). Virus was quantified by protein content using the conversion factor 1 mg/ml pure virion protein=3.4×10^{12} viral particles/ml (P. Lemay et al., 1980, *Virology*, 101: 131-143). The control viruses AdJ5 and AdLuc were previously described (J. B. Glotzer et al., 2001, *J. Virol.*, 75: 2421-2434; J. B. Glotzer et al., 2000, *Nature*, 407: 207-211).

[0183] 14. Testing of GI-GPx Regulators

[0184] As a model system for HCV replication there were utilized three replicon cell lines provided by Prof. R. Bartenschlager (University of Heidelberg, Germany). Cultures were treated for various periods of time with all trans-retinoic acid (RA) for comparative purposes and the other agents selenium, selenium salts, Vitamin D_3 and retinoids, like 9-cis-retinoic acid, C_1-C_{10} alkyl esters of 9-cis-retinoic acid, C_1-C_{10} alkyl amides of 9-cis-retinoic acid, N-(4-hydroxyphenyl) retinamide (4-HPR), 6-[3-(1-adamantyl)-4-hydroxyphenyl]-2-naphthalene carboxylic acid (CD437; AHPN) (obtained from Sigma), paraquat, 4-[E-2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)- 1-propenyl] benzoic acid, 4-hydroxyphenylretinamide, and 4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphtalenyl)carboxamido] benzoic acid.

[0185] Levels of GI-GPx protein expression were measured by Western Blotting using antibodies provided by Prof. Brigelius-Flohe (University of Potsdam, Germany), and RNA levels were measured by Northern blotting using GI-GPx-specific oligonucleotides as probes. Levels of HCV RNA were investigated by Northern Blotting using a DNA oligonucleotide complementary to the neomycin phosphotransferase gene as probe. Concentration of the viral protein

NS5a was determined by Western Blotting with an NS5a-specific antibody (Biogenesis, UK).

[0186] GI-GPx is drastically down-regulated in HCV replicon cells compared with mock-transfected HuH7 cells. Forcing replicon cells to re-express GI-GPx (e.g. by infection with GI-GPx containing Adenovirus) results in reduction of subgenomic HCV RNA and of the HCV protein NS5a to barely detectable levels. According to the present invention the discovery of this inverse correlation was used to develop a method to up-regulate the expression of the cellular, endogenous GI-GPx gene. This up-regulation in replicon cells causes a depletion of HCV.

[0187] Treatment of replicon cells for three days with all-trans-retinoic acid (1 μM) had hardly any effect on GI-GPx and HCV expression. However, after seven days of incubation, a drastic up-regulation of GI-GPx, both at the RNA and protein level (three- to ten-fold) was observed. Concomitantly, expression of subgenomic HCV RNA and of viral protein NS5a was downregulated two- to five-fold, depending on the cell line investigated. Furthermore, it was surprisingly found that a further downregulation of HCV-RNA and NS5a protein was dependent on the addition of selenium or a selenium salt, e.g., sodium selenite (50 nM). This fact implies that downregulation of HCV was promoted firstly by activation of the GI-GPx gene on transcriptional level by retinoic acid and secondly by the synthesis of selenoprotein(s) for which sodium selenite was needed. Indeed it could be shown that all-trans-retinoic acid-induced downregulation of HCV is independent of the innate immune response induced by interferon. Thus, all-trans-retinoic acid did not induce the transcription of PKR (double strand RNA-dependent protein kinase). Severe cytotoxic effects were neither observed for all-trans-retinoic acid nor for sodium selenite, or both in combination.

[0188] The presented findings show that retinoids (in combination with selenium or selenium salts like sodium selenite and cAmp or cAmp analogues) can be used for the treatment of HCV-positive patients. Especially the use of retinoids with high specificity for induction of the GI-GPx, like N-(4-hydroxyphenyl) retinamide (4-HPR) and 6-[3-(1-adamantyl)-4-hydroxyphenyl]-2-naphthalene carboxylic acid (CD437; AHPN), are preferred. 4-HPR and AHPN display significant potential as therapeutic agents in the prophylaxis and treatment of a number of premalignant and malignant conditions in the context of HCV infections. Indeed, the obtained data show that next to all trans-retinoic acid, other nuclear receptor ligands, including 9-cis retinoic acid, salts of 9-cis retinoic acid, C_1-C_{10} alkyl esters of 9-cis retinoic acid, salts of C_1-C_{10} alkyl esters of 9-cis retinoic acid, C_1-C_{10} alkyl amides of 9-cis retinoic acid, salts of C_1-C_{10} alkyl amides of 9-cis retinoic acid, 13-cis retinoic acid, salts of 13-cis retinoic acid, C_1-C_{10} alkyl esters of 13-cis retinoic acid, salts of C_1-C_{10} alkyl esters of 13-cis retinoic acid, C_1-C_{10} alkyl amides of 13-cis retinoic acid, salts of C_1-C_{10} alkyl amides of 13-cis retinoic acid, retinol, retinoic acid adlehyde, etretinate, N-(4-hydroxyphenyl) retinamide (4-HPR), 6-[3-(1-adamantyl)-4-hydroxyphenyl]-2-naphthalene carboxylic acid (CD437; AHPN), all-trans-retinoic acid, C_1-C_{10} esters and amides of all-trans-retinoic acid, paraquat, 4-[E-2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)-1-propenyl]benzoic acid, 4-hydroxyphenylretinamide, and 4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)carboxamido]benzoic acid, are also capable of reducing HCV load.

[0189] All-trans-retinoic acid on replicon cells for six days led to an upregulation of GI-GPx RNA and protein due to the fact that the GI-GPx promoter contains three retinoic acid receptor recognition elements. In the presence of selenium or a selenium salt like sodium selenite, a two- to five-fold reduction of HCV RNA and HCV NS5a protein was observed in the absence of toxic effects.

[0190] Moreover, also the specific retinoids, 9-cis retinoic acid, salts of 9-cis retinoic acid, C_1-C_{10} alkyl esters of 9-cis retinoic acid, salts of C_1-C_{10} alkyl esters of 9-cis retinoic acid, C_1-C_{10} alkyl amides of 9-cis retinoic acid, salts of C_1-C_{10} alkyl amides of 9-cis retinoic acid, 13-cis retinoic acid, salts of 13-cis retinoic acid, C_1-C_{10} alkyl esters of 13-cis retinoic acid, salts of C_1-C_{10} alkyl esters of 13-cis retinoic acid, C_1-C_{10} alkyl amides of 13-cis retinoic acid, salts of C_1-C_{10} alkyl amides of 13-cis retinoic acid, retinol, retinoic acid adlehyde, etretinate, N-(4-hydroxyphenyl) retinamide (4-HPR), 6-[3-(1-adamantyl)-4-hydroxyphenyl]-2-naphthalene carboxylic acid (CD437; AHPN), all-trans-retinoic acid, C_1-C_{10} esters and amides of all-trans-retinoic acid, paraquat, 4-[E-2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)-1-propenyl]benzoic acid, 4-hydroxyphenylretinamide, and 4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)carboxamido]benzoic acid, alone or in combination with each other or with selenium or a selenium salt showed a similar effect.

[0191] 15. Clinical Study

[0192] A randomised, single blinded clinical study was designed, to test the safety, tolerability and preliminary efficacy of all-trans-retinoic acid alone or in combination with pegylated alpha interferon in patients with chronic Hepatitis C infection. In particular, patients who failed to respond to and/or relapsed from previous interferon and ribavirin therapy will be targeted to further prove the efficacy of the suggested treatment for patients who do not respond to interferon.

[0193] The clinical study anticipates a total of 20 patients randomly selected from a pool of patients who failed to respond to interferon and/or interferon and ribavirin combination therapy. The patients will be separated into two groups, Group A and Group B. The following materials were selected for administration in this study:

[0194] 1. Vesanoid™, 10 mg capsule (an orally administered all-trans-retinoic acid compound available from Hoffman-La Roche Ltd.);

[0195] 2. Pegasys™ 180 μg (an injectable form of slow-release pegylated alpha interferon IIa available from Hoffman-La Roche Ltd.); and

[0196] 3. Selen 30 ALLACT, 30 μg capsule ((an over-the-counter supplement including selenium and ALLACT, a garlic powder (Allium Sativum pulvis) and Lactobacillus Bulgaricus supplement)).

[0197] The proposed therapy regimen for Group A includes: 45 mg/m^2 daily Vesanoid™ in two oral doses plus

Selen 30 ALLACT, 1 capsule/day p.o. 12 weeks; follow-up period 12 weeks (without treatment).

[0198] The proposed therapy regimen for Group B includes: 45 mg/m^2 daily Vesanoid™ in two oral doses plus Selen 30 ALLACT, 1 capsule/day p.o. plus Pegasys™ 180 μg/week subcutaneously for 12 weeks; follow-up period 12 weeks (without treatment).

[0199] The publications cited herein are incorporated by reference in their entirety.

[0200] Other variations and embodiments of the invention described herein will now be apparent to those skilled in the art without departing from the scope of the invention as defined in the claims that follow.

SEQUENCE LISTING

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What is claimed is:

1. A method for detecting compounds useful for the prophylaxis and/or treatment of Hepatitis C virus infections comprising:

a) contacting a test compound with the human cellular protein gastrointestinal glutathione peroxidase; and

b) detecting human cellular protein gastrointestinal glutathione peroxidase activity.

2. A method for detecting Hepatitis C virus infections in an individual comprising:

a) providing a sample from said individual; and

b) detecting activity in said sample of human cellular protein gastrointestinal glutathione peroxidase.

3. A method for detecting Hepatitis C virus infections in cells, cell cultures, or cell lysates comprising:

a) providing said cells, cell cultures, or cell lysates; and

b) detecting activity in said cells, cell cultures, or cell lysates of human cellular protein gastrointestinal glutathione peroxidase.

4. A method for preventing and/or treating Hepatitis C virus infection and/or diseases associated with HCV infection in an individual comprising the step of administering a pharmaceutically effective amount of an agent which activates at least partially the activity of said human cellular protein gastrointestinal glutathione peroxidase or which activates or stimulates at least partially the production of said human cellular protein gastrointestinal glutathione peroxidase.

5. A method for preventing and/or treating Hepatitis C virus infection in cells, cell cultures, or cell lysates comprising the step of administering a pharmaceutically effective amount of an agent which activates at least partially the activity of said human cellular protein gastrointestinal glutathione peroxidase or which activates or stimulates at least partially the production of said human cellular protein gastrointestinal glutathione peroxidase.

6. A method for regulating the production of Hepatitis C virus in an individual comprising the step of administering to an individual a pharmaceutically effective amount of an agent wherein said agent activates at least partially the activity of said human cellular protein gastrointestinal glutathione peroxidase or wherein said agent at least partially activates or stimulates the production of said human cellular protein gastrointestinal glutathione peroxidase.

7. A method for regulating the production of Hepatitis C virus in cells, cell culture, or cell lysates comprising the step of administering a pharmaceutically effective amount of an agent wherein said agent activates at least partially the activity of said human cellular protein gastrointestinal glutathione peroxidase or wherein said agent at least partially activates or stimulates the production of said human cellular protein gastrointestinal glutathione peroxidase in the cells or cell culture.

8. A method for regulating the expression of the human cellular protein gastrointestinal glutathione peroxidase in an individual comprising the step of administering to the individual a pharmaceutically effective amount of an agent wherein said agent activates at least partially the transcription of DNA and/or the translation of RNA encoding said human cellular protein gastrointestinal glutathione peroxidase.

9. A method for regulating the expression of the human cellular protein gastrointestinal glutathione peroxidase in cells or cell culture comprising the step of administering to the cells or cell culture a pharmaceutically effective amount of an agent wherein said agent activates at least partially the transcription of DNA and/or the translation of RNA encoding said human cellular protein gastrointestinal glutathione peroxidase.

10. A method for preventing and/or treating Hepatitis C virus infection and/or diseases associated with HCV infection in an individual who fails to respond to interferon therapy, said method comprising the step of administering a pharmaceutically effective amount of an agent which activates at least partially the activity of said human cellular protein gastrointestinal glutathione peroxidase or which activates or stimulates at least partially the production of said human cellular protein gastrointestinal glutathione peroxidase

11. The method according to claims **4-10**, wherein said agent is a combination selected from the group consisting of selenium, selenium salts, Vitamin D_3, and retinoids, including 9-cis retinoic acid, salts of 9-cis retinoic acid, C_1-C_{10} alkyl esters of 9-cis retinoic acid, salts of C_1-C_{10} alkyl esters of 9-cis retinoic acid, C_1-C_{10} alkyl amides of 9-cis retinoic acid, salts of C_1-C_{10} alkyl amides of 9-cis retinoic acid, 13-cis retinoic acid, salts of 13-cis retinoic acid, C_1-C_{10} alkyl esters of 13-cis retinoic acid, salts of C_1-C_{10} alkyl esters of 13-cis retinoic acid, C_1-C_{10} alkyl amides of 13-cis retinoic acid, salts of C_1-C_{10} alkyl amides of 13-cis retinoic acid, retinol, retinoic acid adlehyde, etretinate, N-(4-hydroxyphenyl) retinamide (4-HPR), 6-[3-(1-adamantyl)-4-hydroxyphenyl]-2-naphthalene carboxylic acid (CD437; AHPN), all-trans-retinoic acid, C_1-C_{10} esters and amides of all-trans-retinoic acid, paraquat, 4-[E-2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)-1-propenyl]benzoic acid, 4-hydroxyphenylretinamide, and 4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)carboxamido]benzoic acid.

12. The method according to claim 11, wherein said combination comprises selenium and all-trans-retinoic acid, 9-cis retinoic acid, or 13-cis retinoic acid.

13. The method according to claim 11, wherein said combination further includes alpha interferon.

14. The method according to claim 11, wherein said combination further includes ribavirin.

15. A method for preventing and/or treating Hepatitis C virus infection and/or diseases associated with HCV infection in an individual comprising the step of administering a pharmaceutically effective amount of an agent which inhibits at least partially the activity of said human cellular protein gastrointestinal glutathione peroxidase or which inhibits at least partially the production of said human cellular protein gastrointestinal glutathione peroxidase.

16. A method for preventing and/or treating Hepatitis C virus infection in cells, cell cultures, or cell lysates, comprising the step of administering a pharmaceutically effective amount of an agent which inhibits at least partially the activity of said human cellular protein gastrointestinal glutathione peroxidase or which inhibits at least partially the production of said human cellular protein gastrointestinal glutathione peroxidase.

17. A method for regulating the production of Hepatitis C virus in an individual comprising the step of administering to an individual a pharmaceutically effective amount of an

agent wherein said agent inhibits at least partially the activity of said human cellular protein gastrointestinal glutathione peroxidase or wherein said agent at least partially inhibits the production of said human cellular protein gastrointestinal glutathione peroxidase.

18. A method for regulating the production of Hepatitis C virus in cells, cell culture, or cell lysates comprising the step of administering a pharmaceutically effective amount of an agent wherein said agent inhibits at least partially the activity of said human cellular protein gastrointestinal glutathione peroxidase or wherein said agent at least partially inhibits the production of said human cellular protein gastrointestinal glutathione peroxidase in the cells or cell culture.

19. A method according to any one of claims **15-18**, wherein the agent is a monoclonal or polyclonal antibody which binds to said human cellular protein gastrointestinal glutathione peroxidase.

21. A method according to any one of claims **15-18**, wherein said agent comprises oligonucleotides that bind to the DNA or RNA encoding the human cellular protein gastrointestinal glutathione peroxidase.

22. A method for regulating the expression of the human cellular protein gastrointestinal glutathione peroxidase in an individual comprising the step of administering to the individual a pharmaceutically effective amount of an agent wherein said agent inhibits at least partially the transcription of DNA and/or the translation of RNA encoding said human cellular protein gastrointestinal glutathione peroxidase.

23. A method for regulating the expression of the human cellular protein gastrointestinal glutathione peroxidase in cells or cell culture comprising the step of administering to the cells or cell culture a pharmaceutically effective amount of an agent wherein said agent inhibits at least partially the transcription of DNA and/or the translation of RNA encoding said human cellular protein gastrointestinal glutathione peroxidase.

24. A method according to any one of claims **22** or **23**, wherein said agent is an oligonucleotide which binds to the DNA and/or RNA encoding the human cellular protein gastrointestinal glutathione peroxidase.

25. A method for selective killing of HCV infected cells in an individual comprising the step of administering to the individual a pharmaceutically effective amount of a radical initiator which is capable of generating artificial oxidative stress conditions within the cells.

26. A method for selective killing of HCV infected cells comprising the step of administering to the cells a pharmaceutically effective amount of a radical initiator which is capable of generating artificial oxidative stress conditions.

27. The method according to claims **25** or **26**, wherein the radical initiator is selected from the group consisting of paraquat, 2,2'-bipyridyl, 4,4'-bipyridyl derivatives, bis-6-(2,2'-bipyridyl)-pyrimidines, tris-(2,2'-bipyridyl)-ruthenium, dibenzoylperoxide, diacetylperoxide, hydrogen peroxide, di-tert.-butylperoxide, and diazaisobutyronitril.

28. A method for preventing and/or treating HCV infections in an individual by at least partially compensating the down-regulation of GI-GPx comprising the step of administering to the individual a pharmaceutically effective amount of at least one antioxidant which is capable of supporting the function of GI-GPx present within the cells.

29. A method for preventing and/or treating HCV infections in cells by at least partially compensating the down-regulation of GI-GPx comprising the step of administering to the cells or cell culture a pharmaceutically effective amount of at least one antioxidant which is capable of supporting the function of GI-GPx present within the cells.

30. The method according to claims **28** or **29**, wherein the antioxidant is selected from the group consisting of vitamin E (DL-α-tocopherol), vitamin C (L-ascorbic acid), co-enzyme Q10, zinc, selenium, N-acetyl-L-cycteine, N-acetyl-S-farnesyl-L-cysteine, Bilirubin, caffeic acid, CAPE, catechin, ceruloplasmin, Coelenterazine, copper diisopropylsalicylate, deferoxamine mesylate, R-(-)-depreuyl, DMNQ, DTPA dianhydride, Ebselen, ellagic acid, (-)-epigallocatechin, L-ergothioneine, EUK-8, Ferritin, glutathione, glutathione monoethylester, α-lipoic acid, Luteolin, Manoalide, MCI-186, MnTBAP, MnTMPyP, morin hydrate, NCO-700, NDGA, p-Nitroblue, propyl gallate, Resveratrol, rutin, silymarin, L-stepholidine, taxifolin, tetrandrine, tocopherol acetate, tocotrienol, Trolox®, U-74389G, U-83836E, uric acid, carboxylic acids, citric acid, phenolic compounds, BHA (butylated hydroxyanisole), BHT (butylated hydroxytoluene), propyl gallate, TBHQ (tert-butyl hydroquinone), tocopherols, lecithin, gums, resin guiac, THBP (trihydroxybutyrophenone), thiodipropionic acid, dilauryl thiodipropionate, and glycines.

31. A method for regulating the activity of the human cellular protein gastrointestinal glutathione peroxidase in an individual comprising the step of administering to the individual a pharmaceutically effective amount of an agent wherein said agent interacts with said human cellular protein gastrointestinal glutathione peroxidase.

32. A method for regulating the activity of the human cellular protein gastrointestinal glutathione peroxidase in cells or cell culture comprising the step of administering to the cells or cell culture a pharmaceutically effective amount of an agent wherein said agent interacts with said human cellular protein gastrointestinal glutathione peroxidase.

33. The method according to claim 31 or **32**, wherein the agent is selected from the group comprising small chemical molecules which are organic compounds having a molecular weight below 500 g/mol, interferons, aptamers, antioxidants, and radical initiators.

34. A composition useful for the prophylaxis and/or treatment of an individual afflicted with Hepatitis C virus and/or diseases associated with HCV infection, said composition comprising at least one agent capable of inhibiting activity of said human cellular protein gastrointestinal glutathione peroxidase or capable of decreasing the expression of said human cellular protein gastrointestinal glutathione peroxidase.

35. A composition useful for the prophylaxis and/or treatment of an individual afflicted with Hepatitis C virus and/or diseases associated with HCV infection, said composition comprising at least one agent capable of increasing the activity of said human cellular protein gastrointestinal glutathione peroxidase or capable of activating or stimulating the expression of said human cellular protein gastrointestinal glutathione peroxidase.

36. The composition according to claim 34 or **35**, further comprising pharmaceutically acceptable carriers, excipients, and/or diluents.

* * * * *

IN THE MATTER OF

Indian Patent Application 853/DELNP/2009
In the name of

BRISTOL-MYERS SQUIBB COMPANY

AND IN THE MATTER OF
A pre-grant representation by

DALVIR SINGH

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IN THE MATTER OF

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A pre-grant representation by

DALVIR SINGH

D6 – US Patent 6,664,255

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(12) **United States Patent**
South et al.

(10) **Patent No.: US 6,664,255 B1**
(45) **Date of Patent: Dec. 16, 2003**

(54) **SUBSTITUTED POLYCYCLIC ARYL AND HETEROARYL PYRAZINONES USEFUL FOR SELECTIVE INHIBITION OF THE COAGULATION CASCADE**

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(52) **U.S. Cl.** **514/235.8**; 544/405; 544/237; 544/295; 544/120; 514/255.05; 514/248

(58) **Field of Search** 544/405, 237, 544/295, 120; 514/255.05, 248, 235.8

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,489,096	A	12/1984	Terao et al.
4,851,413	A	7/1989	Terao et al.
4,992,469	A	2/1991	Ozawa et al.
5,008,267	A	4/1991	Katakami et al.
5,304,658	A	4/1994	Terao et al.
5,441,960	A	8/1995	Bernstein et al.
5,656,645	A	8/1997	Tamura et al.
5,658,930	A	8/1997	Tamura et al.
5,668,289	A	9/1997	Sanderson et al.
5,741,819	A	4/1998	Illig et al.
5,792,779	A	8/1998	Sanderson et al.
5,861,380	A	1/1999	Gyorkos et al.
5,866,573	A	2/1999	Sanderson et al.
5,869,487	A	2/1999	Coburn et al.
5,872,138	A	2/1999	Naylor-Olsen et al.
6,011,158	A	1/2000	Tamura et al.
6,037,356	A	3/2000	Lu et al.
6,180,627	B1	1/2001	Blagg et al.

FOREIGN PATENT DOCUMENTS

DE	198 51 421 A1	5/2000
EP	0 354 495 A1	2/1990
EP	528 633 B1	2/1993
EP	826 671 A1	3/1998
EP	936 216 A1	8/1999
EP	940 400 A1	9/1999
EP	997 474 A1	5/2000
WO	WO 93/21214 A1	10/1993
WO	WO 96/18644 A1	6/1996
WO	WO 96/33974 A1	10/1996
WO	WO 96/39380 A1	12/1996
WO	WO 96/40100 A1	12/1996
WO	WO 97/01338 A1	1/1997
WO	WO 97/30708 A1	8/1997
WO	WO 97/40024 A1	10/1997
WO	WO 97/46207 A2	12/1997
WO	WO 98/08840 A1	3/1998
WO	WO 98/09949 A1	3/1998
WO	WO 98/09987 A1	3/1998
WO	WO 98/10763 A1	3/1998
WO	WO 97/17274 A1	4/1998
WO	WO 98/16525 A1	4/1998
WO	WO 98/16547 A1	4/1998
WO	WO 98/31670 A1	7/1998
WO	WO 98/42342 A1	10/1998
WO	WO 98/47876 A1	10/1998
WO	WO 98/50420 A1	11/1998
WO	WO 99/00121 A1	1/1999
WO	WO 99/00126 A1	1/1999
WO	WO 99/00128 A1	1/1999
WO	WO 99/11267 A1	3/1999
WO	WO 99/26920 A1	6/1999
WO	WO 99/26926 A1	6/1999

(List continued on next page.)

OTHER PUBLICATIONS

Tulinsky et al. Novel Asymmetric synthesis of atropisomeric 6–aryl pyrazinones, J. Org. Chem. 64:93–100, 1999.*

(List continued on next page.)

Primary Examiner—Mukund J. Shah
Assistant Examiner—Hong Liu

(57) **ABSTRACT**

The invention relates to substituted polycyclic aryl and heteroaryl pyrazinone compounds useful as inhibitors of serine proteases of the coagulation cascade and compounds, compositions and methods for anticoagulant therapy for the treatment and prevention of a variety of thrombotic conditions including coronary artery and cerebrovascular diseases.

27 Claims, No Drawings

FOREIGN PATENT DOCUMENTS

WO	WO 99/36426 A1	7/1999
WO	WO 99/43660 A1	9/1999
WO	WO 99/48892 A1	9/1999
WO	WO 99/59591 A1	11/1999
WO	WO 99/61442 A1	12/1999
WO	WO 99/62538 A1	12/1999
WO	WO 99/64446 A1	12/1999
WO	WO 00/18762 A1	4/2000
WO	WO 00/26210 A1	5/2000
WO	WO 00/26211 A1	5/2000
WO	WO 00/32574 A1	6/2000
WO	WO 00/39102 A1	7/2000
WO	WO 00/69826 A1	11/2000
WO	WO 00/69832 A1	11/2000
WO	WO 00/69833 A1	11/2000

OTHER PUBLICATIONS

Rauch, et al., Thrombus Formation on Atherosclerotic Plaques: Pathogenesis and Clinical Consequences, Annals of Internal Medicine, 2001, pp. 224–233, vol. 134—No. 3.

Van Aken, et al., Anticoagulation: The Present and Future, Clin. Appl. Thrombosis/Hemostasis, 2001, pp. 195–204, vol. 7—No. 3.

Coburn, C.A., "Small–molecule direct thrombine inhibitors 1997–2000." Expert Opinions on Therapeutic patents, 2001, 721–738, vol. 11, No. 5.

XP–002182132 –Darvas, et al., "Investigation of the Common Mechanism of Action of Antibacterial Compounds Containing .gamma.–pyridone–.beta.–carboxylic acid Structure by Principal Component." Arzneim.–Forshc., 1979, pp. 1334–1339, vol. 29, 9.

XP–002172033 –Kohama et al., "Preparation of Piperidinyloxyacetylaminobenzoylalanine Derivatives and Analogs as Antithrombotics." JP 07,233,148.

XP–002187583 –Moerner, Hoppe–Seyler's Z. Physiol. Chem., 69, 1910; 357.

Patel et al., "Directed Aminomethylation of 3–Hydroxy–3(1H)–pyridinones and 3–hydroxy–4(1H)–pyridinones: Synthesis of iso–Deferiprone." Tetrahedron, 1996, pp. 1835–1840, vol. 52, No. 5.

XP–002182410 –Trecourt et al., "First Synthesis of (+–)–harzianopyridone by Metalation of Polysubstituted O–pyridylcarbamates." J. Heterocycl. Chem., 1995, pp. 1117–1114, vol. 32, No. 4.

* cited by examiner

SUBSTITUTED POLYCYCLIC ARYL AND HETEROARYL PYRAZINONES USEFUL FOR SELECTIVE INHIBITION OF THE COAGULATION CASCADE

CROSS-REFERENCE TO RELATED APPLICATION

This application claims priority from Provisional Application Serial No. 60/134,958 filed on May 19, 1999, now abandoned, which is hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

This invention is in the field of anticoagulant therapy, and specifically relates to compounds, compositions and methods for preventing and treating thrombotic conditions such as coronary artery and cerebrovascular disease. More particularly, the invention relates to substituted polycyclic aryl and heteroaryl pyrazinone compounds that inhibit serine proteases of the coagulation cascade.

BACKGROUND OF THE INVENTION

Physiological systems control the fluidity of blood in mammals [Majerus, P. W. et al: Anticoagulant, Thrombolytic, and Antiplplatelet Drugs. In Hardman, J. G. and Limbird, L. E., editors: Goodman & Gilman's The Pharmacological Basis of Therapeutics. 9th edition. New York, McGraw-Hill Book Co., 1996, pp. 1341–1343]. Blood must remain fluid within the vascular systems and yet be able to undergo hemostasis, cessation of blood loss from a damaged vessel, quickly. Hemostasis or clotting begins when platelets first adhere to macromolecules in subendothelian regions of an injured and/or damaged vessels. These platelets aggregate to form the primary hemostatic plug and stimulate local activation of plasma coagulation factors leading to generation of a fibrin clot that reinforces the aggregated platelets.

Plasma coagulation factors include factors II, V, VII, VIII, IX, X, XI, and XII; these are also called protease zymogens. These coagulation factors or protease zymogens are activated by serine proteases leading to coagulation in a so called "coagulation cascade" or chain reaction [Handin, R. I.: Bleeding and Thrombosis. In Wilson, J., et al. editors: Harrison's Principles of Internal Medicine. 12th Edition, New York, McGraw-Hill Book Co., 1991,p.350]. Coagulation or clotting occurs in two ways through different pathways. An intrinsic or contact pathway leads from XII to XIIa to XIa to IXa and to the conversion of X to Xa. Xa with factor Va converts prothrombin (II) to thrombin (IIa) leading to conversion of fibrinogen to fibrin. Polymerization of fibrin leads to a fibrin clot. An extrinsic pathway is initiated by the conversion of coagulation factor VII to VIIa by Xa. The presence of Tissue Factor and VIIa accelerates formation of Xa in the presence of calcium ion and phospholipids. Formation of Xa leads to thrombin, fibrin, and a fibrin clot as described above. The presence of one or more of these many different coagulation factors and two distinct pathways of clotting could enable the efficacious, selective control and better understanding of parts of the coagulation or clotting process.

While clotting as a result of an injury to a blood vessel is a critical physiological process for mammals such as man, clotting can also lead to disease states. A pathological process called thrombosis results when platelet aggregation and/or a fibrin clot blocks (i.e., occludes) a blood vessel.

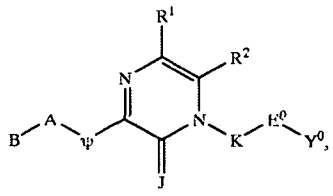
Arterial thrombosis may result in ischemic necrosis of the tissue supplied by the artery. When the thrombosis occurs in a coronary artery, a myocardial infarction or heart attack can result. A thrombosis occurring in a vein may cause tissues drained by the vein to become edematous and inflamed. Thrombosis of a deep vein may be complicated by a pulmonary embolism. Preventing or treating clots in a blood vessel may be therapeutically useful by inhibiting formation of blood platelet aggregates, inhibiting formation of fibrin, inhibiting thrombus formation, inhibiting embolus formation, and for treating or preventing unstable angina, refractory angina, myocardial infarction, transient ischemic attacks, atrial fibrillation, thrombotic stroke, embolic stroke, deep vein thrombosis, disseminated intravascular coagulation, ocular build up of fibrin, and reocclusion or restenosis of recanalized vessels.

There have been several reports of non-peptidic and peptidic compounds that act as an inhibitor of a coagulation factor present in the coagulation cascade or clotting process. In PCG Patent Application WO 97/40024, Sanderson et al. describe alkyl, cycloalkyl, and trifluoromethyl substituted pyrazinones reported to inhibit thrombin activity. In PCG Patent Application WO 98/08840, Duggan et al. describe 2-heterocyclylacetyl derivatives of β-alanine esters reported to inhibit $\alpha v\beta 3$ and $\alpha v\beta 5$ receptors and possess utility in atheriosclerosis. In PCT Patent Application WO 98/09949, Suzuki et al. describe 2-heterocyclylacetamido derivatives of 1,2-diketones and report that they inhibit proteases, especially chymase inhibitors. In PCT Patent Application WO 98/42342, Isaacs et al. describe additional alkyl, cycloalkyl, and trifluoromethyl substituted pyrazinones reported to inhibit human thrombin. In PCG Patent Application WO 99/61442, Sanderson and Naylor-Olsen describe 1-(5-methylenecarboxamidomethyleneimidazo-[1,2-a] pyridinyl) pyrazinones without substitution in the imidazolyl portion and reported that the compounds inhibit thrombin activity. In PCT Patent Application WO 99/59591, Sanderson et al. describe 1-((N-substitutedaminopyridyl and N-substitutedphenyl)amidocarbonylmethylene)pyrazinones reported to inhibit thrombin. In PCT Patent Application WO 99/64446, Lu et al. describe 1-((N-amidinoaminooxyalkylene and N-amidinohydrazinoalkylene) amidocarbonylmethylene) pyrazinones reported to inhibit trypsin-like serine proteases and thrombin. In Japanese Patent Application 99/229491, Black et al. describe thrombin inhibiting halo and alkyl substituted pyrazinone acetamides in which the amide nitrogen is substituted by a group containing a benzimidazole or indole ring

SUMMARY OF THE INVENTION

It is an object of the present invention to provide compounds that are beneficial in anticoagulant therapy and that have a general structure:

Formula (I).



It is another object of the present invention to provide methods for preventing and treating thrombotic conditions,

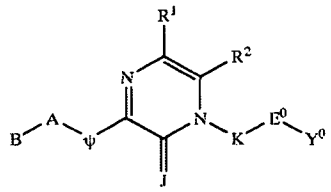
such as coronary artery disease, cerebrovascular disease, and other coagulation related disorders. Such thrombotic conditions are prevented and treated by administering to a patient in need thereof an effective amount of compounds of Formula (I).

Various other objects and advantages of the present invention will become apparent from the following description of the invention.

DESCRIPTION OF THE INVENTION

The present invention relates to a class of compounds comprising Substituted Polycyclic Aryl and Heteroaryl Pyrazinones, which are beneficial in anticoagulant therapy for the treatment and prevention of a variety of thrombotic conditions including coronary artery and cerebrovascular disease, as given in Formula (I):

(I)



or a pharmaceutically acceptable salt thereof, wherein;

J is selected from the group consisting of O and S;

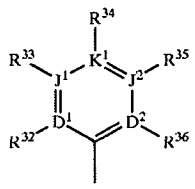
J is optionally selected from the group consisting of CH—R^6 and N—R^6 wherein R^6 is a linear spacer moiety having a chain length of 1 to 4 atoms linked to the point of bonding of a substituent selected from the group consisting of R^{4a}, R^{4b}, R^{39}, R^{40}, R^5, R^{14}, and R^{15} to form a heterocyclyl ring having 5 through 8 contiguous members;

J is optionally selected from the group consisting of CH—R^6 and N—R^6 wherein R^6 is a linear spacer moiety having a chain length of 1 to 4 atoms linked to the points of bonding of both R^{4a} and R^{4b} to form a heterocyclyl ring having 5 through 8 contiguous members;

J is optionally selected from the group consisting of CH—R^6 and N—R^6 wherein R^6 is a linear spacer moiety having a chain length of 1 to 4 atoms linked to the points of bonding of both R^{39} and R^{40} to form a heterocyclyl ring having 5 through 8 contiguous members;

B is formula (V):

(V)



wherein

D^1, D^2, J^1, J^2 and K^1 are independently selected from the group consisting of C, N, O, S and a covalent bond with the provisos that no more than one can be a covalent bond, no more than one of D^1, D^2, J^1, J^2 and K^1 is O no more than one of D^1, D^2, J^1, J^2 and K^1 is S, one of D^1, D^2, J^1, J^2 and K^1 must be a covalent bond when two of D^1, D^2, J^1, J^2 and K^1 are O and S, and no more than four of D^1, D^2, J^1, J^2 and K^1 are N with the proviso that R^{32}, R^{33}, R^{34}, R^{35}, and R^{36} are each independently selected to maintain the tetravalent nature of carbon, trivalent nature of nitrogen, the divalent nature of sulfur, and the divalent nature of oxygen;

R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{16}, R^{17}, R^{18}, R^{19}, R^{32}, R^{33}, R^{34}, R^{35}, and R^{36} are independently selected from the group consisting of hydrido, acetamido, haloacetamido, amidino, guanidino, dialkylsulfonium, trialkylphosphonium, dialkylsulfoniumalkyl, carboxy, heteroaralkylthio, heteroaralkoxy, cycloalkylamino, acylalkyl, acylalkoxy, aryloylalkoxy, heterocyclyloxy, aralkylaryl, aralkyl, aralkenyl, aralkynyl, heterocyclyl, perhaloaralkyl, aralkylsulfonyl, aralkylsulfonylalkyl, aralkylsulfinyl, aralkylsulfinylalkyl, halocycloalkyl, halocycloalkenyl, cycloalkylsulfinyl, cycloalkylsulfinylalkyl, cycloalkylsulfonyl, cycloalkylsulfonylalkyl, heteroarylamino, N-heteroarylamino-N-alkylamino, heteroarylaminoalkyl, haloalkylthio, alkanoyloxy, alkoxy, alkoxyalkyl, haloalkoxylalkyl, heteroaralkoxy, cycloalkoxy, cycloalkenyloxy, cycloalkoxyalkyl, cycloalkylalkoxy, cycloalkenyloxyalkyl, cycloalkylenedioxy, halocycloalkoxy, halocycloalkoxyalkyl, halocycloalkenyloxy, halocycloalkenyloxyalkyl, hydroxy, amino, alkoxyamino, thio, nitro, lower alkylamino, alkylthio, alkylthioalkyl, arylamino, aralkylamino, arylthio, arylthioalkyl, heteroaralkoxyalkyl, alkylsulfinyl, alkylsulfinylalkyl, arylsulfinylalkyl, aryl sulfonylalkyl, heteroarylsulfinylalkyl, heteroarylsulfonylalkyl, alkylsulfonyl, alkylsulfonylalkyl, haloalkylsulfinylalkyl, haloalkylsulfonylalkyl, alkylsulfonamido, alkylaminosulfonyl, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, monoarylamidosulfonyl, arylsulfonamido, diarylamidosulfonyl, monoalkyl monoaryl amidosulfonyl, arylsulfinyl, arylsulfonyl, heteroarylthio, heteroarylsulfinyl, heteroarylsulfonyl, heterocyclylsulfonyl, heterocyclylthio, alkanoyl, alkenoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, haloalkanoyl, alkyl, alkenyl, alkynyl, alkenyloxy, alkenyloxyalky, alkylenedioxy, haloalkylenedioxy, cycloalkyl, cycloalkylalkanoyl, cycloalkenyl, lower cycloalkylalkyl, lower cycloalkenylalkyl, halo, haloalkyl, haloalkenyl, haloalkoxy, hydroxyhaloalkyl, hydroxyaralkyl, hydroxyalkyl, alkylenylamino, hydoxyheteroaralkyl, haloalkoxyalkyl, aryl, aralkyl, aryloxy, aralkoxy, aryloxyalkyl, saturated heterocyclyl, partially saturated heterocyclyl, heteroaryl, heteroaryloxy, heteroaryloxyalkyl, arylalkyl, heteroarylalkyl, arylalkenyl, heteroarylalkenyl, carboxyalkyl, carboalkoxy, alkoxycarboxamido, alkylamidocarbonylamido, arylamidocarbonylamido, carboalkoxyalkyl, carboalkoxyalkenyl, carboxy, carboaralkoxy, carboxamido, carboxamidoalkyl, cyano, carbohaloalkoxy, phosphono, phosphonoalkyl, diaralkoxyphosphono, and diaralkoxyphosphonoalkyl;

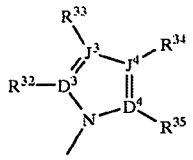
R^{16}, R^{19}, R^{32}, R^{33}, R^{34}, R^{35}, and R^{36} are independently optionally Q^b with the proviso that no more than one of R^{16} and R^{19} is Q^b at the same time and that Q^b is Q^{be};

R^{32} and R^{33}, R^{33} and R^{34}, R^{34} and R^{35}, and R^{35} and R^{36} are independently optionally selected to form a spacer pair wherein a spacer pair is taken together to form a linear moiety having from 3 through 6 contiguous atoms connecting the points of bonding of said spacer pair members to form a ring selected from the group consisting of a cycloalkenyl ring having 5 through 8 contiguous members, a partially saturated heterocyclyl ring having 5 through 8 contiguous members, a heteroaryl ring having 5 through 6 contiguous members, and an aryl with the proviso that no more than one of the group consisting of spacer pairs R^{32} and R^{33}, R^{33} and R^{34}, R^{34} and R^{35}, and R^{35} and R^{36} are used at the same time;

R^9 and R^{10}, R^{10} and R^{11}, R^{11} and R^{12}, and R^{12} and R^{13} are independently optionally selected to form a spacer pair wherein a spacer pair is taken together to form a linear moiety having from 3 through 6 contiguous atoms connecting the points of bonding of said spacer pair members to form a ring selected from the group consisting of a cycloalkenyl ring having 5 through 8 contiguous members, a partially saturated heterocyclyl ring having 5 through 8 contiguous members, a heteroaryl ring having 5 through 6 contiguous members, and an aryl with the proviso that no more than one of the group consisting of spacer pairs R^9 and R^{10}, R^{10} and R^{11}, R^{11} and R^{12}, and R^{12} and R^{13} are used at the same time;

B is optionally formula (VI):

(VI)



wherein D^3, D^4, J^3, and J^4 are independently selected from the group consisting of C, N, O, and S, no more than one of D^3, D^4, J^3, and J^4 is O, no more than one of D^3, D^4, J^3, and J^4 is S, and no more than three of D^1, D^2, J^1, and J^2 are N with the proviso that R^{32}, R^{33}, R^{34}, and R^{35} are each independently selected to maintain the tetravalent nature of carbon, trivalent nature of nitrogen, the divalent nature of sulfur, and the divalent nature of oxygen;

B is optionally selected from the group consisting of hydrido, trialkylsilyl, C2–C8 alkyl, C3–C8 alkenyl, C3–C8 alkylenyl, C3–C8 alkynyl, C2–C8 haloalkyl, and C3–C8 haloalkenyl wherein each member of group B is optionally substituted at any carbon up to and including 6 atoms from the point of attachment of B to A with one or more of the group consisting of R_{32}, R_{33}, R_{34}, R_{35}, and R_{36};

B is optionally selected from the group consisting of C3–C15 cycloalkyl, C5–C10 cycloalkenyl, C4–C12 saturated heterocyclyl, and C4–C9 partially saturated heterocyclyl, wherein each ring carbon is optionally substituted with R^{33}, a ring carbon other than the ring carbon at the point of attachment of B to A is optionally substituted with oxo provided that no more than one ring carbon is substituted by oxo at the same time, ring carbon and nitrogen atoms adjacent to the carbon atom at the point of attachment is optionally substituted with R^9 or R^{13}, a ring carbon or nitrogen atom adjacent to the R^9 position and two atoms from the point of attachment is optionally substituted with R^{10}, a ring carbon or nitrogen atom adjacent to the R^{13} position and two atoms from the point of attachment is optionally substituted with R^{12}, a ring carbon or nitrogen atom three atoms from the point of attachment and adjacent to the R^{10} position is optionally substituted with R^{11}, a ring carbon or nitrogen atom three atoms from the point of attachment and adjacent to the R^{12} position is optionally substituted with R^{33}, and a ring carbon or nitrogen atom four atoms from the point of attachment and adjacent to the R^{11} and R^{33} positions is optionally substituted with R^{34};

A is selected from the group consisting of single covalent bond, $(W^7)_{rr}$—$(CH(R^{15}))_{pa}$ and $(CH(R^{15}))_{pa}$—$(W^7)_{rr}$ wherein rr is an integer selected from 0 through 1, pa is an integer selected from 0 through 6, and W^7 is selected from the group consisting of O, S, C(O), C(S), C(O)S, C(S)O, C(O)N(R^7), C(S)N(R^7), (R^7)NC(O), (R^7)NC(S), S(O), $S(O)_2$, $S(O)_2N(R^7)$, (R^7)$NS(O)_2$, Sc(O), $Sc(O)_2$, $Sc(O)_2N(R^7)$, (R^7)$NSc(O)_2$, P(O)(R^8), N(R^7)P(O)(R^8), P(O)(R^8)N(R^7), C(NR^7)N(R^7), (R^7)NC(NR^7), (R^7)NC(NR^7)NR^7, and N(R^7) with the proviso that no more than one of the group consisting of rr and pa is 0 at the same time;

R^7 and R^8 are independently selected from the group consisting of hydrido, hydroxy, alkyl, alkenyl, aryl, aralkyl, aryloxy, alkoxy, alkenyloxy, alkylthio, alkylamino, arylthio, arylamino, acyl, aroyl, heteroaroyl, aralkoxyalkyl, heteroaralkoxyalkyl, aryloxyalkyl, alkoxyalkyl, alkenyloxyalkyl, alkylthioalkyl, arylthioalkyl, aralkoxyalkyl, heteroaralkoxyalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, heteroaryl, heteroaryloxy, heteroarylamino, heteroaralkyl, heteroaralkyloxy, heteroaralkylamino, and heteroaryloxyalkyl;

R^{14}, R^{15}, R^{37}, R^{38}, R^{39}, R^{40}, R^{41} and R^{42} are independently selected from the group consisting of amidino, hydroxyamino, hydrido, hydroxy, halo, cyano, aryloxy, amino, alkylamino, dialkylamino, hydroxyalkyl, aminoalkyl, acyl, aroyl, heteroaroyl, heteroaryloxyalkyl, sulfhydryl, acylamido, alkoxy, alkylthio, arylthio, alkyl, alkenyl, alkynyl, aryl, aralkyl, aryloxyalkyl, aralkoxyalkylalkoxy, alkylsulfinylalkyl, alkylsulfonylalkyl, aralkylthioalkyl, heteroaralkoxythioalkyl, alkoxyalkyl, heteroaryloxyalkyl, alkenyloxyalkyl, alkylthioalkyl, arylthioalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkenyl, cycloalkenylalkyl, haloalkyl, haloalkenyl, halocycloalkyl, halocycloalkenyl, haloalkoxy, haloalkoxyalkyl, haloalkenyloxyalkyl, halocycloalkoxy, halocycloalkoxyalkyl, halocycloalkenyloxyalkyl, saturated heterocyclyl, partially saturated heterocyclyl, heteroaryl, heteroarylalkyl, heteroarylthioalkyl, heteroaralkylthioalkyl, monocarboalkoxyalkyl, dicarboalkoxyalkyl, monocyanoalkyl, dicyanoalkyl, carboalkoxycyanoalkyl, alkylsulfinyl, alkylsulfonyl, haloalkylsulfinyl, haloalkylsulfonyl, arylsulfinyl, arylsulfinylalkyl, arylsulfonyl, arylsulfonylalkyl, aralkylsulfinyl, aralkylsulfonyl, cycloalkylsulfinyl, cycloalkylsulfonyl, cycloalkylsulfinylalkyl, cycloalkylsufonylalkyl, heteroarylsulfonylalkyl,

heteroarylsulfinyl, heteroarylsulfonyl, heteroarylsulfinylalkyl, aralkylsulfinylalkyl, aralkylsulfonylalkyl, carboxy, carboxyalkyl, carboalkoxy, carboxamide, carboxamidoalkyl, carboaralkoxy, trialkylsilyl, dialkoxyphosphono, diaralkoxyphosphono, dialkoxyphosphonoalkyl, and diaralkoxyphosphonoalkyl with the proviso that R^{37} and R^{38} are independently selected from other than formyl and 2-oxoacyl;

R^{14} and R^{14}, when bonded to different carbons, are optionally taken together to form a group selected from the group consisting of covalent bond, alkylene, haloalkylene, and a linear moiety spacer selected to form a ring selected from the group consisting of cycloalkyl ring having from 5 through 8 contiguous members, cycloalkenyl ring having from 5 through 8 contiguous members, and a heterocyclyl having from 5 through 8 contiguous members;

R^{14} and R^{15}, when bonded to different carbons, are optionally taken together to form a group selected from the group consisting of covalent bond, alkylene, haloalkylene, and a linear moiety spacer selected to form a ring selected from the group consisting of a cycloalkyl ring having from 5 through 8 contiguous members, a cycloalkenyl ring having from 5 through 8 contiguous members, and a heterocyclyl having from 5 through 8 contiguous members;

R^{15} and R^{15}, when bonded to different carbons, are optionally taken together to form a group selected from the group consisting of covalent bond, alkylene, haloalkylene, and a linear moiety spacer selected to form a ring selected from the group consisting of cycloalkyl ring having from 5 through 8 contiguous members, cycloalkenyl ring having from 5 through 8 contiguous members, and a heterocyclyl having from 5 through 8 contiguous members;

Ψ is selected from the group consisting of NR^5, O, C(O), C(S), S, S(O), $S(O)_2$, $ON(R^5)$, $P(O)(R^8)$, and $CR^{39}R^{40}$;

R^5 is selected from the group consisting of hydrido, hydroxy, amino, alkyl, alkenyl, alkynyl, aryl, aralkyl, aryloxy, aralkoxy, alkoxy, alkenyloxy, alkylthio, arylthio, aralkoxyalkyl, heteroaralkoxyalkyl, aryloxyalkyl, alkoxyalkyl, alkenyloxyalkyl, alkylthioalkyl, arylthioalkyl, aralkoxyalkyl, heteroaralkoxyalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkenyl, cycloalkenylalkyl, haloalkyl, haloalkenyl, halocycloalkyl, halocycloalkenyl, haloalkoxyalkyl, haloalkenyloxyalkyl, halocycloalkoxyalkyl, halocycloalkenyloxyalkyl, heteroaryl, heteroarylalkyl, monocarboalkoxyalkyl, monocarboalkoxy, dicarboalkoxyalkyl, monocarboxamido, monocyanoalkyl, dicyanoalkyl, carboalkoxycyanoalkyl, acyl, aroyl, heteroaroyl, heteroaryloxyalkyl, and dialkoxyphosphonoalkyl;

R^{39} and R^{40}, when bonded to the same carbon, are optionally taken together to form a group selected from a group consisting of oxo, thiono, R^5—N, alkylene, haloalkylene, and a linear moiety spacer having from 2 through 7 contiguous atoms to form a ring selected from the group consisting of a cycloalkyl ring having from 3 through 8 contiguous members, a cycloalkenyl ring having from 3 through 8 contiguous members, and a heterocyclyl ring having from 3 through 8 contiguous members;

R^2 and R^1 are independently selected from the group consisting of Z^0—Q, hydrido, alkyl, alkenyl, and halo with the provisos that R^2 is selected from other than the group consisting of hydrido, alkyl, cycloalkyl, and trifluoromethyl and R^1 is selected from other than the group consisting of hydrido and halo unless E^1 is other than C(O)NH, or unless E^0 is selected from the group consisting of E^2 and E^3, or unless K is other than $(CR^{4a}R^{4b})_n$ wherein n is 1 unless one of R^{4a} and R^{4b} are independently selected from other than hydrido, or unless Ψ is selected from other than NR^5, or unless R^5 is selected from other than hydrido, or unless Y^0 is selected from other than wherein Q^s is C_{1-4} alkyl, C_{3-4} alkenyl or C_{3-4} alkynyl where the C_{1-4} alkyl, C_{3-4} alkenyl or C_{3-4} alkynyl group is bonded concurrently to E^1 wherein E^1 is C(O)NH and to the 4-position of an imidazole, the 4-position of a thiazole or the 5-position of a thiazole, or unless a spacer pair is present selected from the group of spacer pairs consisting of R^2 and R^{4a}, R^2 and R^{4b}, R^2 together with both R^{4a} and R^{4b}, R^2 and R^{14}, R^2 and R^{15}, and R^6 with another group selected from the group consisting of R^{4a}, R^{4b}, R^{4a} and R^{4b} together, R^{39}, R^{40}, R^{39} and R^{40} together, R^{14}, R^{15}, and R^5, that R^2 is selected from other than the group consisting of alkyl, aryl, and heteroaryl and R^1 is selected from other than the group consisting of hydrido unless E^1 is other than C(O)NH, or unless E^0 is selected from the group consisting of E^2 and E^3, or unless K is other than $(CR^{4a}R^{4b})_n$ wherein n is 1 unless one of $R^{4a}$and R^{4b} are independently selected from other than hydrido, or unless Ψ is selected from other than NR^5, or unless R^5 is selected from other than hydrido, or unless R^{37} and R^{38} are independently selected from other than formyl and 2-oxoacyl, that R^2 is selected from other than the group consisting of hydroxymethyl, methyl, methoxymethyl, methylthiomethyl, phenylthiomethyl, methylsulfinyl, methylthio, alkoxy, cycloalkoxy, alkylthio, alkylsulfinyl, alkysulfonyl, cycloalkylthio, cycloalkylsulfinyl, and cycloalkysulfonyl, when Y^o is other than phenyl, mono-substituted phenyl, di-substituted phenyl, 5(2-amino)pyridindyl, or 4-(2-amino)pyridindyl, and that R^2 is selected from other than the group consisting of hydrido, halo, alkyl, cycloalkyl when Y^o is methyleneimidazo(1,2-a) pyridinyl, 4,5-benzimidazol-5-yl, or indol-5-yl unless R^1 is selected from other than the group consisting of hydrido or halo, or unless E^1 is other than C(O)NH, or unless E^0 is selected from the group consisting of E^2 and E^3, or unless K is other than $(CR^{4a}R^{4b})_n$ wherein n is 1 unless one of R^{4a} and R^{4b} are independently selected from other than hydrido, or unless Ψ is selected from other than NR^5 wherein R^5 is hydrido;

R^1 is optionally selected from the group consisting of amino, aminoalkyl, alkylamino, amidino, guanidino, hydroxy, hydroxyamino, alkoxy, hydroxyalkyl, alkoxyamino, thiol, alkylthio, dialkylsulfonium, trialkylphosphonium, dialkylsulfoniumalkyl, heteroarylamino, nitro, arylamino, aralkylamino, alkanoyl, alkenoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, haloalkanoyl, hydroxyhaloalkyl, cyano, and phosphono;

R^2 is optionally selected from the group consisting of amidino, guanidino, dialkylsulfonium, trialkylphosphonium, dialkylsulfoniumalkyl, heteroarylamino, amino, nitro, alkylamino, arylamino, aralkylamino, alkanoyl, alkenoyl, aroyl, heteroaroyl,

aralkanoyl, heteroaralkanoyl, haloalkanoyl, hydroxyhaloalkyl, cyano, and phosphono;

R^2 and R^1 are optionally taken together to form a spacer pair wherein the spacer pair forms a linear moiety having from 3 through 6 contiguous atoms connecting the points of bonding of said spacer pair members to form a ring selected from the group consisting of a cycloalkenyl ring having from 5 through 8 contiguous members and a partially saturated heterocyclyl ring having from 5 through 8 contiguous members;

R^2 and R^1 spacer pairs are optionally selected to be —W═X—Y═Z— forming a ring selected from the group consisting of a heteroaryl ring having from 5 through 6 contiguous members and an aryl, wherein W, X, Y, and Z are independently selected from the group consisting of $C(R^9)$, N, $N(R^{10})$, O, S and a covalent bond with the provisos that one of W, X, Y, and Z is independently selected to be a covalent bond when one of W, X, Y, and Z is selected from the group consisting of O and S, no more than one of W, X, Y, and Z is selected from the group consisting of O and S, no more than three of W, X, Y, and Z are selected from the group consisting of N and $N(R^{10})$, and $C(R^9)$, N, $N(R^{10})$, O, and S are independently selected to maintain the tetravalent nature of carbon, trivalent nature of nitrogen, the divalent nature of sulfur, the divalent nature of oxygen, and the aromaticity of the ring;

R^2 and R^{4a}, R^2 and R^{4b}, R^2 and R^{14}, and R^2 and R^{15} are optionally independently selected to form spacer pairs wherein a spacer pair is taken together to form a linear moiety having from 2 through 5 contiguous atoms connecting the points of bonding of said spacer pair members to form a heterocyclyl ring having from 5 through 8 contiguous members with the proviso that no more than one of the group of spacer pairs consisting of R^2 and R^{4a}, R^2 and R^{4b}, R^2 and R^{14}, and R^2 and R^{15} is used at the same time;

R^2 is optionally independently selected to form a linear moiety having from 2 through 5 contiguous atoms linked to the points of bonding of both R^{4a} and R^{4b} to form a heterocyclyl ring having from 5 through 8 contiguous members;

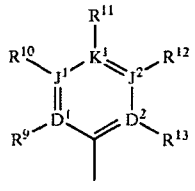
Z^0 is selected from the group consisting of covalent single bond, $(CR^{41}R^{42})_q$ wherein q is an integer selected from 1 through 6, $(CH(R^{41}))_g$—W^0—$(CH(R^{42}))_p$ wherein g and p are integers independently selected from 0 through 3 and W^0 is selected from the group consisting of O, S, C(O), C(S), C(O)O, C(S)O, C(O)S, C(S)S, C(O)N(R^{41}), (R^{41})NC(O), C(S)N(R^{41}), (R^{41})NC(S), OC(O)N(R^{41}), (R^{41})NC(O)O, SC(S)N(R^{41}), (R^{41})NC(S)S, SC(O)N(R^{41}), (R^{41})NC(O)S, OC(S)N(R^{41}), (R^{41})NC(S)O, N(R^{42})C(O)N(R^{41}) (R^{41})NC(O)N(R^{42}), N(R^{42})C(S)N(R^{41}), (R^{41})NC(S)N(R^{42}), S(O), $S(O)_2$, $S(O)_2N(R^{41})$, $N(R^{41})S(O)_2$, Se, Se(O), $Se(O)_2$, $Se(O)_2$ $N(R^{41})$, $N(R^{41})Se(O)_2$, P(O)(R^8), N(R^7)P(O)(R^8), P(O)(R^8)N(R^7), N(R^{41}), ON(R^{41}), and $SiR^{28}R^{29}$, and (CH $(R^{41})_e$—W^{22}—$(CH(R^{42}))_h$ wherein e and h are integers independently selected from 0 through 2 and W^{22} is selected from the group consisting of CR^{41}═CR^{42}, $CR^{41}R^{42}$═C; vinylidene), ethynylidene (C≡C; 1,2-ethynyl), 1,2-cyclopropyl, 1,2-cyclobutyl, 1,2-cyclohexyl, 1,3-cyclohexyl, 1,2-cyclopentyl, 1,3-cyclopentyl, 2,3-morpholinyl, 2,4-morpholinyl, 2,6-morpholinyl, 3,4-morpholinyl, 3,5-morpholinyl, 1,2-piperazinyl, 1,3-piperazinyl, 2,3-piperazinyl, 2,6-piperazinyl, 1,2-piperidinyl, 1,3-piperidinyl, 2,3-piperidinyl, 2,4-piperidinyl, 2,6-piperidinyl, 3,4-piperidinyl, 1,2-pyrrolidinyl, 1,3-pyrrolidinyl, 2,3-pyrrolidinyl, 2,4-pyrrolidinyl, 2,5-pyrrolidinyl, 3,4pyrrolidinyl, 2,3-tetrahydrofuranyl, 2,4-tetrahydrofuranyl, 2,5-tetrahydrofuranyl, and 3,4-tetrahydrofuranyl, with the provisos that R^{41} and R^{42} are selected from other than halo and cyano when directly bonded to N and Z^0 is directly bonded to the pyrazinone ring;

R^{28} and R^{29} are independently selected from the group consisting of hydrido, hydroxyalkyl, alkyl, alkenyl, alkynyl, aryl, aralkyl, aryloxyalkyl, acyl, aroyl, aralkanoyl, heteroaroyl, aralkoxyalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, aralkylthioalkyl, heteroaralkylthioalkyl, alkoxyalkyl, heteroaryloxyalkyl, alkenyloxyalkyl, alkylthioalkyl, arylthioalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkenyl, cycloalkenylalkyl, haloalkyl, haloalkenyl, halocycloalkyl, halocycloalkenyl, haloalkoxyalkyl, haloalkenyloxyalkyl, halocycloalkoxy, halocycloalkoxyalkyl, halocycloalkenyloxyalkyl, perhaloaryl, perhaloaralkyl, perhaloaryloxyalkyl, heteroaryl, heteroarylalkyl, heteroarylthioalkyl, heteroaralkylthioalkyl, cyanoalkyl, dicyanoalkyl, carboxamidoalkyl, dicarboxamidoalkyl, cyanocarboalkoxyalkyl, carboalkoxyalkyl, dicarboalkoxyalkyl, cyanocycloalkyl, dicyanocycloalkyl, carboxamidocycloalkyl, dicarboxamidocycloalkyl, carboalkoxycyanocycloalkyl, carboalkoxycycloalkyl, dicarboalkoxycycloalkyl, formylalkyl, acylalkyl, arylsulfinylalkyl, arylsulfonylalkyl, aralkylsulfinyl, cycloalkylsulfinylalkyl, cycloalkylsufonylalkyl, heteroarylsulfonylalkyl, heteroarylsulfinylalkyl, aralkylsulfinylalkyl, aralkylsulfonylalkyl, carboxy, dialkoxyphosphono, diaralkoxyphosphono, dialkoxyphosphonoalkyl and diaralkoxyphosphonoalkyl;

R^{28} and R^{29} are optionally taken together to form a linear moiety spacer having from 2 through 7 contiguous atoms and forming a ring selected from the group consisting of a cycloalkyl ring having from 3 through 8 contiguous members, a cycloalkenyl ring having from 3 through 8 contiguous members and a heterocyclyl ring having from 3 through 8 contiguous members;

Q is formula (II):

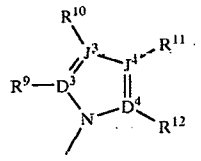
(II)



wherein D^1, D^2, J^1, J^2 and K^1 are independently selected from the group consisting of C, N, O, S and a covalent bond with the provisos that no more than one can be a covalent bond, no more than one of D^1, D^2, J^1, J^2 and K^1 can be O, no more than one of D^1, D^2, J^1, J^2 and K^1 can be S, one of D^1, D^2, J^1, J^2 and K^1 must be a covalent bond when two of D^1, D^2, J^1, J^2 and K^1 are O and S, and no more than four of D^1, D^2, J^1, J^2 and K^1 can be N, with the proviso that R^9, R^{10}, R^{11}, R^{12}, and R^{13} are each independently

selected to maintain the tetravalent nature of carbon, trivalent nature of nitrogen, the divalent nature of sulfur, and the divalent nature of oxygen;

Q is optionally selected from formula (III):



(III)

wherein D^3, D^4, J^3, and J^4 are independently selected from the group consisting of C, N, O, and S, no more than one of D^3, D^4, J^3, and J^4 is O, no more than one of D^3, D^4, J^3, and J^4 is S, and no more than three of D^1, D^2, J^1, and J^2 are N with the proviso that R^9, R^{10}, R^{11}, and R^{12} are each independently selected to maintain the tetravalent nature of carbon, trivalent nature of nitrogen, the divalent nature of sulfur, and the divalent nature of oxygen;

Q is optionally selected from the group consisting of hydrido, alkyl, alkoxy, alkylamino, alkylthio, haloalkylthio, alkenyl, alkynyl, saturated heterocyclyl, partially saturated heterocyclyl, acyl, aroyl, heteroaroyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, cycloalkylalkenyl, haloalkyl, haloalkoxy, haloalkenyl, halocycloalkyl, halocycloalkenyl, haloalkoxyalkyl, haloalkenyloxyalkyl, halocycloalkoxyalkyl, and halocycloalkenyloxyalkyl with the proviso that Z^0 is selected from other than a single covalent bond when Q is hydrido;

K is $(CR^{4a}R^{4b})_n$ wherein n is an integer selected from 1 through 4;

R^{4a} and R^{4b} are independently selected from the group consisting of halo, hydrido, hydroxy, cyano, hydroxyalkyl, alkyl, alkenyl, aryl, aralkyl, aralkoxyalkyl, aryloxyalkyl, alkoxyalkyl, heteroaryloxyalkyl, alkenyloxyalkyl, alkylthioalkyl, aralkylthioalkyl, arylthioalkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, haloalkenyl, heteroaryl, heteroarylalkyl, heteroarylthioalkyl, heteroaralkylthioalkyl, cyanoalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, haloalkylsulfinyl, arylsulfinylalkyl, arylsulfonylalkyl, heteroarylsulfonylalkyl, heteroarylsulfinylalkyl, aralkylsulfinylalkyl, and aralkylsulfonylalkyl with the provisos that halo, hydroxy, and cyano are bonded to different carbons when simultaneously present and that R^{4a} and R_{4b} are other than hydroxy or cyano when bonded to the carbon directly bonded to the pyrazinone nitrogen;

R^{4a} and R^{4b}, when bonded to the same carbon, are optionally taken together to form a group selected from the group consisting of oxo, thiono, and a linear spacer moiety having from 2 through 7 contiguous atoms connected to form a ring selected from the group consisting of a cycloalkyl ring having 3 through 8 contiguous members, a cycloalkenyl ring having 5 through 8 contiguous members, and a heterocyclyl ring having 5 through 8 contiguous members with the proviso that R^{4a} and R^{4b} taken together is other than oxo or thiono when the common carbon is directly bonded to the pyrazinone nitrogen;

E^0 is E^1, when K is $(CR^{4a}R^{4b})_n$, wherein E^1 is selected from the group consisting of a covalent single bond, O, S, C(O), C(S), C(O)O, C(S)O, C(O)S, C(S)S, C(O)N(R^7), (R^7)NC(O), C(S)N(R^7), (R^7)NC(S), OC(O)N(R^7), (R^7)NC(O)O, SC(S)N(R^7), (R^7)NC(S)S, SC(O)N(R^7), (R^7)NC(O)S, OC(S)N(R^7), (R^7)NC(S)O, N(R^8)C(O)N(R^7), (R^7)NC(O)N(R^8), N(R^8)C(S)N(R^7), (R^7)NC(S)N(R^8), S(O), $S(O)_2$, $S(O)_2N(R^7)$, $N(R^7)S(O)_2$, $S(O)_2N(R^7)C(O)$, $C(O)N(R^7)S(O)_2$, Se, Se(O), $Se(O)_2$, $Se(O)_2N(R^7)$, $N(R^7)Se(O)_2$, P(O)(R^8), N(R^7)P(O)(R^8), P(O)(R^8)N(R^7), N(R^7), ON(R^7), $SiR^{28}R^{29}$, CR^{4a}=CR^{4b}, ethynylidene (C≡C; 1,2-ethynyl), and C=$CR^{4a}R^{4b}$;

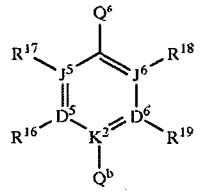
K is optionally selected to be $(CH(R^{14}))_j$—T wherein j is selected from a integer from 0 through 3 and T is selected from the group consisting of single covalent bond, O, S, and N(R^7) with the provisos that R^{14} is other than hydroxy, cyano, halo, amino, alkylamino, dialkylamino, and sulfhydryl when j is 1 and that $(CH(R^{14}))_j$ is bonded to the pyrazinone ring;

E^0 is optionally E^2, when K is $(CH(R^{14}))_j$—T, wherein E^2 is selected from the group consisting of a covalent single bond, C(O), C(S), C(O)O, C(S)O, C(O)S, C(S)S, C(O)N(R^7), (R^7)NC(O), C(S)N(R^7), (R^7)NC(S), (R^7)NC(O)O, (R^7)NC(S)S, (R^7)NC(O)S, (R^7)NC(S)O, N(R^8)C(O)N(R^7), (R^7)NC(O)N(R^8), N(R^8)C(S)N(R^7), (R^7)NC(S)N(R^8), S(O), $S(O)_2$, $S(O)_2N(R^7)$, $N(R^7)S(O)_2$, $S(O)_2N(H)C(O)$, $C(O)N(H)S(O)_2$, Se(O), $Se(O)_2$, $Se(O)_2N(R^7)$, $N(R^7)Se(O)_2$, P(O)(R^8), N(R^7)P(O)(R^8), P(O)(R^8)N(R^7), and N(R^7);

K is optionally selected to be G—$(CH(R^{15}))_k$ wherein k is selected from an integer from 1 through 3 and G is selected from the group consisting of O, S, and N(R^7) with the proviso that R^{15} is other than hydroxy, cyano, halo, amino, alkylamino, dialkylamino, and sulfhydryl when k is 1;

E^0 is optionally E^3 when K is G—$(CH(R^{15}))_k$ wherein E^3 is selected from the group consisting of a covalent single bond, O, S, C(O), C(S), C(O)O, C(S)O, C(O)S, C(S)S, C(O)N(R^7), (R^7)NC(O), C(S)N(R^7), (R^7)NC(S), OC(O)N(R^7), (R^7)NC(O)O, SC(S)N(R^7), (R^7)NC(S)S, SC(O)N(R^7), (R^7)NC(O)S, OC(S)N(R^7), (R^7)NC(S)O, N(R^8)C(O)N(R^7), (R^7)NC(O)N(R^8), N(R^8)C(S)N(R^7), (R^7)NC(S)N(R^8), S(O), $S(O)_2$, $S(O)_2N(R^7)$, $N(R^7)S(O)_2$, Se, Se(O), $Se(O)_2N(R^7)$, $N(R^7)Se(O)_2$, P(O)(R^8), N(R^7)P(O)(R^8) P(O)(R^8)N(R^7), N(R^7), ON(R^7), $SiR^{28}R^{29}$, CR^{4a}=CR^{4b}, ethynylidene (C≡C; 1,2-ethynyl), and C=$CR^{4a}R^{4b}$;

Y^0 is formula (IV):



(IV)

wherein

D^5, D^6, J^5, and J^6 are independently selected from the group consisting of C, N, O, S and a covalent bond with the provisos that no more than one is a covalent bond, K^2 is independently selected from the group consisting of C and N^+, no more than one of D^5, D^6, J^5, and J^6 is O, no more than one of D^5, D^6, J^5, and J^6 is S, one of D^5, D^6, J^5, and J^6 must be a covalent bond when two of D^5, D^6, J^5, and J^6 are O and S, no

more than three of D^5, D^6, J^5, and J^6 are N when K^2 is N^+, and no more than four of D^5, D^6, J^5, and J^6 are N when K^2 is carbon with the provisos that R^{16}, R^{17}, R^{18}, and R^{19} are each independently selected to maintain the tetravalent nature of carbon, trivalent nature of nitrogen, the divalent nature of sulfur, and the divalent nature of oxygen;

R^{16} and R^{17} are independently optionally taken together to form a linear moiety spacer having from 3 through 6 contiguous atoms connected to form a ring selected from the group consisting of a cycloalkenyl ring having from 5 through 8 contiguous members, a partially saturated heterocyclyl ring having from 5 through 8 contiguous members, a heteroaryl having from 5 through 6 contiguous members, and an aryl;

R^{18} and R^{19} are independently optionally taken together to form a linear moiety spacer having from 3 through 6 contiguous atoms connected to form a ring selected from the group consisting of a cycloalkenyl ring having from 5 through 8 contiguous members, a partially saturated heterocyclyl ring having from 5 through 8 contiguous members, a heteroaryl having from 5 through 6 contiguous members, and an aryl;

Q^b is selected from the group consisting of $NR^{20}R^{21}$, $^+NR^{20}R^{21}R^{22}$, oxy, alkyl, aminoalkylenyl, alkylamino, dialkylamino, dialkylsulfoniumalkyl, acylamino and Q^{bc} wherein Q^{bc} is hydrido and R^{20}, R^{21}, and R^{22} are independently selected from the group consisting of hydrido, amino, alkyl, hydroxy, alkoxy, aminoalkylenyl, alkylamino, dialkylamino, and hydroxyalkyl with the provisos that no more than one of R^{20}, R^{21}, and R^{22} is hydroxy, alkoxy, alkylamino, amino, and dialkylamino at the same time and that R^{20}, R^{21}, and R^{22} must be other than be hydroxy, alkoxy, alkylamino, amino, and dialkylamnino when K^2 is N^+;

R^{20} and R^{21}, R^{20} and R^{22}, and R^{21} and R^{22} are independently optionally selected to form a spacer pair wherein a spacer pair is taken together to form a linear moiety having from 4 through 7 contiguous atoms connecting the points of bonding of said spacer pair members to form a heterocyclyl ring having 5 through 8 contiguous members with the proviso that no more than one of the group consisting of spacer pairs R^{20} and R^{21}, R^{20} and R^{22}, and R^{21} and R^{22} is used at the same time;

Q^b is optionally selected from the group consisting of $N(R^{26})SO_2N(R^{23})(R^{24})$, $N(R^{26})C(O)OR^5$, $N(R^{26})C(O)SR^5$, $N(R^{26})C(S)OR^5$ and $N(R^{26})C(S)SR^5$ with the proviso that no more than one of R^{23}, R^{24}, and R^{26} can be hydroxy, alkoxy, alkyleneamino, alkylamino, amino, or dialkylamino when two of the group consisting of R^{23}, R^{24}, and R^{26} are bonded to the same atom;

Q^b is optionally selected from the group consisting of dialkylsulfonium, trialkylphosphonium, $C(NR^{25})NR^{23}R^{24}$, $N(R^{26})C(NR^{25})N(R^{23})(R^{24})$, $N(R^{26})C(O)N(R^{23})(R^{24})$, $N(R^{26})C(S)N(R^{23})(R^{24})$, $C(NR^{25})OR^5$, $C(O)N(R^{26})C(NR^{25})N(R^{23})(R^{24})$, $C(S)N(R^{26})C(NR^{25})N(R^{23})(R^{24})$, $N(R^{26})N(R^{26})C(NR^{25})N(R^{23})(R^{24})$, $ON(R^{26})C(NR^{25})N(R^{23})(R^{24})$, $N(R^{26})N(R^{26})SO_2N(R^{23})(R^{24})$, $C(NR^{25})SR^5$, $C(O)NR^{23}R^{24}$, and $C(O)NR^{23}R^{24}$ with the provisos that no more than one of R^{23}, R^{24}, and R^{26} can be hydroxy, alkoxy, alkylamino, amino, or dialkylamino when any two of the group consisting of R^{23}, R^{24}, and R^{26} are bonded to the same atom and that said Q^b group is bonded directly to a carbon atom;

R^{23}, R^{24}, R^{25}, and R^{26} are independently selected from the group consisting of hydrido, alkyl, hydroxy, alkoxy, alkylenylamino, amino, alkylamino, dialkylamino, and hydroxyalkyl;

R^{23} and R^{24} are optionally taken together to form a linear spacer moiety having from 4 through 7 contiguous atoms connecting the points of bonding to form a heterocyclyl ring having 5 through 8 contiguous members;

R^{23} and R^{25}, R^{24} and R^{25}, R^{25} and R^{26}, R^{24} and R^{26}, and R^{23} and R^{26} are independently optionally selected to form a spacer pair wherein a spacer pair is taken together from the points of bonding of selected spacer pair members to form the group L—U—V wherein L, U, and V are independently selected from the group consisting of O, S, C(O), C(S), $C(J_H)_2S(O)$, SO_2, $OP(OR^{31})R^{30}$, $P(O)R^{30}$, $P(S)R^{30}$, $C(R^{30})R^{31}$, $C{=}C(R^{30})R^{31}$, $(O)_2POP(O)_2$, $R^{30}(O)POP(O)R^{30}$, $Si(R^{29})R^{28}$, $Si(R^{29})R^{28}Si(R^{29})R^{28}$, $Si(R^{29})R^{28}OSi(R^{29})R^{28}$, $(R^{28})R^{29}COC(R^{28})R^{29}$, $(R^{28})R^{29}CSC(R^{28})R^{29}$, $C(O)C(R^{30}){=}C(R^{31})$, $C(S)C(R^{30}){=}C(R^{31})$, $S(O)C(R^{30}){=}C(R^{31})$, $SO_2C(R^{30}){=}C(R^{31})$, $PR^{30}C(R^{30}){=}C(R^{31})$, $P(O)R^{30}C(R^{30}){=}C(R^{31})$, $P(S)R^{30}C(R^{30}){=}C(R^{31})$, $DC(R^{30})(R^{31})D$, $OP(OR^{31})R^{30}$, $P(O)R^{30}$, $P(S)R^{30}$, $Si(R^{28})R^{29}$ and $N(R^{30})$, and a covalent bond with the proviso that no more than any two of L, U and V are simultaneously covalent bonds and the heterocyclyl comprised of by L, U, and V has from 5 through 10 contiguous member;

D is selected from the group consisting of oxygen, C=O, C=S, $S(O)_m$ wherein m is an integer selected from 0 through 2;

J_H is independently selected from the group consisting of OR^{27}, SR^{27} and $N(R^{20})R^{21}$;

R^{27} is selected from the group consisting of hydrido, alkyl, alkenyl, alkynyl, aralkyl, aryloxyalkyl, aralkoxyalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, aralkylthioalkyl, heteroaralkylthioalkyl, alkoxyalkyl, heteroaryloxyalkyl, alkenyloxyalkyl, alkylthioalkyl, arylthioalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkenyl, cycloalkenylalkyl, haloalkyl, haloalkenyl, halocycloalkyl, halocycloalkenyl, haloalkoxyalkyl, haloalkenyloxyalkyl, halocycloalkoxyalkyl, halocycloalkenyloxyalkyl, perhaloaryloxyalkyl, heteroaryl, heteroarylalkyl, heteroarylthioalkyl, heteroaralkylthioalkyl, arylsulfinylalkyl, arylsulfonylalkyl, cycloalkylsulfinylalkyl, cycloalkylsufonylalkyl, heteroarylsulfonylalkyl, heteroarylsulfinylalkyl, aralkylsulfinylalkyl and aralkylsulfonylalkyl;

R^{30} and R^{31} are independently selected from the group consisting of hydrido, hydroxy, thiol, aryloxy, amino, alkylamino, dialkylamino, hydroxyalkyl, heteroaryloxyalkyl, alkoxy, alkylthio, arylthio, alkyl, alkenyl, alkynyl, aryl, aralkyl, aryloxyalkyl, aralkoxyalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, aralkylthioalkyl, heteroaralkoxythioalkyl, alkoxyalkyl, heteroaryloxyalkyl, alkenyloxyalkyl, alkylthioalkyl, arylthioalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkenyl, cycloalkenylalkyl, haloalkyl, haloalkenyl, haloaralkylsulfinylalkyl, aralkylsulfonylalkyl,

cyanoalkyl, dicyanoalkyl, carboxamidoalkyl, dicarboxamidoalkyl, cyanocarboalkoxyalkyl, carboalkoxyalkyl, dicarboalkoxyalkyl, cyanocycloalkyl, dicyanocycloalkyl, carboxamidocycloalkyl, dicarboxamidocycloalkyl, carboalkoxycyanocycloalkyl, carboalkoxycycloalkyl, dicarboalkoxycycloalkyl, formylalkyl, acylalkyl, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, phosphonoalkyl, dialkoxyphosphonoalkoxy, diaralkoxyphosphonoalkoxy, phosphonoalkoxy, dialkoxyphosphonoalkylamino, diaralkoxyphosphonoalkylamino, phosphonoalkylamino, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, sulfonylalkyl, alkoxysulfonylalkyl, aralkoxysulfonylalkyl, alkoxysulfonylalkoxy, aralkoxysulfonylalkoxy, sulfonylalkoxy, alkoxysulfonylalkylamino, aralkoxysulfonylalkylamino, and sulfonylalkylamino;

R^{30} and R^{31} are optionally taken to form a linear moiety spacer group having from 2 through 7 contiguous atoms to form a ring selected from the group consisting of a cycloalkyl ring having from 3 through 8 contiguous members, a cycloalkenyl ring having from 3 through 8 contiguous members, and a heterocyclyl ring having from 3 through 8 contiguous members;

R^{23} and R^{25}, R^{24} and R^{25}, R^{25} and R^{26}, R^{24} and R^{26}, and R^{23} and R^{26} are independently optionally selected to form a spacer pair wherein a spacer pair is taken together from the points of bonding of selected spacer pair members to form the group L—U—V wherein L, U, and V are independently selected from the group of 1,2-disubstituted radicals consisting of a cycloalkyl radical, a cycloalkenyl radical wherein cycloalkyl and cycloalkenyl radicals are substituted with one or more groups selected from R^{30} and R^{31}, an aryl radical, an heteroaryl radical, a saturated heterocyclic radical and a partially saturated heterocyclic radical wherein said 1,2-substitutents are independently selected from C═O, C═S, $C(R^{28})R^{32}$, S(O), $S(O)_2$, $OP(OR^{31})R^{30}$, $P(O)R^{30}$, $P(S)R^{30}$ and $Si(R^{28})R^{29}$;

R^{23} and R^{25}, R^{24} and R^{25}, R^{25} and R^{26}, R^{24} and R^{26}, and R^{23} and R^{26} are independently optionally selected to form a spacer pair wherein a spacer pair is taken together from the points of bonding of selected spacer pair members to form the group L—U—V wherein L, U, and V are independently selected from the group of radicals consisting of 1,2-disubstituted alkylene radicals and 1,2-disubstituted alkenylene radical wherein said 1,2-substitutents are independently selected from C═O, C═S, $C(R^{28})R^{29}$, S(O), $S(O)_2$, $OP(OR^{31})R^{30}$, $P(O)R^{30}$, $P(S)R^{30}$, and $Si(R^{28})R^{29}$ and said alkylene and alkenylene radical are substituted with one or more R^{30} or R^{31} substituents;

Q^e is selected from the group consisting of a single covalent bond, $(CR^{37}R^{38})_b$—$(W^0)_{az}$ wherein az is an integer selected from 0 through 1, b is an integer selected from 1 through 4, and W^0 is selected from the group consisting of O, S, C(O), C(S), C(O)O, C(S)O, C(O)S, C(S)S, $C(O)N(R^{14})$, $(R^{14})NC(O)$, $C(S)N(R^{14})$, $(R^{14})NC(S)$, $OC(O)N(R^{14})$, $SC(S)N(R^{14})$, $SC(O)N(R^{14})$, $OC(S)N(R^{14})$, $N(R^{15})C(O)N(R^{14})$, $(R^{14})NC(O)N(R^{15})$, $N(R^{15})C(S)N(R^{14})$, $(R^{14})NC(S)N(R^{15})$, S(O), $S(O)_2$, $S(O)_2N(R^{14})$, $N(R^{14})S(O)_2$, Se, Se(O), $Se(O)_2$, $Se(O)_2N(R^{14})$, $N(R^{14})Se(O)_2$, $P(O)(R^8)$, $N(R^7)P(O)(R^8)$, $P(O)(R^8)N(R^7)$, $N(R^{14})$, $ON(R^{14})$, and $SiR^{28}R^{29}$, $(CH(R^{14}))_e$—W^1—$(CH(R^{15}))_d$ wherein c and d are integers independently selected from 1 through 4, and W^1 is selected from the group consisting of O, S, C(O), C(S), C(O)O, C(S)O, C(O)S, C(S)S, $C(O)N(R^{14})$, $(R^{14})NC(O)$, $C(S)N(R^{14})$, $(R^{14})NC(S)$, $OC(O)N(R^{14})$, $(R^{14})NC(O)O$, $SC(S)N(R^{14})$, $(R^{14})NC(S)S$, $SC(O)N(R^{14})$, $(R^{14})NC(O)S$, $OC(S)N(R^{14})$, $(R^{14})NC(S)O$, $N(R^{15})C(O)N(R^{14})$, $(R^{14})NC(O)N(R^{14})$, $N(R^{15})C(S)N(R^{14})$, $(R^{14})NC(S)N(R^{15})$, S(O), $S(O)_2$, $S(O)_2N(R^{14})$, $N(R^{14})S(O)_2$, Se, Se(O), $Se(O)_2$, $Se(O)_2N(R^{14})$, $N(R^{14})Se(O)_2$, $P(O)(R^8)$, $N(R^7)P(O)(R^8)$, $P(O)(R^8)N(R^7)$, $N(R^{14})$, $ON(R^{14})$, $SiR^{28}R^{29}$, and $(CH(R^{14}))_e$—W^{22}—$(CH(R^{15}))_h$ wherein e and h are integers independently selected from 0 through 2 and W^{22} is selected from the group consisting of $CR^{41}═CR^{42}$, $CR^{41}R^{42}═C$; vinylidene), ethynylidene (C≡C; 1,2-ethynyl), 1,2-cyclopropyl, 1,2-cyclobutyl, 1,2-cyclohexyl, 1,3-cyclohexyl, 1,2-cyclopentyl, 1,3-cyclopentyl, 2,3-morpholinyl, 2,4-morpholinyl, 2,6-morpholinyl, 3,4-morpholinyl, 3,5-morpholinyl, 1,2-piperazinyl, 1,3-piperazinyl, 2,3-piperazinyl, 2,6-piperazinyl, 1,2-piperidinyl, 1,3-piperidinyl, 2,3-piperidinyl, 2,4-piperidinyl, 2,6-piperidinyl, 3,4-piperidinyl, 1,2-pyrrolidinyl, 1,3-pyrrolidinyl, 2,3-pyrrolidinyl, 2,4-pyrrolidinyl, 2,5-pyrrolidinyl, 3,4-pyrrolidinyl, 2,3-tetrahydrofuranyl, 2,4-tetrahydrofuranyl, 2,5-tetrahydrofuranyl, and 3,4-tetrahydrofuranyl, with the provisos that R^{14} and R^{15} are selected from other than halo and cyano when directly bonded to N and that $(CR^{37}R^{38})_b$, $(CH(R^{14}))_c$, $(CH(R^{14}))_e$ and are bonded to E^0;

R^{37} and R^{37}, when bonded to different carbons, are optionally taken together to form a linear moiety spacer having from 1 through 7 contiguous atoms to form a ring selected from the group consisting of a cycloalkyl ring having from 3 through 8 contiguous members, a cycloalkenyl ring having from 3 through 8 contiguous members, and a heterocyclyl ring having from 3 through 8 contiguous members;

R^{37} and R^{38}, when bonded to different carbons, are taken together to form a linear moiety spacer having from 1 through 7 contiguous atoms to form a ring selected from the group consisting of a cycloalkyl ring having from 3 through 8 contiguous members, a cycloalkenyl ring having from 3 through 8 contiguous members, and a heterocyclyl ring having from 3 through 8 contiguous members;

R^{38} and R^{38}, when bonded to different carbons, are taken together to form a linear moiety spacer having from 1 through 7 contiguous atoms to form a ring selected from the group consisting of a cycloalkyl ring having from 3 through 8 contiguous members, a cycloalkenyl ring having from 3 through 8 contiguous members, and a heterocyclyl ring having from 3 through 8 contiguous members;

R^{37} and R^{38}, when bonded to the same carbon, are taken together to form a group selected from a group consisting of oxo, thiono, alkylene, haloalkylene, and a linear moiety spacer having from 2 through 7 contiguous atoms to form a ring selected from the group consisting of a cycloalkyl ring having from 3 through 8 contiguous members, a cycloalkenyl ring having from 3 through 8 contiguous members, and a

heterocyclyl ring having from 3 through 8 contiguous members;

Y^0 is optionally Q^b—Q^{ss} wherein Q^{ss} is selected from the group consisting of $(CR^{37}R^{38})_f$ wherein f is an integer selected from 1 through 6, $(CH(R^{14}))_c$—W^1—$(CH(R^{15}))_d$ wherein c and d are integers independently selected from 1 through 4, and W^1 is selected from the group consisting of W^1 is selected from the group consisting of O, S, C(O), C(S), C(O)O, C(S)O, C(O)S, C(S)S, C(O)N(R^{14}), (R^{14})NC(O), C(S)N(R^{14}), (R^{14})NC(S), OC(O)N(R^{14}), (R^{14})NC(O)O, SC(S)N(R^{14}), (R^{14})NC(S)S, SC(O)N(R^{14}), (R^{14})NC(O)S, OC(S)N(R^{14}), (R^{14})NC(S)O, N(R^{15})C(O)N(R^{14}), (R^{14})NC(O)N(R^{15}), N(R^{15})C(S)N(R^{14}), (R^{14})NC(S)N(R^{15}), S(O), $S(O)_2$, $S(O)_2N(R^{14})$, $N(R^{14})S(O)_2$, Sc, Sc(O), $Sc(O)_2$, $Se(O)_2N(R^{14})$, $N(R^{14})Se(O)_2$, P(O)(R^8), N(R^7)P(O)(R^8), P(O)(R^8)N(R^7), N(R^{14}), ON(R^{14}) $SiR^{28}R^{29}$, and $(CH(R^{14}))_e$—W^2—$(CH(R^{15}))_h$ wherein e and h are integers independently selected from 0 through 2 and W^2 is selected from the group consisting of CR^{4a}=CR^{4b}, ethynylidene (C≡C; 1,2-ethynyl), and C=$CR^{4a}R^{4b}$ with the provisos that R^{14} and R^{15} are selected from other than halo and cyano when directly bonded to N, that $(CR^{37}R^{38})_f$, $(CH(R^{15}))_c$, and $(CH(R^{15}))_e$ are bonded to E^0, and Q^b is selected from other than N(R^{26})N(R^{26})C(NR^{25})N(R^{23})(R^{24}) or ON(R^{26})C(NR^{25})N(R^{23})(R^{24}) when Q^{ss} is $(CR^{37}R^{38})_f$ wherein f is other than the integer 1;

Y^0 is optionally Q^b—Q^{sss} wherein Q^{sss} is $(CH(R^{38}))_r$—W^3, r is an integer selected from 1 through 3, W^3 is selected from the group consisting of 1,1-cyclopropyl, 1,2-cyclopropyl, 1,1-cyclobutyl, 1,2-cyclobutyl, 1,2-cyclohexyl, 1,3-cyclohexyl, 1,4-cyclohexyl, 1,2-cyclopentyl, 1,3-cyclopentyl, 2,3-morpholinyl, 2,4-morpholinyl, 2,5-morpholinyl, 2,6-morpholinyl, 3,4-morpholinyl, 3,5-morpholinyl, 1,2-piperazinyl, 1,3-piperazinyl, 1,4-piperazinyl, 2,3-piperazinyl, 2,5-piperazinyl, 2,6-piperazinyl, 1,2-piperidinyl, 1,3-piperidinyl, 1,4-piperidinyl, 2,3-piperidinyl, 2,4-piperidinyl, 2,5-piperidinyl, 2,6-piperidinyl, 3,4-piperidinyl, 3,5-piperidinyl, 3,6-piperidinyl, 1,2-pyrrolidinyl, 1,3-pyrrolidinyl, 2,3-pyrrolidinyl, 2,4-pyrrolidinyl, 2,5-pyrrolidinyl, 3,4-pyrrolidinyl, 2H-2,3-pyranyl, 2H-2,4-pyranyl, 2H-2,5-pyranyl, 4H-2,3-pyranyl, 4H-2,4-pyranyl, 4H-2,5-pyranyl, 2H-pyran-2-one-3,4-yl, 2H-pyran-2-one-4,5-yl, 4H-pyran4-one-2, 3-yl, 2,3-tetrahydrofuranyl, 2,4-tetrahydrofuranyl, 2,5-tetrahydrofuranyl, 3,4-tetrahydrofuranyl, 2,3-tetrahydropyranyl, 2,4-tetrahydropyranyl, 2,5-tetrahydropyranyl, 2,6-tetrahydropyranyl, 3,4-tetrahydropyranyl, and 3,5-tetrahydropyranyl, and each carbon and hyrido containing nitrogen member of the ring of the W^3 other than the points of attachment is optionally substituted with one or more of the group consisting of R^9, R^{10}, R^{11}, and R^{12}, with the proviso that $(CH(R^{38}))_r$ is bonded to E^0 and Q^b is bonded to lowest numbered substituent position of each W^3;

Y^0 is optionally Q^b—Q^{sssr} wherein Q^{sssr} is $(CH(R^{38})_r$—W^4, is an integer selected from 1 through 3, W^4 is selected from the group consisting of 1,2-cyclobutyl, 1,2-cyclohexyl, 1,3-cyclohexyl, 1,4-cyclohexyl, 1,2-cyclopentyl, 1,3-cyclopentyl, 2,3-morpholinyl, 2,4-morpholinyl, 2,5-morpholinyl, 2,6-morpholinyl, 3,4-morpholinyl, 3,5-morpholinyl, 1,2-piperazinyl, 1,3-piperazinyl, 1,4-piperazinyl, 2,3-piperazinyl, 2,5piperazinyl, 2,6-piperazinyl, 1,2-piperidinyl, 1,3-piperidinyl, 1,4-piperidinyl, 2,3-piperidinyl, 2,4-piperidinyl, 2,5-piperidinyl, 2,6-piperidinyl, 3,4-piperidinyl, 3,5-piperidinyl, 3,6-piperidinyl, 1,2-pyrrolidinyl, 1,3-pyrrolidinyl, 2,3-pyrrolidinyl, 2,4-pyrrolidinyl, 2,5-pyrrolidinyl, 3,4-pyrrolidinyl, 2H-2,3-pyranyl, 2H-2,4-pyranyl, 2H-2,5-pyranyl, 4H-2,3-pyranyl, 4H-2,4-pyranyl, 4H-2,5-pyranyl, 2H-pyran-2-one-3,4-yl, 2H-pyran-2-one4,5-yl, 4H-pyran-4-one-2, 3-yl, 2,3-tetrahydrofuranyl, 2,4-tetrahydrofuranyl, 2,5-tetrahydrofuranyl, 3,4-tetrahydrofuranyl, 2,3-tetrahydropyranyl, 2,4-tetrahydropyranyl, 2,5-tetrahydropyranyl, 2,6-tetrahydropyranyl, 3,4-tetrahydropyranyl, and 3,5-tetrahydropyranyl, and each carbon and hydrido containing nitrogen member of the ring of the W^4 other than the points of attachment is optionally substituted with one or more of the group consisting of R^9, R^{10}, R^{11}, and R^{12}, with the provisos that $(CH(R^{38}))_r$ is bonded to E^0 and Q^b is bonded to highest number substituent position of each W^4;

Y^0 is optionally Q^b—Q^{ssss} wherein Q^{ssss} is $(CH(R^{38}))_r$—W^5, r is an integer selected from 1 through 3, W^5 is selected from the group consisting of 1,4-indenyl, 1,5-indenyl, 1,6-indenyl, 1,7-indenyl, 2,7-indenyl, 2,6-indenyl, 2,5-indenyl, 2,4-indenyl, 3,4-indenyl, 3,5-indenyl, 3,6-indenyl, 3,7-indenyl, 2,4-benzofuranyl, 2,5-benzofuranyl, 2,6-benzofuranyl, 2,7-benzofuranyl, 3,4-benzofuranyl, 3,5-benzofuranyl, 3,6-benzofuranyl, 3,7-benzofuranyl, 2,4benzothiophenyl, 2,5-benzothiophenyl, 2,6-benzothiophenyl, 2,7-benzothiophenyl, 3,5-benzothiophenyl, 3,5-benzothiophenyl, 3,6-benzothiophenyl, 3,7-benzothiophenyl, 2,4-imidazo(1,2-a)pyridinyl, 2,5-imidazo(1,2-a)pyridinyl, 2,6-imidazo(1,2-a)pyridinyl, 2,7-imidazo(1,2-a)pyridinyl, 3,4-imidazo(1,2-a)pyridinyl, 3,5-imidazo(1,2-a)pyridinyl, 3,6-imidazo(1,2-a)pyridinyl, 3,7-imidazo(1,2-a)pyridinyl, 2,4-indolyl, 2,5-indolyl, 2,6-indolyl, 2,7-indolyl, 3,4-indolyl, 3,5-indolyl, 3,6-indolyl, 3,7-indolyl, 1,4-isoindolyl, 1,5-isoindolyl, 1,6-isoindolyl, 2,4-isoindolyl, 2,5-isoindolyl, 2,6-isoindolyl, 2,7-isoindolyl, 1,3-isoindolyl, 3,4-indazolyl, 3,5-indazolyl, 3,6-indazolyl, 3,7-indazolyl, 2,4-benzoxazolyl, 2,5-benzoxazolyl, 2,6-benzoxazolyl, 2,7-benzoxazolyl, 3,4-benzisoxazolyl, 3,5-benzisoxazolyl, 3,6-benzisoxazolyl, 3,7-benzisoxazolyl, 1,4-naphthyl, 1,5-naphthyl, 1,6-naphthyl, 1,7-naphthyl, 1,8-naphthyl, 2,4-naphthyl, 2,5-naphthyl, 2,6-naphthyl, 2,7-naphthyl, 2,8-naphthyl, 2,4-quinolinyl, 2,5-quinolinyl, 2,6-quinolinyl, 2,7-quinolinyl, 2,8-quinolinyl, 3,4-quinolinyl, 3,5-quinolinyl, 3,6-quinolinyl, 3,7-quinolinyl, 3,8-quinolinyl, 4,5-quinolinyl, 4,6-quinolinyl, 4,7-quinolinyl, 4,8-quinolinyl, 1,4-isoquinolinyl, 1,5-isoquinolinyl, 1,6-isoquinolinyl, 1,7-isoquinolinyl, 1,8-isoquinolinyl, 3,4-isoquinolinyl, 3,5-isoquinolinyl, 3,6-isoquinolinyl, 3,7-isoquinolinyl, 3,8-isoquinolinyl, 4,5-isoquinolinyl, 4,6-isoquinolinyl, 4,7-isoquinolinyl, 4,8-isoquinolinyl, 3,4-cinnolinyl, 3,5-cinnolinyl, 3,6cinnolinyl, 3,7-cinnolinyl, 3,8-cinnolinyl, 4,5-cinnolinyl, 4,6-cinnolinyl, 4,7-cinnolinyl, and 4,8-cinnolinyl, and each carbon and hydrido containing nitrogen member of the ring of the W^5 other than the points of attachment is optionally

substituted with one or more of the group consisting of R^9, R^{10}, R^{11}, and R^{12}, with the proviso that Q^b is bonded to lowest number substituent position of each W^5 and that $(CH(R^{38}))_r$ is bonded to E^0;

Y^0 is optionally Q^b—Q^{ssssr} wherein Q^{ssssr} is $(CH(R^{38}))_r$—W^6, r is an integer selected from 1 through 3, W^6 is selected from the group consisting of 1,4-indenyl, 1,5-indenyl, 1,6-indenyl, 1,7-indenyl, 2,7-indenyl, 2,6-indenyl, 2,5-indenyl, 2,4-indenyl, 3,4-indenyl, 3,5-indenyl, 3,6-indenyl, 3,7-indenyl, 2,4-benzofuranyl, 2,5-benzofuranyl, 2,6-benzofuranyl, 2,7-benzofuranyl, 3,4-benzofuranyl, 3,5-benzofuranyl, 3,6-benzofuranyl, 3,7-benzofuranyl, 2,4-benzothiophenyl, 2,5-benzothiophenyl, 2,6-benzothiophenyl, 2,7-benzothiophenyl, 3,4-benzothiophenyl, 3,5-benzothiophenyl, 3,6-benzothiophenyl, 3,7-benzothiophenyl, 2,4-imidazo(1,2-a)pyridinyl, 2,5-imidazo(1,2-a)pyridinyl, 2,6-imidazo(1,2-a)pyridinyl, 2,7-imidazo(1,2-a)pyridinyl, 3,4-imidazo(1,2-a)pyridinyl, 3,5-imidazo(1,2-a)pyridinyl, 3,6-imidazo(1,2-a)pyridinyl, 3,7-imidazo(1,2-a)pyridinyl, 2,4-indolyl, 2,5-indolyl, 2,6-indolyl, 2,7-indolyl, 3,4-indolyl, 3,5-indolyl, 3,6-indolyl, 3,7-indolyl, 1,4-isoindolyl, 1,5-isoindolyl, 1,6-isoindolyl, 2,4-isoindolyl, 2,5-isoindolyl, 2,6-isoindolyl, 2,7-isoindolyl, 1 3-isoindolyl, 3,4-indazolyl, 3,5-indazolyl, 3,6-indazolyl, 3,7-indazolyl, 2,4-benzoxazolyl, 2,5-benzoxazolyl, 2,6-benzoxazolyl, 2,7-benzoxazolyl, 3,4-benzisoxazolyl, 3,5-benzisoxazolyl, 3,6-benzisoxazolyl, 3,7-benzisoxazolyl, 1,4-naphthyl, 1,5-naphthyl, 1,6-naphthyl, 1,7-naphthyl, 1,8-naphthyl, 2,4-naphthyl, 2,5-naphthyl, 2,6-naphthyl, 2,7-naphthyl, 2,8-naphthyl, 2,4-quinolinyl, 2,5-quinolinyl, 2,6-quinolinyl, 2,7-quinolinyl, 2,8-quinolinyl, 3,4-quinolinyl, 3,5-quinolinyl, 3,6-quinolinyl, 3,7-quinolinyl, 3,8-quinolinyl, 4,5-quinolinyl, 4,6quinolinyl, 4,7-quinolinyl, 4,8-quinolinyl, 1,4-isoquinolinyl, 1,5-isoquinolinyl, 1,6-isoquinolinyl, 1,7-isoquinolinyl, 1,8-isoquinolinyl, 3,4-isoquinolinyl, 3,5-isoquinolinyl, 3,6-isoquinolinyl, 3,7-isoquinolinyl, 3,8-isoquinolinyl, 4,5-isoquinolinyl, 4,6-isoquinolinyl, 4,7-isoquinolinyl, 4,8-isoquinolinyl, 3,4-cinnolinyl, 3,5-cinnolinyl, 3,6-cinnolinyl, 3,7-cinnolinyl, 3,8-cinnolinyl, 4,5-cinnolinyl, 4,6-cinnolinyl, 4,7-cinnolinyl, and 4,8-cinnolinyl, and each carbon and hydrido containing nitrogen member of the ring of the W^6 other than the points of attachment is optionally substituted with one or more of the group consisting of R^9, R^{10}, R^{11}, and R^{12}, with the proviso that Q^b is bonded to highest number substituent position of each W^6 and that $(CH(R^{38}))_r$ is bonded to E^0.

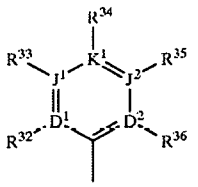
In an embodiment of compounds of Formula I or a pharmaceutically acceptable salt thereof,

J is selected from the group consisting of O and S;

J is optionally selected from the group consisting of CH—R^6 and N—R^6 wherein R^6 is a linear spacer moiety having a chain length of 1 to 4 atoms linked to the point of bonding of a substituent selected from the group consisting of R^{4a}, R^{4b}, R^{39}, R^{40}, R^5, R^{14}, and R^{15} to form a heterocyclyl ring having 5 through 8 contiguous members;

B is formula (V):

(V)



wherein

D^1, D^2, J^1, J^2 and K^1 are independently selected from the group consisting of C, N, O, S and a covalent bond with the provisos that no more than one is a covalent bond, no more than one of D^1, D^2, J^1, J^2 and K^1 is O, no more than one of D^1, D^2, J^1, J^2 and K^1 is S, one of D^1, D^2, J^1, J^2 and K^1 must be a covalent bond when two of D^1, D^2, J^1, J^2 and K^1 are O and S, and no more than four of D^1, D^2, J^1, J^2 and K^1 are N with the proviso that R^{32}, R^{33}, R^{34}, R^{35}, and R^{36} are each independently selected to maintain the tetravalent nature of carbon, trivalent nature of nitrogen, the divalent nature of sulfur, and the divalent nature of oxygen;

R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{16}, R^{17}, R^{18}, R^{19}, R^{32}, R^{33}, R^{34}, R^{35}, and R^{36} are independently selected from the group consisting of hydrido, acetamido, haloacetamido, amidino, guanidino, dialkylsulfonium, trialkylphosphonium, dialkylsulfoniumalkyl, carboxy, heteroaralkylthio, heteroaralkoxy, cycloalkylamino, acylalkyl, acylalkoxy, aryloylalkoxy, heterocyclyloxy, aralkylaryl, aralkyl, aralkenyl, aralkynyl, heterocyclyl, perhaloaralkyl, aralkylsulfonyl, aralkylsulfonylalkyl, aralkylsulfinyl, aralkylsulfinylalkyl, halocycloalkyl, halocycloalkenyl, cycloalkylsulfinyl, cycloalkylsulfinylalkyl, cycloalkylsulfonyl, cycloalkylsulfonylalkyl, heteroarylamino, N-heteroarylamino-N-alkylaamino, heteroarylaminoalkyl, haloalkylthio, alkanoyloxy, alkoxy, alkoxyalkyl, haloalkoxylalkyl, heteroaralkoxy, cycloalkoxy, cycloalkenyloxy, cycloalkoxyalkyl, cycloalkylalkoxy, cycloalkenyloxyalkyl, cycloalkylenedioxy, halocycloalkoxy, halocycloalkoxyalkyl, halocycloalkenyloxy, halocycloalkenyloxyalkyl, hydroxy, amino, alkoxyamino, thio, nitro, lower alkylamino, alkylthio, alkylthioalkyl, arylamino, aralkylamino, arylthio, arylthioalkyl, heteroaralkoxyalkyl, alkylsulfinyl, alkylsulfinylalkyl, arylsulfinylalkyl, aryl sulfonyl alkyl, heteroarylsulfinylalkyl, heteroarylsulfonylalkyl, alkylsulfonyl, alkylsulfonylalkyl, haloalkylsulfinylalkyl, haloalkylsulfonylalkyl, alkylsulfonamido, alkylaminosulfonyl, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, monoarylamidosulfonyl, arylsulfonamido, diarylamidosulfonyl, monoalkyl monoaryl amidosulfonyl, arylsulfinyl, arylsulfonyl, heteroarylthio, heteroarylsulfinyl, heteroarylsulfonyl, heterocyclylsulfonyl, heterocyclylthio, alkanoyl, alkenoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, haloalkanoyl, alkyl, alkenyl, alkynyl, alkenyloxy,

alkenyloxyalky, alkylenedioxy, haloalkylenedioxy, cycloalkyl, cycloalkylalkanoyl, cycloalkenyl, lower cycloalkylalkyl, lower cycloalkenylalkyl, halo, haloalkyl, haloalkenyl, haloalkoxy, hydroxyhaloalkyl, hydroxyaralkyl, hydroxyalkyl, alkylenylamino, hydoxyheteroaralkyl, haloalkoxyalkyl, aryl, aralkyl, aryloxy, aralkoxy, aryloxyalkyl, saturated heterocyclyl, partially saturated heterocyclyl, heteroaryl, heteroaryloxy, heteroaryloxyalkyl, arylalkyl, heteroarylalkyl, arylalkenyl, heteroarylalkenyl, carboxyalkyl, carboalkoxy, alkoxycarboxamido, alkylamidocarbonylamido, arylamidocarbonylamido, carboalkoxyalkyl, carboalkoxyalkenyl, carboxy, carboaralkoxy, carboxamido, carboxamidoalkyl, cyano, carbohaloalkoxy, phosphono, phosphonoalkyl, diaralkoxyphosphono, and diaralkoxyphosphonoalkyl;

R^{16}, R^{19}, R^{32}, R^{33}, R^{34}, R^{35}, and R^{36} are independently optionally Q^b with the proviso that no more than one of R^{16} and R^{19} is Q^b at the same time and that Q^b is Q^{be};

R^{32} and R^{33}, R^{33} and R^{34}, R^{34} and R^{35}, and R^{35} and R^{36} are independently optionally selected to form a spacer pair wherein a spacer pair is taken together to form a linear moiety having from 3 through 6 contiguous atoms connecting the points of bonding of said spacer pair members to form a ring selected from the group consisting of a cycloalkenyl ring having 5 through 8 contiguous members, a partially saturated heterocyclyl ring having 5 through 8 contiguous members, a heteroaryl ring having 5 through 6 contiguous members, and an aryl with the proviso that no more than one of the group consisting of spacer pairs R^{32} and R^{33}, R^{33} and R^{34}, R^{34} and R^{35}, and R^{35} and R^{36} can be used at the same time;

R^9 and R^{10}, R^{10} and R^{11}, R^{11} and R^{12}, and R^{12} and R^{13} are independently optionally selected to form a spacer pair wherein a spacer pair is taken together to form a linear moiety having from 3 through 6 contiguous atoms connecting the points of bonding of said spacer pair members to form a ring selected from the group consisting of a cycloalkenyl ring having 5 through 8 contiguous members, a partially saturated heterocyclyl ring having 5 through 8 contiguous members, a heteroaryl ring having 5 through 6 contiguous members, and an aryl with the proviso that no more than one of the group consisting of spacer pairs R^9 and R^{10}, R^{10} and R^{11}, R^{11} and R^{12}, and R^{12} and R^{13} can be used at the same time;

B is optionally selected from the group consisting of hydrido, trialkylsilyl, C2–C8 alkyl, C3–C8 alkylenyl, C3–C8 alkenyl, C3–C8 alkynyl, C2–C8 haloalkyl, and C3–C8 haloalkenyl wherein each member of group B may be optionally substituted at any carbon up to and including 6 atoms from the point of attachment of B to A with one or more of the group consisting of R^{32}, R^{33}, R^{34}, R^{35}, and R^{36};

B is optionally selected from the group consisting of C3–C15 cycloalkyl, C5–C10 cycloalkenyl, C4–C12 saturated heterocyclyl, and C4–C9 partially saturated heterocyclyl, wherein each ring carbon is optionally substituted with R^{33}, a ring carbon other than the ring carbon at the point of attachment of B to A is optionally substituted with oxo provided that no more than one ring carbon is substituted by oxo at the same time, ring carbon and nitrogen atoms adjacent to the carbon atom at the point of attachment is optionally substituted with R^9 or R^{13}, a ring carbon or nitrogen atom adjacent to the R^9 position and two atoms from the point of attachment is optionally substituted with R^{10}, a ring carbon or nitrogen atom adjacent to the R^{13} position and two atoms from the point of attachment is optionally substituted with R^{12}, a ring carbon or nitrogen atom three atoms from the point of attachment and adjacent to the R^{10} position is optionally substituted with R^{11}, a ring carbon or nitrogen atom three atoms from the point of attachment and adjacent to the R^{12} position is optionally substituted with R^{33}, and a ring carbon or nitrogen atom four atoms from the point of attachment and adjacent to the R^{11} and R^{33} positions is optionally substituted with R^{34};

A is selected from the group consisting of single covalent bond, $(W^7)_{rr}$—$(CH(R^{15}))_{pa}$ and $(CH(R^{15}))_{pa}$—$(W^7)_{rr}$ wherein rr is an integer selected from 0 through 1, pa is an integer selected from 0 through 6, and W^7 is selected from the group consisting of O, S, C(O), C(S), C(O)S, C(S)O, C(O)N(R^7), C(S)N(R^7), (R^7)NC(O), (R^7)NC(S), S(O), $S(O)_2$, $S(O)_2N(R^7)$, (R^7)$NS(O)_2$, P(O)(R^8), N(R^7)P(O)(R^8), P(O)(R^8)N(R^7), C(NR^7)N(R^7), (R^7)NC(NR^7), (R^7)NC(NR^7)NR^7, and N(R^7) with the proviso that no more than one of the group consisting of rr and pa can be 0 at the same time;

R^7 and R^8 are independently selected from the group consisting of hydrido, hydroxy, alkyl, acyl, aroyl, heteroaroyl, and alkoxyalkyl;

R^{14}, R^{15}, R^{37}, and R^{38} are independently selected from the group consisting of hydrido, hydroxy, halo, cyano, hydroxyalkyl, alkoxy, alkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, haloalkyl, haloalkenyl, haloalkoxy, haloalkoxyalkyl, haloalkenyloxyalkyl, halocycloalkoxy, halocycloalkoxyalkyl, halocycloalkenyloxyalkyl, carboxy, carboxyalkyl, carboalkoxy, carboxamide, and carboxamidoalkyl;

R^{14} and R^{38} can be independently selected from the group consisting of acyl, aroyl, and heteroaroyl with the proviso that acyl is selected from other than formyl and 2-oxoacyl;

Ψ is selected from the group consisting of NR^5, O, C(O), C(S), S, S(O), $S(O)_2$, $ON(R^5)$, P(O)(R^8), and $CR^{39}R^{40}$;

R^5 is selected from the group consisting of hydrido, hydroxy, amino, alkyl, alkoxy, alkoxyalkyl, haloalkyl, acyl, aroyl, and heteroaroyl;

R^{39} and R^{40} are independently selected from the group consisting of hydrido, hydroxy, halo, cyano, hydroxyalkyl, acyl, aroyl, heteroaroyl, acylamido, alkoxy, alkyl, alkoxyalkyl, haloalkyl, haloalkoxy, haloalkoxyalkyl, alkylsulfonyl, haloalkylsulfonyl, carboxy, carboxyalkyl, carboalkoxy, carboxamide, and carboxamidoalkyl;

R^2 and R^1 are independently selected from the group consisting of Z^0—Q, hydrido, alkyl, alkenyl, and halo with the provisos that R^2 is selected from other than the group consisting of hydrido, alkyl, cycloalkyl, and trifluoromethyl and R^1 is selected from other than the group consisting of hydrido and halo unless E^1 is other than C(O)NH, or unless E^0 is selected from the group consisting of E^2 and E^3, or unless K is other than $(CR^{4a}R^{4b})_n$ wherein n is 1 unless one of R^{4a} and R^{4b} are independently selected from other than hydrido, or unless Ψ is selected from other than NR^5, or unless R^5

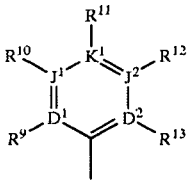
is selected from other than hydrido, or unless Y^0 is selected from other than wherein Q^s is C_{1-4} alkyl, C_{3-4} alkenyl or C_{3-4} alkynyl where the C_{1-4} alkyl, C_{3-4} alkenyl or C_{3-4} alkynyl group is bonded concurrently to E^1 wherein E^1 is C(O)NH and to the 4-position of an imidazole, the 4-position of a thiazole or the 5-position of a thiazole, or unless a spacer pair is present selected from the group of spacer pairs consisting of R^2 and R^{4a}, R^2 and R^{4b}, R^2 together with both R^{4a} and R^{4b}, R^2 and R^{14}, R^2 and R^{15}, and R^6 with another group selected from the group consisting of R^{4a}, R^{4b}, R^{4a} and R^{4b} together, R^{39} R^{40}, R^{39} and R^{40} together, R^{14}, R^{15}, and R^5, that R^2 is selected from other than the group consisting of hydroxymethyl, methyl, methoxymethyl, methylthiomethyl, phenylthiomethyl, methylsulfinyl, methylthio, alkoxy, cycloalkoxy, alkylthio, alkylsulfinyl, alkysulfonyl, cycloalkylthio, cycloalkylsulfinyl, and cycloalkysulfonyl, when Y^o is other than phenyl, mono-substituted phenyl, and di-substituted phenyl 5-(2-amino)pyridindyl, or 4-(2-amino)pyridindyl, and that R^2 is selected from other than the group consisting of hydrido, halo, alkyl, cycloalkyl when Y^o is methyleneimidazo(1,2-a) pyridinyl, 4,5-benzimidazol-5-yl, or indol-5-yl unless R^1 is selected from other than the group consisting of hydrido or halo, or unless E^1 is other than C(O)NH, or unless E^0 is selected from the group consisting of E^2 and E^3, or unless K is other than $(CR^{4a}R^{4b})_n$ wherein n is 1 unless one of R^{4a} and R^{4b} are independently selected from other than hydrido, or unless Ψ is selected from other than NR^5 wherein R^5 is hydrido;

R^1 is optionally selected from the group consisting of amino, aminoalkyl, alkylamino, amidino, guanidino, hydroxy, hydroxyamino, alkoxy, hydroxyalkyl, alkoxyamino, thiol, alkylthio, dialkylsulfonium, trialkylphosphonium, dialkylsulfoniumalkyl, heteroarylamino, nitro, arylamino, aralkylamino, alkanoyl, alkenoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, haloalkanoyl, hydroxyhaloalkyl, cyano, and phosphono;

Z^0 is selected from the group consisting of covalent single bond, $(CR^{41}R^{42})_q$ wherein q is an integer selected from 1 through 6, $(CH(R^{41}))_g$—W^0—$(CH(R^{42}))_p$ wherein g and p are integers independently selected from 0 through 3 and W^0 is selected from the group consisting of O, S, C(O), C(S), C(O)O, C(S)O, C(O)S, C(S)S, C(O)N(R^{41}), (R^{41})NC(O), C(S)N(R^{41}), (R^{41})NC(S), OC(O)N(R^{41}), (R^{41})NC(O)O, SC(S)N(R^{41}), (R^{41})NC(S)S, SC(O)N(R^{41}), (R^{41})NC(O)S, OC(S)N(R^{41}), (R^{41})NC(S)O, N(R^{42})C()N(R^{41}), (R^{41})NC(O)N(R^{41}), N(R^{42})C(S)N(R^{41}), (R^{41})NC(S)N(R^{42}), S(O), $S(O)_2$, $S(O)_2N(R^{41})$, N(R^{41})$S(O)_2$, Se, Se(O), $Se(O)_2$, $Se(O)_2$ N(R^{41}), N(R^{41})$Sc(O)_2$, P(O)(R^8), N(R^7)P(O)(R^8), P(O)(R^8)N(R^7), N(R^{41}), ON(R^{41}), and $SiR^{28}R^{29}$, and $(CH(R^{41}))_e$—W^{22}—$(CH(R^{42}))_h$ wherein e and h are integers independently selected from 0 through 2 and W^{22} is selected from the group consisting of CR^{41}=CR^{42}, $CR^{41}R^{42}$=C; vinylidene), ethynylidene (C≡C; 1,2-ethynyl), 1,2-cyclopropyl, 1,2-cyclobutyl, 1,2-cyclohexyl, 1,3-cyclohexyl, 1,2-cyclopentyl, 1,3-cyclopentyl, 2,3-morpholinyl, 2,4-morpholinyl, 2,6-morpholinyl, 3,4-morpholinyl, 3,5-morpholinyl, 1,2-piperazinyl, 1,3-piperazinyl, 2,3-piperazinyl, 2,6-piperazinyl, 1,2-piperidinyl, 1,3-piperidinyl, 2,3-piperidinyl, 2,4-piperidinyl, 2,6-piperidinyl, 3,4-piperidinyl, 1,2-pyrrolidinyl, 1,3-pyrrolidinyl, 2,3-pyrrolidinyl, 2,4-pyrrolidinyl, 2,5-pyrrolidinyl, 3,4-pyrrolidinyl, 2,3-tetrahydrofuranyl, 2,4-tetrahydrofuranyl, 2,5-tetrahydrofuranyl, and 3,4-tetrahydrofuranyl, with the provisos that R^{41} and R^{42} are selected from other than halo and cyano when directly bonded to N and Z^0 is directly bonded to the pyrazinone ring;

R^{41} and R^{42} are independently selected from the group consisting of amidino, hydroxyamino, hydrido, hydroxy, amino, halo, cyano, aryloxy, hydroxyalkyl, acyl, aroyl, heteroaroyl, heteroaryloxyalkyl, alkoxy, alkyl, aryl, aralkyl, aryloxyalkyl, aralkoxyalkylalkoxy, alkoxyalkyl, heteroaryloxyalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkenyl, cycloalkenylalkyl, haloalkyl, haloalkenyl, halocycloalkyl, halocycloalkenyl, haloalkoxy, haloalkoxyalkyl, haloalkenyloxyalkyl, halocycloalkoxy, halocycloalkoxyalkyl, halocycloalkenyloxyalkyl, saturated heterocyclyl, partially saturated heterocyclyl, heteroaryl, heteroaralkyl, heteroarylthioalkyl, heteroaralkylthioalkyl, alkylsulfonyl, haloalkylsulfonyl, arylsulfonyl, arylsulfonylalkyl, aralkylsulfonyl, cycloalkylsulfonyl, cycloalkylsufonylalkyl, heteroarylsulfonylalkyl, heteroaryl sulfonyl, and aralkylsulfonylalkyl;

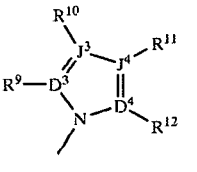
Q^b is formula (II):



(II)

wherein D^1, D^2, J^1, J^2 and K^1 are independently selected from the group consisting of C, N, O, S and a covalent bond with the provisos that no more than one is a covalent bond, no more than one of D^1, D^2, J^1, J^2 and K^1 is O, no more than one of D^1, D^2, J^1, J^2 and K^1 is S, one of D^1, D^2, J^1, J^2 and K^1 must be a covalent bond when two of D^1, D^2, J^1, J^2 and K^1 are O and S, and no more than four of D^1, D^2, J^1, J^2 and K^1 are N, with the proviso that R^9, R^{10}, R^{11}, R^{12}, and R^{13} are each independently selected to maintain the tetravalent nature of carbon, trivalent nature of nitrogen, the divalent nature of sulfur, and the divalent nature of oxygen;

Q is optionally selected from formula (III):



(III)

wherein D^3, D^4, J^3, and J^4 are independently selected from the group consisting of C, N, O and S, no more than one of D^3, D^4, J^3, and J^4 is O, no more than one of D^3, D^4, J^3, and J^4 is S, and no more than three of D^1, D^2, J^1, and J^2 are N with the proviso that R^9, R^{10}, R^{11}, and R^{12} are each independently selected to maintain the tetravalent nature of carbon, trivalent nature of nitrogen, the divalent nature of sulfur, and the divalent nature of oxygen;

Q is optionally selected from the group consisting of hydrido, alkyl, alkoxy, alkylamino, alkylthio, haloalkylthio, alkenyl, alkynyl, saturated heterocyclyl, partially saturated heterocyclyl, acyl, aroyl, heteroaroyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, cycloalkylalkenyl, haloalkyl, haloalkoxy, haloalkenyl, halocycloalkyl, halocycloalkenyl, haloalkoxyalkyl, haloalkenyloxyalkyl, halocycloalkoxyalkyl, and halocycloalkenyloxyalkyl with the proviso that Z^O is selected from other than a single covalent bond when Q is hydrido;

K is $(CR^{4a}R^{4b})_n$ wherein n is an integer selected from 1 through 2;

R^{4a} and R^{4b} are independently selected from the group consisting of halo, hydrido, hydroxy, cyano, hydroxyalkyl, alkyl, alkenyl, alkoxyalkyl, aralkyl, heteroaralkyl, alkylthioalkyl, haloalkyl, haloalkenyl, and cyanoalkyl;

E^O is E^1, when K is $(CR^{4a}R^{4b})_n$ wherein E^1 is selected from the group consisting of a covalent single bond, O, S, C(O), C(S), C(O)O, C(S)O, C(O)S, C(S)S, C(O)N(R^7), (R^7)NC(O), C(S)N(R^7), (R^7)NC(S), OC(O)N(R^7), (R^7)NC(O)O, SC(S)N(R^7), (R^7)NC(S)S, SC(O)N(R^7), (R^7)NC(O)S, OC(S)N(R^7), (R^7)NC(S)O, N(R^8)C(O)N(R^7), (R^7)NC(O)N(R^8), N(R^8)C(S)N(R^7), (R^7)NC(S)N(R^8), S(O), $S(O)_2$, $S(O)_2N(R^7)$, $N(R^7)S(O)_2$, $S(O)_2N(R^7)C(O)$, $C(O)N(R^7)S(O)_2$, P(O)(R^8), N(R^7)P(O)(R^8), P(O)(R^8)N(R^7), N(R^7), ON(R^7), $CR^{4a}{=}CR^{4b}$, ethynylidene (C≡C; 1,2-ethynyl), and $C{=}CR^{4a}R^{4b}$;

K is optionally $(CH(R^{14}))_j$—T wherein j is selected from a integer from 0 through 2 and T is selected from the group consisting of single covalent bond, O, S, and N(R^7) with the proviso that $(CH(R^{14}))_j$ is bonded to the pyrazinone ring;

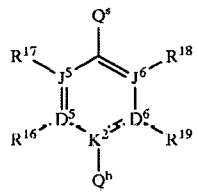
E^O is optionally E^2, when K is $(CH(R^{14}))_j$—T, wherein E^2 is selected from the group consisting of a covalent single bond, C(O), C(S), C(O)O, C(S)O, C(O)S, C(S)S, C(O)N(R^7), (R^7)NC(O), C(S)N(R^7), (R^7)NC(S), (R^7)NC(O)O, (R^7)NC(S)S, (R^7)NC(O)S, (R^7)NC(S)O, N(R^8)C(O)N(R^7), (R^7)NC(O)N(R^8), N(R^8)C(S)N(R^7), (R^7)NC(S)N(R^8), S(O), $S(O)_2$, $S(O)_2N(R^7)$, N(R^7)S$(O)_2$, $S(O)_2N(H)C(O)$, $C(O)N(H)S(O)_2$, P(O)(R^8), N(R^7)P(O)(R^8), P(O)(R^8)N(R^7), and N(R^7);

K is optionally G—$(CH(R^{15}))_k$ wherein k is selected from an integer from 1 through 2 and G is selected from the group consisting of O, S, and N(R^7) with the proviso that R^{15} is other than hydroxy, cyano, halo, amino, alkylamino, dialkylamino, and sulfhydryl when k is 1;

E^O is optionally E^3 when K is G—$(CH(R^{15}))_k$, wherein E^3 is selected from the group consisting of a covalent single bond, O, S, C(O), C(S), C(O)O, C(S)O, C(O)S, C(S)S, C(O)N(R^7), (R^7)NC(O), C(S)N(R^7), (R^7)NC(S), OC(O)N(R^7), (R^7)NC(O)O, SC(S)N(R^7), (R^7)NC(S)S, SC(O)N(R^7), (R^7)NC(O)S, OC(S)N(R^7), (R^7)NC(S)O, N(R^8)C(O)N(R^7), (R^7)NC(O)N(R^8), N(R^8)C(S)N(R^7), (R^7)NC(S)N(R^8), S(O), $S(O)_2$, $S(O)_2N(R^7)$, N(R^7)S$(O)_2$, P(O)(R^8), N(R^7)P(O)(R^8), P(O)(R^8)N(R^7), N(R^7), ON(R^7), $CR^{4a}{=}CR^{4b}$, ethynylidene (C≡C; 1,2-ethynyl), and $C{=}CR^{4a}R^{4b}$;

Y^O is formula (IV):

(IV)



wherein

D^5, D^6, J^5, and J^6 are independently selected from the group consisting of C, N, O, S and a covalent bond with the provisos that no more than one is a covalent bond, K^2 is independently selected from the group consisting of C and N^+, no more than one of D^5, D^6, J^5, and J^6 is O, no more than one of D^5, D^6, J^5, and J^6 is S, one of D^5, D^6, J^5, and J^6 must be a covalent bond when two of D^5, D^6, J^5, and J^6 are O and S, no more than three of D^5, D^6, J^5, and J^6 is N when K^2 is N^+, and no more than four of D^5, D^6, J^5, and J^6 are N when K^2 is carbon with the provisos that R^{16}, R^{17}, R^{18}, and R^{19} are each independently selected to maintain the tetravalent nature of carbon, trivalent nature of nitrogen, the divalent nature of sulfur, and the divalent nature of oxygen;

R^{16} and R^{17} are optionally independently taken together to form a linear moiety spacer having from 3 through 6 contiguous atoms connected to form a ring selected from the group consisting of a cycloalkenyl ring having from 5 through 8 contiguous members, a partially saturated heterocyclyl ring having from 5 through 8 contiguous members, a heteroaryl having from 5 through 6 contiguous members, and an aryl;

Q^b is selected from the group consisting of $NR^{20}R^{21}$, $^+NR^{20}R^{21}R^{22}$, oxy, alkyl, aminoalkylenyl, alkylamino, dialkylamino, dialkylsulfoniumalkyl, acylamino and Q^{be}, wherein Q^{be} is hydrido and R^{20}, R^{21}, and R^{22} are independently selected from the group consisting of hydrido, amino, alkyl, hydroxy, alkoxy, aminoalkylenyl, alkylamino, dialkylamino, and hydroxyalkyl with the provisos that no more than one of R^{20}, R^{21}, and R^{22} is hydroxy, alkoxy, alkylamino, amino, and dialkylamino at the same time and that R^{20}, R^{21}, and R^{22} must be other than be hydroxy, alkoxy, alkylamino, amino, and dialkylamino when K^2 is N^+;

R^{20} and R^{21}, R^{20} and R^{22}, and R^{21} and R^{22} are independently optionally selected to form a spacer pair wherein a spacer pair is taken together to form a linear moiety having from 4 through 7 contiguous atoms connecting the points of bonding of said spacer pair members to form a heterocyclyl ring having 5 through 8 contiguous members with the proviso that no more than one of the group consisting of spacer pairs R^{20} and R^{21}, R^{20} and R^{22}, and R^{21} and R^{22} is used at the same time;

Q^b is optionally selected from the group consisting of $N(R^{26})SO_2N(R^{23})(R^{24})$, $N(R^{26})C(O)OR^5$, $N(R^{26})C(O)SR^5$, $N(R^{26})C(S)OR^5$ and $N(R^{26})C(S)SR^5$ with the proviso that no more than one of R^{23}, R^{24}, and R^{26} is hydroxy, alkoxy, alkylamino, amino, and dialkylamino when two of the group consisting of R^{23}, R^{24}, and R^{26} are bonded to the same atom;

Q^b is optionally selected from the group consisting of dialkylsulfonium, trialkylphosphonium, C(NR^{25})

$NR^{23}R^{24}$, $N(R^{26})C(NR^{25})N(R^{23})(R^{24})$, $N(R^{26})C(O)N(R^{23})(R^{24})$, $N(R^{26})C(S)N(R^{23})(R^{24})$, $C(NR^{25})OR^{5}$, $C(O)N(R^{26})C(NR^{25})N(R^{23})(R^{24})$, $C(S)N(R^{26})C(NR^{25})N(R^{23})(R^{24})$, $N(R^{26})N(R^{26})C(NR^{25})N(R^{23})(R^{24})$, $ON(R^{26})C(NR^{25})N(R^{23})(R^{24})$, $N(R^{26})N(R^{26})SO_2N(R^{23})(R^{24})$, $C(NR^{25})SR^{5}$, $C(O)NR^{23}R^{24}$, and $C(O)NR^{23}R^{24}$ with the provisos that no more than one of R^{23}, R^{24}, and R^{26} can be hydroxy, alkoxy, alkylaminol, amino, or dialkylamino when two of the group consisting of R^{23}, R^{24}, and R^{26} are bonded to the same atom and that said Q^b group is bonded directly to a carbon atom;

R^{23}, R^{24}, R^{25}, and R^{26} are independently selected from the group consisting of hydrido, alkyl, hydroxy, alkoxy, aminoalkylenyl, alkylamino, dialkylamino, amino, and hydroxyalkyl;

R^{23} and R^{24} are optionally taken together to form a linear spacer moiety having from 4 through 7 contiguous atoms connecting the points of bonding to form a heterocyclyl ring having 5 through 8 contiguous members;

Q^s is selected from the group consisting of a single covalent bond, $(CR^{37}R^{38})_b$—$(W^0)_{az}$ wherein az is an integer selected from 0 through 1, b is an integer selected from 1 through 4, and W^0 is selected from the group consisting of O, S, C(O), C(S), C(O)O, C(S)O, C(O)S, C(S)S, C(O)N(R^{14}), (R^{14})NC(O), C(S)N(R^{14}), (R^{14})NC(S), OC(O)N(R^{14}), SC(S)N(R^{14}), SC(O)N(R^{14}), OC(S)N(R^{14}) N(R^{15})C(O)N(R^{14}) (R^{14})NC(O)N(R^{15}), N(R^{15})C(S)N(R^{14}), (R^{14})NC(S)N(R^{15}) S(O), $S(O)_2$, $S(O)_2N(R^{14})$, $N(R^{14})S(O)_2$, $P(O)(R^8)$, $N(R^7)P(O)(R^8)$, $P(O)(R^8)N(R^7)$, $N(R^{14})$, $ON(R^{14})$, $(CH(R^{14}))_cW^1$—$(CH(R^{15}))_d$ wherein c and d are integers independently selected from 1 through 4, and W^1 is selected from the group consisting of O, S, C(O), C(S), C(O)O, C(S)O, C(O)S, C(S)S, C(O)N(R^{14}), (R^{14})NC(O), C(S)N(R^{14}), (R^{14})NC(S), OC(O)N(R^{14}), (R^{14})NC(O)O, SC(S)N(R^{14}), (R^{14})NC(S)S, SC(O)N(R^{14}), (R^{14})NC(O)S, OC(S)N(R^{14}), (R^{14})NC(S)O, N(R^{15})C(O)N(R^{14}), (R^{14})NC(O)N(R^{15}), N(R^{15})C(S)N(R^{14}), (R^{14})NC(S)N(R^{15}), S(O), $S(O)_2$, $S(O)_2N(R^{14})$, $N(R^{14})S(O)_2$, $P(O)(R^8)$, $N(R^7)P(O)(R^8)$, $P(O)(R^8)N(R^7)$, $N(R^{14})$, $ON(R^{14})$, and $(CH(R^{14}))_e$—W^{22}—$(CH(R^{15}))_h$ wherein e and h are integers independently selected from 0 through 2 and W^{22} is selected from the group consisting of CR^{41}=CR^{42}, $CR^{41}R^{42}$=C; vinylidene), ethynylidene (C≡C; 1,2-ethynyl), 1,2-cyclopropyl, 1,2-cyclobutyl, 1,2-cyclohexyl, 1,3-cyclohexyl, 1,2-cyclopentyl, 1,3-cyclopentyl, 2,3-morpholinyl, 2,4-morpholinyl, 2,6-morpholinyl, 3,4-morpholinyl, 3,5-morpholinyl, 1,2-piperazinyl, 1,3-piperazinyl, 2,3-piperazinyl, 2,6-piperazinyl, 1,2-piperidinyl, 1,3-piperidinyl, 2,3-piperidinyl, 2,4-piperidinyl, 2,6-piperidinyl, 3,4-piperidinyl, 1,2-pyrrolidinyl, 1 3-pyrrolidinyl, 2,3-pyrrolidinyl, 2,4-pyrrolidinyl, 2,5-pyrrolidinyl, 3,4-pyrrolidinyl, 2,3-tetrahydrofuranyl, 2,4-tetrahydrofuranyl, 2,5-tetrahydrofuranyl, and 3,4-tetrahydrofuranyl, with the provisos that R^{14} and R^{15} are selected from other than halo and cyano when directly bonded to N and that $(CR^{37}R^{38})_b$, $(CH(R^{14}))_c$, $(CH(R^{14}))_e$ and are bonded to E^0;

Y^0 is optionally Q^b—Q^{ss} wherein Q^{ss} is selected from the group consisting of $(CR^{37}R^{38})_f$ wherein f is an integer selected from 1 through 6, $(CH(R^{14}))_c$—W^1—$(CH(R^{15}))_d$ wherein c and d are integers independently selected from 1 through 4, and W^1 is selected from the group consisting of W^1 is selected from the group consisting of O, S, C(O), C(S), C(O)O, C(S)O, C(O)S, C(S)S, C(O)N(R^{14}), (R^{14})NC(O), C(S)N(R^{14}), (R^{14})NC(S), OC(O)N(R^{14}), (R^{14})NC(O)O, SC(S)N(R^{14}), (R^{14})NC(S)S, SC(O)N(R^{14}), (R^{14})NC(O)S, OC(S)N(R^{14}), (R^{14})NC(S)O, N(R^{15})C(O)N(R^{14}), (R^{14})NC()N(R^{15}) N(R^{15})C(S)N(R^{14}). (R^{14})NC(S)N(R^{15}). S(O), $S(O)_2$, $S(O)_2N(R^{14})$, $N(R^{14})S(O)_2$, $P(O)(R^8)$, $N(R^7)P(O)(R^8)$, $P(O)(R^8)N(R^7)$, $N(R^{14})$, $ON(R^{14})$, and $(CH(R^{14}))_e$—W^2—$(CH(R^{15}))_h$ wherein e and h are integers independently selected from 0 through 2 and W^2 is selected from the group consisting of CR^{4a}=CR^{4b}, ethynylidene (C≡C; 1,2-ethynyl), and C=$CR^{4a}R^{4b}$ with the provisos that R^{14} and R^{15} are selected from other than halo and cyano when directly bonded to N and that $(CR^{37}R^{38})_b$, $(CH(R^{14}))_c$, and $(CH(R^{14}))_e$ are bonded to E^0;

Y^0 is optionally Q^b—Q^{sss} wherein Q^{sss} is $(CH(R^{38}))_r$—W^3, r is an integer selected from 1 through 3, W^3 is selected from the group consisting of 1,1-cyclopropyl, 1,2-cyclopropyl, 1,1-cyclobutyl, 1,2-cyclobutyl, 1,2-cyclohexyl, 1,3-cyclohexyl, 1,4-cyclohexyl, 1,2-cyclopentyl, 1,3-cyclopentyl, 2,3-morpholinyl, 2,4-morpholinyl, 2,5-morpholinyl, 2,6-morpholinyl, 3,4-morpholinyl, 3,5-morpholinyl, 1,2-piperazinyl, 1,3-piperazinyl, 1,4-piperazinyl, 2,3-piperazinyl, 2,5-piperazinyl, 2,6-piperazinyl, 1,2-piperidinyl, 1,3-piperidinyl, 1,4-piperidinyl, 2,3-piperidinyl, 2,4-piperidinyl, 2,5-piperidinyl, 2,6-piperidinyl, 3,4-piperidinyl, 3,5-piperidinyl, 3,6-piperidinyl, 1,2-pyrrolidinyl, 1,3-pyrrolidinyl, 2,3-pyrrolidinyl, 2,4-pyrrolidinyl, 2,5-pyrrolidinyl, 3,4-pyrrolidinyl, 2H-2,3-pyranyl, 2H-2,4-pyranyl, 2H-2,5-pyranyl, 4H-2,3-pyranyl, 4H-2,4-pyranyl, 4H-2,5-pyranyl, 2H-pyran-2-one-3,4-yl, 2H-pyran-2-one-4,5-yl, 4H-pyran-4-one-2, 3-yl, 2,3-tetrahydrofuranyl, 2,4-tetrahydrofuranyl, 2,5-tetrahydrofuranyl, 3,4-tetrahydrofuranyl, 2,3-tetrahydropyranyl, 2,4-tetrahydropyranyl, 2,5-tetrahydropyranyl, 2,6-tetrahydropyranyl, 3,4-tetrahydropyranyl, and 3,5-tetrahydropyranyl, and each carbon and hyrido containing nitrogen member of the ring of the W^3 other than the points of attachment is optionally substituted with one or more of the group consisting of R^9, R^{10}, R^{11}, and R^{12}, with the proviso that $(CH(R^{38}))_r$ is bonded to E^0 and Q^b is bonded to lowest numbered substituent position of each W^3;

Y^0 is optionally Q^b—Q^{sssr} wherein Q^{sssr} is $(CH(R^{38}))_r$—W^4, r is an integer selected from 1 through 3, W^4 is selected from the group consisting of 1,2-cyclobutyl, 1,2-cyclohexyl, 1,3-cyclohexyl, 1,4-cyclohexyl, 1,2-cyclopentyl, 1,3-cyclopentyl, 2,3-morpholinyl, 2,4-morpholinyl, 2,5-morpholinyl, 2,6-morpholinyl, 3,4-morpholinyl, 3,5-morpholinyl, 1,2-piperazinyl, 1,3-piperazinyl, 1,4-piperazinyl, 2,3-piperazinyl, 2,5-piperazinyl, 2,6-piperazinyl, 1,2-piperidinyl, 1,3-piperidinyl, 1,4-piperidinyl, 2,3-piperidinyl, 2,4-piperidinyl, 2,5-piperidinyl, 2,6-piperidinyl, 3,4-piperidinyl, 3,5-piperidinyl, 3,6-piperidinyl, 1,2-pyrrolidinyl, 1,3-pyrrolidinyl, 2,3-pyrrolidinyl, 2,4-pyrrolidinyl, 2,5-pyrrolidinyl, 3,4-pyrrolidinyl, 2H-2,3-pyranyl, 2H-2,4-pyranyl, 2H-2,5-pyranyl, 4H-2,3-pyranyl, 4H-2,4-pyranyl, 4H-2,5-pyranyl, 2H-pyran-2-one-3,4-yl, 2H-pyran-2-one4,5-yl, 4H-pyran-4-one-2, 3-yl, 2,3-tetrahydrofuranyl, 2,4-tetrahydrofuranyl, 2,5-tetrahydrofuranyl, 3,4-tetrahydrofuranyl, 2,3-tetrahydropyranyl, 2,4-tetrahydropyranyl, 2,5-

tetrahydropyranyl, 2,6-tetrahydropyranyl, 3,4-tetrahydropyranyl, and 3,5-tetrahydropyranyl, and each carbon and hydrido containing nitrogen member of the ring of the W^4 other than the points of attachment is optionally substituted with one or more of the group consisting of R^9, R^{10}, R^{11}, and R^{12}, with the provisos that $(CH(R^{38}))_r$ is bonded to E^0 and Q^b is bonded to highest number substituent position of each W^4;

Y^0 is optionally Q^b—Q^{ssss} wherein Q^{ssss} is $(CH(R^{38}))_r$—W^5, r is an integer selected from 1 through 3, W^5 is selected from the group consisting of 1,4-indenyl, 1,5 indenyl, 1,6 indenyl, 1,7-indenyl, 2,7 indenyl, 2,6-indenyl, 2,5-indenyl, 2,4-indenyl, 3,4-indenyl, 3,5-indenyl, 3,6-indenyl, 3,7-indenyl, 2,4-benzofuranyl, 2,5-benzofuranyl, 2,6-benzofuranyl, 2,7-benzofuranyl, 3,4-benzofuranyl, 3,5-benzofuranyl, 3,6-benzofuranyl, 3,7-benzofuranyl, 2,4-benzothiophenyl, 2,5-benzothiophenyl, 2,6-benzothiophenyl, 2,7-benzothiophenyl, 3,4-benzothiophenyl, 3,5-benzothiophenyl, 3,6-benzothiophenyl, 3,7-benzothiophenyl, 2,7-imidazo(1,2-a)pyridinyl, 3,4-imidazo(1,2-a)pyridinyl, 3,5-imidazo(1,2-a)pyridinyl, 3,6-imidazo(1,2-a)pyridinyl, 3,7-imidazo(1,2-a)pyridinyl, 2,4-indolyl, 2,5-indolyl, 2,6-indolyl, 2,7-indolyl, 3,4-indolyl, 3,5-indolyl, 3,6-indolyl, 3,7-indolyl, 1,4-isoindolyl, 1,5-isoindolyl, 1,6-isoindolyl, 2,4-isoindolyl, 2,5-isoindolyl, 2,6-isoindolyl, 2,7-isoindolyl, 1,3-isoindolyl, 3,4-indazolyl, 3,5-indazolyl, 3,6-indazolyl, 3,7-indazolyl, 2,4-benzoxazolyl, 2,5-benzoxazolyl, 2,6-benzoxazolyl, 2,7-benzoxazolyl, 3,4-benzisoxazolyl, 3,5-benzisoxazolyl, 3,6-benzisoxazolyl, 3,7-benzisoxazolyl, 1,4-naphthyl, 1,5-naphthyl, 1,6-naphthyl, 1,7-naphthyl, 1,8-naphthyl, 2,4naphthyl, 2,5-naphthyl, 2,6-naphthyl, 2,7-naphthyl, 2,8-naphthyl, 2,4-quinolinyl, 2,5-quinolinyl, 2,6-quinolinyl, 2,7-quinolinyl, 2,8-quinolinyl, 3,4-quinolinyl, 3,5-quinolinyl, 3,6-quinolinyl, 3,7-quinolinyl, 3,8-quinolinyl, 4,5-quinolinyl, 4,6-quinolinyl, 4,7-quinolinyl, 4,8-quinolinyl, 1,4-isoquinolinyl, 1,5-isoquinolinyl, 1,6-isoquinolinyl, 1,7-isoquinolinyl, 1,8-isoquinolinyl, 3,4-isoquinolinyl, 3,5-isoquinolinyl, 3,6-isoquinolinyl, 3,7-isoquinolinyl, 3,8-isoquinolinyl, 4,5isoquinolinyl, 4,6-isoquinolinyl, 4,7-isoquinolinyl, 4,8-isoquinolinyl, 3,4cinnolinyl, 3,5-cinnolinyl, 3,6-cinnolinyl, 3,7-cinnolinyl, 3,8-cinnolinyl, 4,5-cinnolinyl, 4,6-cinnolinyl, 4,7-cinnolinyl, and 4,8-cinnolinyl, and each carbon and hydrido containing nitrogen member of the ring of the W^5 other than the points of attachment is optionally substituted with one or more of the group consisting of R^9, R^{10}, R^{11}, and R^{12}, with the proviso that Q^b is bonded to lowest number substituent position of each W^5 and that $(CH(R^{38}))_r$ is bonded to E^0;

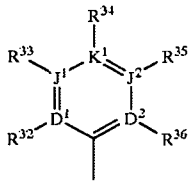
Y^0 is optionally Q^b—Q^{ssssr} wherein, Q^{ssssr} is $(CH(R^{38}))_r$—W^6, r is an integer selected from 1 through 3, W^6 is selected from the group consisting of 1,4-indenyl, 1,5-indenyl, 1,6-indenyl, 1,7-indenyl, 2,7-indenyl, 2,6-indenyl, 2,5-indenyl, 2,4-indenyl, 3,4-indenyl, 3,5-indenyl, 3,6-indenyl, 3,7-indenyl, 2,4-benzofuranyl, 2,5-benzofuranyl, 2,6-benzofuranyl, 2,7-benzofuranyl, 3,4-benzofuranyl, 3,5-benzofuranyl, 3,6-benzofuranyl, 3,7-benzofuranyl, 2,4-benzothiophenyl, 2,5-benzothiophenyl, 2,6-benzothiophenyl, 2,7-benzothiophenyl, 3,4-benzothiophenyl, 3,5-benzothiophenyl, 3,6-benzothiophenyl, 3,7-benzothiophenyl, 2,7-imidazo(1,2-a)pyridinyl, 3,4-imidazo(1,2-a)pyridinyl, 3,5-imidazo(1,2-a)pyridinyl, 3,6-imidazo(1,2-a)pyridinyl, 3,7-imidazo(1,2-a)pyridinyl, 2,4-indolyl, 2,5-indolyl, 2,6-indolyl, 2,7-indolyl, 3,4-indolyl, 3,5-indolyl, 3,6-indolyl, 3,7-indolyl, 1,4-isoindolyl, 1,5-isoindolyl, 1,6-isoindolyl, 2,4-isoindolyl, 2,5-isoindolyl, 2,6-isoindolyl, 2,7-isoindolyl, 1,3-isoindolyl, 3,4-indazolyl, 3,5-indazolyl, 3,6-indazolyl, 3,7-indazolyl, 2,4-benzoxazolyl, 2,5-benzoxazolyl, 2,6-benzoxazolyl, 2,7-benzoxazolyl, 3,4-benzisoxazolyl, 3,5-benzisoxazolyl, 3,6-benzisoxazolyl, 3,7-benzisoxazolyl, 1,4-naphthyl, 1,5-naphthyl, 1,6-naphthyl, 1,7-naphthyl, 1,8-naphthyl, 2,4-naphthyl, 2,5-naphthyl, 2,6-naphthyl, 2,7-naphthyl, 2,8-naphthyl, 2,4-quinolinyl, 2,5-quinolinyl, 2,6-quinolinyl, 2,7-quinolinyl, 2,8-quinolinyl, 3,4-quinolinyl, 3,5-quinolinyl, 3,6-quinolinyl, 3,7-quinolinyl, 3,8-quinolinyl, 4,5-quinolinyl, 4,6-quinolinyl, 4,7-quinolinyl, 4,8-quinolinyl, 1,4-isoquinolinyl, 1,5-isoquinolinyl, 1,6-isoquinolinyl, 1,7-isoquinolinyl, 1,8-isoquinolinyl, 3,4-isoquinolinyl, 3,5-isoquinolinyl, 3,6-isoquinolinyl, 3,7-isoquinolinyl, 3,8-isoquinolinyl, 4,5-isoquinolinyl, 4,6-isoquinolinyl, 4,7-isoquinolinyl, 4,8-isoquinolinyl, 3,4cinnolinyl, 3,5-cinnolinyl, 3,6-cinnolinyl, 3,7-cinnolinyl, 3,8-cinnolinyl, 4,5-cinnolinyl, 4,6-cinnolinyl, 4,7-cinnolinyl, and 4,8-cinnolinyl, and each carbon and hydrido containing nitrogen member of the ring of the W^6 other than the points of attachment is optionally substituted with one or more of the group consisting of R^9, R^{10}, R^{11}, and R^{12}, with the proviso that Q^b is bonded to highest number substituent position of each W^6 and that $(CH(R^{38}))_r$ is bonded to E^0.

In another embodiment of compounds of Formula I or a pharmaceutically acceptable salt thereof,

J is selected from the group consisting of O and S;

B is formula (V):

(V)



wherein

D^1, D^2, J^1, J^2 and $K^1$are independently selected from the group consisting of C, N, O, S and a covalent bond with the provisos that no more than one is a covalent bond, no more than one of D^1, D^2, J^1, J^2 and K^1 is O, no more than one of D^1, D^2, J^1, J^2 and K^1 is S, one of D^1, D^2, J^1, J^2 and K^1 must be a covalent bond when two of D^1, D^2, J^1, J^2 and K^1 are O and S, and no more than four of D^1, D^2, J^1, J^2 and K^1 are N;

R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{16}, R^{17}, R^{18}, R^{19}, R^{32}, R^{33}, R^{34}, R^{35}, and R^{36} are independently selected from the group consisting of hydrido, acetamido, haloacetamido, amidino, guanidino, dialkylsulfonium, trialkylphosphonium, dialkylsulfoniumalkyl, carboxy, heteroaralkylthio, heteroaralkoxy, cycloalkylamino, acylalkyl, acylalkoxy, aryloylalkoxy, heterocyclyloxy, aralkylaryl, aralkyl, aralkenyl, aralkynyl, heterocyclyl, perhaloaralkyl, aralkylsulfonyl, aralkylsulfonylalkyl, aralkylsulfinyl,

aralkylsulfinylalkyl, halocycloalkyl, halocycloalkenyl, cycloalkylsulfinyl, cycloalkylsulfinylalkyl, cycloalkylsulfonyl, cycloalkylsulfonylalkyl, heteroarylamino, N-heteroarylamino-N-alkylamino, heteroarylaminoalkyl, haloalkylthio, alkanoyloxy, alkoxy, alkoxyalkyl, haloalkoxylalkyl, heteroaralkoxy, cycloalkoxy, cycloalkenyloxy, cycloalkoxyalkyl, cycloalkylalkoxy, cycloalkenyloxyalkyl, cycloalkylenedioxy, halocycloalkoxy, halocycloalkoxyalkyl, halocycloalkenyloxy, halocycloalkenyloxyalkyl, hydroxy, amino, alkoxyamino, thio, nitro, lower alkylamino, alkylthio, alkylthioalkyl, arylamino, aralkylamino, arylthio, arylthioalkyl, heteroaralkoxyalkyl, alkylsulfinyl, alkylsulfinylalkyl, arylsulfinylalkyl, arylsulfonylalkyl, heteroarylsulfinylalkyl, heteroarylsulfonylalkyl, alkylsulfonyl, alkylsulfonylalkyl, haloalkylsulfinylalkyl, haloalkylsulfonylalkyl, alkylsulfonamido, alkylaminosulfonyl, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, monoarylamidosulfonyl, arylsulfonamido, diarylamidosulfonyl, monoalkyl monoaryl amidosulfonyl, arylsulfinyl, arylsulfonyl, heteroarylthio, heteroarylsulfinyl, heteroarylsulfonyl, heterocyclylsulfonyl, heterocyclylthio, alkanoyl, alkenoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, haloalkanoyl, alkyl, alkenyl, alkynyl, alkenyloxy, alkenyloxyalky, alkylenedioxy, haloalkylenedioxy, cycloalkyl, cycloalkylalkanoyl, cycloalkenyl, lower cycloalkylalkyl, lower cycloalkenylalkyl, halo, haloalkyl, haloalkenyl, haloalkoxy, hydroxyhaloalkyl, hydroxyaralkyl, hydroxyalkyl, alkylenylamino, hydoxyheteroaralkyl, haloalkoxyalkyl, aryl, aralkyl, aryloxy, aralkoxy, aryloxyalkyl, saturated heterocyclyl, partially saturated heterocyclyl, heteroaryl, heteroaryloxy, heteroaryloxyalkyl, arylalkyl, heteroarylalkyl, arylalkenyl, heteroarylalkenyl, carboxyalkyl, carboalkoxy, alkoxycarboxamido, alkylamidocarbonylamido, arylamidocarbonylamido, carboalkoxyalkyl, carboalkoxyalkenyl, carboxy, carboaralkoxy, carboxamido, carboxamidoalkyl, cyano, carbohaloalkoxy, phosphono, phosphonoalkyl, diaralkoxyphosphono, and diaralkoxyphosphonoalkyl;

R^{16}, R^{19}, R^{32}, R^{33}, R^{34}, R^{35}, and R^{36} are independently optionally Q^b with the proviso that no more than one of R^{16} and R^{19} is Q^b at the same time and that Q^b is Q^{be};

B is optionally selected from the group consisting of hydrido, trialkylsilyl, C2–C8 alkyl, C3–C8 alkylenyl, C3–C8 alkenyl, C3–C8 alkynyl, C2–C8 haloalkyl, and C3–C8 haloalkenyl wherein each member of group B is optionally substituted at any carbon up to and including 6 atoms from the point of attachment of B to A with one or more of the group consisting of R^{32}, R^{33}, R^{34}, R^{35}, and R^{36};

B is optionally selected from the group consisting of C3–C12 cycloalkyl, C5–C10 cycloalkenyl, and C4–C9 saturated heterocyclyl, wherein each ring carbon is optionally substituted with R^{33}, a ring carbon other than the ring carbon at the point of attachment of B to A is optionally substituted with oxo provided that no more than one ring carbon is substituted by oxo at the same time, ring carbon and nitrogen atoms adjacent to the carbon atom at the point of attachment is optionally substituted with R^9 or R^{13}, a ring carbon or nitrogen atom adjacent to the R^9 position and two atoms from the point of attachment is optionally substituted with R^{10}, a ring carbon or nitrogen atom adjacent to the R^{13} position and two atoms from the point of attachment is optionally substituted with R^{12}, a ring carbon or nitrogen atom three atoms from the point of attachment and adjacent to the R^{10} position is optionally substituted with R^{11}, a ring carbon or nitrogen atom three atoms from the point of attachment and adjacent to the R^{12} position is optionally substituted with R^{33}, and a ring carbon or nitrogen atom four atoms from the point of attachment and adjacent to the R^{11} and R^{33} positions is optionally substituted with R^{34};

A is selected from the group consisting of single covalent bond, $(W^7)_{rr}$—$(CH(R^{15}))_{pa}$ and $(CH(R^{15}))_{pa}$—$(W^7)_{rr}$ wherein rr is an integer selected from 0 through 1, pa is an integer selected from 0 through 6, and W^7 is selected from the group consisting of O, S, C(O), C(O)N(R^7), C(S)N(R^7), (R^7)NC(O), (R^7)NC(S), and N(R^7) with the proviso that no more than one of the group consisting of rr and pa can be 0 at the same time;

R^7 and R^8 are independently selected from the group consisting of hydrido, hydroxy, alkyl, and alkoxyalkyl;

R^{14}, R^{15}, R^{37}, and R^{38} are independently selected from the group consisting of hydrido, hydroxy, halo, alkyl, alkoxyalkyl, haloalkyl, haloalkoxy, and haloalkoxyalkyl;

R^{14} and R^{38} can be independently selected from the group consisting of aroyl and heteroaroyl;

Ψ is selected from the group consisting of NR^5, C(O), and $S(O)_2$;

R^5 is selected from the group consisting of hydrido, hydroxy, alkyl, and alkoxy;

R^{39} and R^{40} are independently selected from the group consisting of hydrido, hydroxy, halo, hydroxyalkyl, alkyl, alkoxyalkyl, haloalkyl, haloalkoxy, and haloalkoxyalkyl;

R^1 is selected from the group consisting of hydrido, alkyl, alkenyl, cyano, halo, haloalkyl, haloalkoxy, haloalkylthio, amino, aminoalkyl, alkylamino, amidino, guanidino, hydroxy, hydroxyamino, alkoxy, hydroxyalkyl, alkoxyamino, thiol, alkylthio, and phosphono;

R^2 is Z^0—Q;

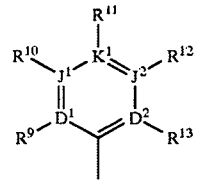
Z^0 is selected from the group consisting of covalent single bond, $(CR^{R41}R^{42})_q$ wherein q is an integer selected from 1 through 3, $(CH(R^{41}))_g$—W^0—$(CH(R^{42}))_p$ wherein g and p are integers independently selected from 0 through 3 and W^0 is selected from the group consisting of O, S, C(O), S(O), $S(O)_2$, N(R^{41}), and ON(R^{41}), and $(CH(R^{41}))_e$—W^{22}—$(CH(R^{42}))_h$ wherein e and h are integers independently selected from 0 through 2 and W^{22} is selected from the group consisting of CR^{41}=CR^{42}, 1,2-cyclopropyl, 1,2-cyclobutyl, 1,2-cyclohexyl, 1,3-cyclohexyl, 1,2-cyclopentyl, 1,3-cyclopentyl, 2,3-morpholinyl, 2,4-morpholinyl, 2,6-morpholinyl, 3,4-morpholinyl, 3,5-morpholinyl, 1,2-piperazinyl, 1,3-piperazinyl, 2,3-piperazinyl, 2,6-piperazinyl, 1,2-piperidinyl, 1,3-piperidinyl, 2,3-piperidinyl, 2,4-piperidinyl, 2,6-piperidinyl, 3,4-

piperidinyl, 1,2-pyrrolidinyl, 1,3-pyrrolidinyl, 2,3-pyrrolidinyl, 2,4-pyrrolidinyl, 2,5-pyrrolidinyl, 3,4-pyrrolidinyl, 2,3-tetrahydrofuranyl, 2,4-tetrahydrofuranyl, 2,5-tetrahydrofuranyl, and 3,4-tetrahydrofuranyl, with the proviso that Z is directly bonded to the pyrazinone ring;

R^{41} and R^{42} are independently selected from the group consisting of amidino, hydroxyamino, hydrido, hydroxy, amino, and alkyl;

Q^b is selected from the group consisting of hydrido, with the proviso that Z^0 is other than a covalent single bond, the formula (II):

(II)



wherein D^1, D^2, J^1, J^2 and K^1 are independently selected from the group consisting of C, N, O, S and a covalent bond with the provisos that no more than one is a covalent bond, no more than one of D^1, D^2, J^1, J^2 and K^1 is O, no more than one of D^1, D^2, J^1, J^2 and K^1 is S, one of D^1, D^2, J^1, J^2 and K^1 must be a covalent bond when two of D^1, D^2, J^1, J^2 and K^1 are O and S, and no more than four of D^1, D^2, J^1, J^2 and K^1 is N, with the proviso that R^9, R^{10}, R^{11}, R^{12}, and R^{13} are each independently selected to maintain the tetravalent nature of carbon, trivalent nature of nitrogen, the divalent nature of sulfur, and the divalent nature of oxygen;

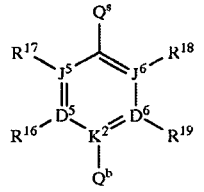
K is $(CR^{4a}R^{4b})_n$ wherein n is an integer selected from 1 through 2;

R^{4a} and R^{4b} are independently selected from the group consisting of halo, hydrido, hydroxyalkyl, alkyl, alkoxyalkyl, alkylthioalkyl, and haloalkyl;

E^0 is selected from the group consisting of a covalent single bond, C(O), C(S), C(O)N(R^7), (R^7)NC(O), S(O)$_2$, (R^7)NS(O)$_2$, and S(O)$_2$N(R^7);

Y^0 is formula (IV):

(IV)



wherein

D^5, D^6, J^5, and J^6 are independently selected from the group consisting of C, N, O, S and a covalent bond with the provisos that no more than one is a covalent bond, K^2 is C, no more than one of D^5, D^6, J^5, and J^6 is O, no more than one of, D^5, D^6, J^5, and J^6 is S one of D^5, D^6, J^5, and J^6 must be a covalent bond when two of D^5, D^6, J^5, and J^6 are O and S, and no more than four of D^5, D^6, J^5, and J^6 are N when K^2 is carbon with the provisos that R^{16}, R^{17}, R^{18}, and R^{19} are each independently selected to maintain the tetravalent nature of carbon, trivalent nature of nitrogen, the divalent nature of sulfur, and the divalent nature of oxygen;

Q^b is selected from the group consisting of $NR^{20}R^{21}$, $^+NR^{20}R^{21}R^{22}$, aminoalkylenyl, and Q^{be}, wherein Q^{be} is hydrid and R^{20}, R^{21}, and R^{22} are independently selected from the group consisting of hydrido, alkyl, hydroxy, amino, aminoalkylenyl, dialkylamino, alkylamino, and hydroxyalkyl with the proviso that no more than one of R^{20} and R^{21} is hydroxy, amino, alkylamino, or dialkylamino at the same time;

Q^b is optionally selected from the group consisting of $C(NR^{25})NR^{23}R^{24}$, $N(R^{26})C(NR^{25})N(R^{23})(R^{24})$, $C(O)N(R^{26})C(NR^{25})N(R^{23})(R^{24})$, $N(R^{26})N(R^{26})C(NR^{25})N(R^{23})(R^{24})$, and $ON(R^{26})C(NR^{25})N(R^{23})(R^{24})$ with the provisos that no more than one of R^{23}, R^{24}, and R^{26} is hydroxy, alkylamino, amino, or dialkylamino when two of the group consisting of R^{23}, R^{24}, and R^{26} are bonded to the same atom;

R^{23}, R^{24}, R^{25}, and R^{26} are independently selected from the group consisting of hydrido, alkyl, hydroxy, amino, alkylenylamino, dialkylamino, alkylamino, and hydroxyalkyl;

Q^s is selected from the group consisting of a single covalent bond, $(CR^{37}R^{38})_b$—$(W^0)_{az}$ wherein az is an integer selected from 0 through 1, b is an integer selected from 1 through 5, and W^0 is selected from the group consisting of O, C(O), S(O), S(O)$_2$, S(O)$_2$N(R^{14}), N(R^{14})S(O)$_2$, and N(R^{14}), $(CH(R^{14}))_c$—W^1—$(CH(R^{15})$ wherein c and d are integers independently selected from 1 through 4 and W^1 is selected from the group consisting of O, S, C(O), C(S), C(O)O, C(S)O, C(O)S, C(S)S, C(O)N(R^{14}), (R^{14})NC(O), C(S)N(R^{14}), (R^{14})NC(S), OC(O)N(R^{14}), (R^{14})NC(O)O, SC(S)N(R^{14}), (R^{14})NC(S)S, SC(O)N(R^{14}), (R^{14})NC(O)S, OC(S)N(R^{14}), (R^{14})NC(S)O, N(R^{15})C(O)N(R^{14}), (R^{14})NC(O)N(R^{15}). N(R^{15})C(S)N(R^{14}), (R^{14})NC(S)N(R^{15}), S(O), S(O)$_2$, S(O)$_2$N(R^{14}), N(R^{14})S(O)$_2$, P(O)(R^8), N(R^7)P(O)(R^8), P(O)(R^8)N(R^7), N(R^{14}), ON(R^{14}), and $(CH(R^{14}))_e$—W^{22}—$(CH(R^{15}))_h$ wherein e and h are integers independently selected from 0 through 2 and W^{22} is selected from the group consisting of CR^{41}=CR^{42}, CR^{41}=R^{42}=C; vinylidene), ethynylidene (C≡C; 1,2-ethynyl), 1,2-cyclopropyl, 1,2-cyclobutyl, 1,2-cyclohexyl, 1,3-cyclohexyl, 1,2-cyclopentyl, 1,3-cyclopentyl, 2,3-morpholinyl, 2,4-morpholinyl, 2,6-morpholinyl, 3,4-morpholinyl, 3,5-morpholinyl, 1,2-piperazinyl, 1,3-piperazinyl, 2,3-piperazinyl, 2,6-piperazinyl, 1,2-piperidinyl, 1,3-piperidinyl, 2,3-piperidinyl, 2,4-piperidinyl, 2,6-piperidinyl, 3,4-piperidinyl, 1,2-pyrrolidinyl, 1,3-pyrrolidinyl, 2,3-pyrrolidinyl, 2,4-pyrrolidinyl, 2,5-pyrrolidinyl, 3,4-pyrrolidinyl, 2,3-tetrahydrofuranyl, 2,4-tetrahydrofuranyl, 2,5-tetrahydrofuranyl, and 3,4-tetrahydrofuranyl, with the provisos that R^{14} and R^{15} are selected from other than halo and cyano when directly bonded to N and that $(CR^{37}R^{38})_b$, $(CH(R^{14}))_c$, and $(CH(R^{14}))_e$ are bonded to E^0;

Y is optionally Q^b—Q^{ss} wherein Q^{ss} is selected from the group consisting of $(CR^{37}R^{38})_f$ wherein f is an integer selected from 1 through 4, $(CH(R^{14}))_c$—W^1—$CH(R^{15}))_d$ wherein c and d are integers independently selected from 1 through 2, and W^1 is selected from the group consisting of W^1 is selected from the group consisting of O, S, C(O), C(O)N(R^{14}), (R^{14})NC(O),

$N(R^{15})C(O)N(R^{14})$ $(R^{14})NC(O)N(R^{15})$, $N(R^{14})$, $ON(R^{14})$, and $(CH(R^{14}))_e—W^2—(CH(R^{15}))_h$ wherein e and h are integers independently selected from 0 through 2 and W^2 is selected from the group consisting of $CR^{4a}=CR^{4b}$, ethynylidene (C≡C; 1,2-ethynyl), and $C=CR^{4a}R^{4b}$ with the provisos that R^{14} and R^{15} are selected from other than halo when directly bonded to N and that $(CR^{37}R^{38})_p$ $(CH(R^{14}))_e$, and $(CH(R^{14}))_e$ are bonded to E^0;

Y^0 is optionally $Q^b—Q^{sss}$ wherein Q^{sss} is $(CH(R^{38}))_r—W^3$, r is an integer selected from 1 through 2, W^3 is selected from the group consisting of 1,1-cyclopropyl, 1,2-cyclopropyl, 1,1-cyclobutyl, 1,2-cyclobutyl, 1,2-cyclohexyl, 1,3-cyclohexyl, 1,4-cyclohexyl, 1,2-cyclopentyl, 1,3-cyclopentyl, 2,3-morpholinyl, 2,4-morpholinyl, 2,5-morpholinyl, 2,6-morpholinyl, 3,4-morpholinyl, 3,5-morpholinyl, 1,2-piperazinyl, 1,3-piperazinyl, 1,4-piperazinyl, 2,3-piperazinyl, 2,5-piperazinyl, 2,6-piperazinyl, 1,2-piperidinyl, 1,3-piperidinyl, 1,4-piperidinyl, 2,3-piperidinyl, 2,4-piperidinyl, 2,5-piperidinyl, 2,6-piperidinyl, 3,4-piperidinyl, 3,5-piperidinyl, 3,6-piperidinyl, 1,2-pyrrolidinyl, 1,3-pyrrolidinyl, 2,3-pyrrolidinyl, 2,4-pyrrolidinyl, 2,5-pyrrolidinyl, 3,4-pyrrolidinyl, 2H-2,3-pyranyl, 2H-2,4-pyranyl, 2H-2,5-pyranyl, 4H-2,3-pyranyl, 4H-2,4-pyranyl, 4H-2,5-pyranyl, 2H-pyran-2-one-3,4-yl, 2H-pyran-2-one-4,5-yl, 4H-pyran-4-one-2, 3-yl, 2,3-tetrahydrofuranyl, 2,4-tetrahydrofuranyl, 2,5-tetrahydrofuranyl, 3,4-tetrahydrofuranyl, 2,3-tetrahydropyranyl, 2,4-tetrahydropyranyl, 2,5-tetrahydropyranyl, 2,6-tetrahydropyranyl, 3,4-tetrahydropyranyl, and 3,5-tetrahydropyranyl, and each carbon and hyrido containing nitrogen member of the ring of the W^3 other than the points of attachment is optionally substituted with one or more of the group consisting of R^9, R^{10}, R^{11}, and R^{12}, with the proviso that $(CH(R^{38}))_r$ is bonded to E^0 and Q^b is bonded to lowest numbered substituent position of each W^3;

Y^0 is optionally $Q^b—Q^{sssr}$ wherein Q^{sssr} is $(CH(R^{38}))_r—W^4$, r is integer selected from 1 through 2, W^4 is selected from the group consisting of 1,2-cyclobutyl, 1,2-cyclohexyl, 1,3-cyclohexyl, 1,4-cyclohexyl, 1,2-cyclopentyl, 1,3-cyclopentyl, 2,3-morpholinyl, 2,4-morpholinyl, 2,5-morpholinyl, 2,6-morpholinyl, 3,4-morpholinyl, 3,5-morpholinyl, 1,2-piperazinyl, 1,3-piperazinyl, 1,4-piperazinyl, 2,3-piperazinyl, 2,5-piperazinyl, 2,6-piperazinyl, 1,2-piperidinyl, 1,3-piperidinyl, 1,4-piperidinyl, 2,3-piperidinyl, 2,4-piperidinyl, 2,5-piperidinyl, 2,6-piperidinyl, 3,4-piperidinyl, 3,5-piperidinyl, 3,6-piperidinyl, 1,2-pyrrolidinyl, 1,3-pyrrolidinyl, 2,3-pyrrolidinyl, 2,4-pyrrolidinyl, 2,5-pyrrolidinyl, 3,4-pyrrolidinyl, 2H-2,3-pyranyl, 2H-2,4-pyranyl, 2H-2,5-pyranyl, 4H-2,3-pyranyl, 4H-2,4-pyranyl, 4H-2,5-pyranyl, 2H-pyran-2-one-3,4-yl, 2H-pyran-2-one-4,5-yl, 4H-pyran-4-one-2, 3-yl, 2,3-tetrahydrofuranyl, 2,4-tetrahydrofuranyl, 2,5-tetrahydrofuranyl, 3,4-tetrahydrofuranyl, 2,3-tetrahydropyranyl, 2,4-tetrahydrofuranyl, 2,5-tetrahydropyranyl, 2,6-tetrahydropyranyl, 3,4-tetrahydropyranyl, and 3,5-tetrahydropyranyl, and each carbon and hyrido containing nitrogen member of the ring of the W^4 other than the points of attachment is optionally substituted with one or more of the group consisting of R^9, R^{10}, R^{11}, and R^{12}, with the provisos that $(CH(R^{38}))_r$ is bonded to E^0 and Q^b is bonded to highest number substituent position of each W^4;

Y^0 is optionally $Q^b—Q^{ssss}$ wherein Q^{ssss} $(CH(R^{38}))_r—W^5$, r is an integer selected from 1 through 2, W^5 is selected from the group consisting of 1,4-indenyl, 1,5-indenyl, 1,6-indenyl, 1,7-indenyl, 2,7-indenyl, 2,6-indenyl, 2,5-indenyl, 2,4-indenyl, 3,4-indenyl, 3,5-indenyl, 3,6-indenyl, 3,7-indenyl, 2,4-benzofuranyl, 2,5-benzofuranyl, 2,6-benzofuranyl, 2,7-benzofuranyl, 3,4-benzofuranyl, 3,5-benzofuranyl, 3,6-benzofuranyl, 3,7-benzofuranyl, 2,4-benzothiophenyl, 2,5-benzothiophenyl, 2,6-benzothiophenyl, 2,7-benzothiophenyl, 3,4-benzothiophenyl, 3,5benzothiophenyl, 3,6-benzothiophenyl, 3,7-benzothiophenyl, 2,7-imidazo(1,2-a)pyridinyl, 3,4-imidazo(1,2-a)pyridinyl, 3,5-imidazo(1,2-a)pyridinyl, 3,6-imidazo(1,2-a)pyridinyl, 3,7-imidazo(1,2-a) pyridinyl, 2,4-indolyl, 2,5-indolyl, 2,6-indolyl, 2,7-indolyl, 3,4-indolyl, 3,5-indolyl, 3,6-indolyl, 3,7-indolyl, 1,4-isoindolyl, 1,5-isoindolyl, 1,6-isoindolyl, 2,4-isoindolyl, 2,5-isoindolyl, 2,6-isoindolyl, 2,7-isoindolyl, 1,3-isoindolyl, 3,4-indazolyl, 3,5-indazolyl, 3,6-indazolyl, 3,7-indazolyl, 2,4-benzoxazolyl, 2,5-benzoxazolyl, 2,6-benzoxazolyl, 2,7-benzoxazolyl, 3,4-benzisoxazolyl, 3,5-benzisoxazolyl, 3,6-benzisoxazolyl, 3,7-benzisoxazolyl, 1,4-naphthyl, 1,5-naphthyl, 1,6-naphthyl, 1,7-naphthyl, 1,8-naphthyl, 2,4-naphthyl, 2,5-naphthyl, 2,6-naphthyl, 2,7-naphthyl, 2,8-naphthyl, 2,4-quinolinyl, 2,5-quinolinyl, 2,6-quinolinyl, 2,7-quinolinyl, 2,8-quinolinyl, 3,4-quinolinyl, 3,5-quinolinyl, 3,6-quinolinyl, 3,7-quinolinyl, 3,8-quinolinyl, 4,5-quinolinyl, 4,6-quinolinyl, 4,7-quinolinyl, 4,8-quinolinyl, 1,4-isoquinolinyl, 1,5-isoquinolinyl, 1,6-isoquinolinyl, 1,7-isoquinolinyl, 1,8-isoquinolinyl, 3,4-isoquinolinyl, 3,5-isoquinolinyl, 3,6-isoquinolinyl, 3,7-isoquinolinyl, 3,8-isoquinolinyl, 4,5-isoquinolinyl, 4,6-isoquinolinyl, 4,7-isoquinolinyl, 4,8-isoquinolinyl, 3,4cinnolinyl, 3,5-cinnolinyl, 3,6-cinnolinyl, 3,7-cinnolinyl, 3,8-cinnolinyl, 4,5-cinnolinyl, 4,6-cinnolinyl, 4,7-cinnolinyl, and 4,8-cinnolinyl, and each carbon and hyrido containing nitrogen member of the ring of the W^5 other than the points of attachment is optionally substituted with one or more of the group consisting of R^9, R^{10}, R^{11}, and R^{12}, with the proviso that Q^b is bonded to lowest number substituent position of each W^5 and that $(CH(R^{38}))_r$ is bonded to E^0;

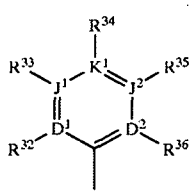
Y^0 is $Q^b—Q^{sssss}$ wherein Q^{sssss} is $(CH(R^{38}))_r—W^6$, r is an integer selected from 1 through 2, W^6 is selected from the group consisting of 1,4-indenyl, 1,5-indenyl, 1,6-indenyl, 1,7-indenyl, 2,7-indenyl, 2,6-indenyl, 2,5-indenyl, 2,4-indenyl, 3,4-indenyl, 3,5-indenyl, 3,6-indenyl, 3,7-indenyl, 2,4-benzofuranyl, 2,5-benzofuranyl, 2,6-benzofuranyl, 2,7-benzofuranyl, 3,4-benzofuranyl, 3,5-benzofuranyl, 3,6-benzofuranyl, 3,7-benzofuranyl, 2,4-benzothiophenyl, 2,5-benzothiophenyl, 2,6-benzothiophenyl, 2,7-benzothiophenyl, 3,4-benzothiophenyl, 3,5-benzothiophenyl, 3,6-benzothiophenyl, 3,7-benzothiophenyl, 2,7-imidazo(1,2-a)pyridinyl, 3,4-imidazo(1,2-a)pyridinyl, 3,5-imidazo(1,2-a)pyridinyl, 3,6-imidazo(1,2-a)pyridinyl, 3,7-imidazo(1,2-a) pyridinyl, 2,4-indolyl, 2,5-indolyl, 2,6-indolyl, 2,7-indolyl, 3,4-indolyl, 3,5-indolyl, 3,6-indolyl, 3,7-indolyl, 1,4-isoindolyl, 1,5-isoindolyl, 1,6-isoindolyl, 2,4-isoindolyl, 2,5-isoindolyl, 2,6-isoindolyl, 2,7-isoindolyl, 1,3-isoindolyl, 3,4-indazolyl, 3,5-indazolyl, 3,6-indazolyl, 3,7-indazolyl, 2,4-benzoxazolyl, 2,5-benzoxazolyl, 2,6-benzoxazolyl, 2,7-benzoxazolyl, 3,4-benzisoxazolyl, 3,5-benzisoxazolyl, 3,6-benzisoxazolyl, 3,7-benzisoxazolyl, 1,4-naphthyl, 1,5-

naphthyl, 1,6-naphthyl, 1,7-naphthyl, 1,8-naphthyl, 2,4-naphthyl, 2,5-naphthyl, 2,6-naphthyl, 2,7-naphthyl, 2,8-naphthyl, 2,4-quinolinyl, 2,5-quinolinyl, 2,6-quinolinyl, 2,7-quinolinyl, 2,8-quinolinyl, 3,4-quinolinyl, 3,5-quinolinyl, 3,6-quinolinyl, 3,7-quinolinyl, 3,8-quinolinyl, 4,5-quinolinyl, 4,6-quinolinyl, 4,7-quinolinyl, 4,8-quinolinyl, 1,4-isoquinolinyl, 1,5-isoquinolinyl, 1,6-isoquinolinyl, 1,7-isoquinolinyl, 1,8-isoquinolinyl, 3,4-isoquinolinyl, 3,5-isoquinolinyl, 3,6-isoquinolinyl, 3,7-isoquinolinyl, 3,8-isoquinolinyl, 4,5-isoquinolinyl, 4,6-isoquinolinyl, 4,7-isoquinolinyl, 4,8-isoquinolinyl, 3,4-cinnolinyl, 3,5-cinnolinyl, 3,6-cinnolinyl, 3,7-cinnolinyl, 3,8-cinnolinyl, 4,5-cinnolinyl, 4,6-cinnolinyl, 4,7-cinnolinyl, and 4,8-cinnolinyl, and each carbon and hyrido containing nitrogen member of the ring of the W^6 other than the points of attachment is optionally substituted with one or more of the group consisting of R^9, R^{10}, R^{11}, and R^{12}, with the proviso that Q^b is bonded to highest number substituent position of each W^6 and that $(CH(R^{38}))_r$ is bonded to E^0.

In a preferred embodiment of compounds of Formula I or a pharmaceutically acceptable salt thereof,

J is O;

B is formula (V):



(V)

wherein

D^1, D^2, J^1, J^2 and K^1 are independently selected from the group consisting of C, N, O, S and a covalent bond with the provisos that no more than one is a covalent bond, no more than one of D^1, D^2, J^1, J^2 and K^1 is O, no more than one of D^1, D^2, J^1, J^2 and K^1 is S, one of D^1, D^2, J^1, J^2 and K^1 must be a covalent bond when two of D^1, D^2, J^1, J^2 and K^1 are O and S, and no more than four of D^1, D^2, J^1, J^2 and K^1 are N;

R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{32}, R^{33}, R^{34}, R^{35}, and R^{36} are independently selected from the group consisting of hydrido, acetamido, haloacetamido, amidino, guanidino, alkylenedioxy, haloalkylthio, alkanoyloxy, alkoxy, alkoxyalkyl, haloalkoxylalkyl, hydroxy, amino, alkoxyamino, nitro, lower alkylamino, alkylthio, alkylthioalkyl, alkylsulfinyl, alkylsulfonyl, alkylsulfonylalkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heterocyclyl, alkylsulfonamido, alkylaminosulfonyl, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, alkanoyl, haloalkanoyl, alkyl, alkenyl, halo, haloalkyl, haloalkenyl, haloalkoxy, hydroxyhaloalkyl, hydroxyalkyl, aminoalkyl, haloalkoxyalkyl, carboxyalkyl, carboalkoxy, carboxy, carboxamido, carboxamidoalkyl, and cyano;

R^{16}, R^{19}, R^{32}, R^{33}, R^{34}, R^{35}, and R^{36} are independently optionally Q^b with the proviso that no more than one of R^{16} and R^{19} is Q^b at the same time and that Q^b is Q^{be};

B is optionally selected from the group consisting of hydrido, trialkylsilyl, C2–C8 alkyl, C3–C8 alkylenyl, C3–C8 alkenyl, C3–C8 alkynyl, and C2–C8 haloalkyl, wherein each member of group B may be optionally substituted at any carbon up to and including 6 atoms from the point of attachment of B to A with one or more of the group consisting of R^{32}, R^{33}, R^{34}, R^{35}, and R^{36};

B is optionally selected from the group consisting of C3–C12 cycloalkyl and C4–C9 saturated heterocyclyl, wherein each ring carbon may be optionally substituted with R^{33}, a ring carbon other than the ring carbon at the point of attachment of B to A may be optionally substituted with oxo provided that no more than one ring carbon is substituted by oxo at the same time, ring carbon and nitrogen atoms adjacent to the carbon atom at the point of attachment may be optionally substituted with R^9 or R^{13}, a ring carbon or nitrogen atom adjacent to the R^9 position and two atoms from the point of attachment may be substituted with R^{10}, a ring carbon or nitrogen atom adjacent to the R^{13} position and two atoms from the point of attachment may be substituted with R^{12}, a ring carbon or nitrogen atom three atoms from the point of attachment and adjacent to the R^{10} position may be substituted with R^{11}, a ring carbon or nitrogen atom three atoms from the point of attachment and adjacent to the R^{12} position may be substituted with R^{33}, and a ring carbon or nitrogen atom four atoms from the point of attachment and adjacent to the R^{11} and R^{33} positions may be substituted with R^{34};

A is selected from the group consisting of single covalent bond, $(W^7)_{rr}$—$(CH(R^{15}))_{pa}$ and $(CH(R^{15}))_{pa}$—$(W^7)_{rr}$ wherein rr is an integer selected from 0 through 1, pa is an integer selected from 0 through 6, and W^7 is selected from the group consisting of O, S, C(O), (R^7)NC(O), (R^7)NC(S), and N(R^7) with the proviso that no more than one of the group consisting of rr and pa is 0 at the same time;

R^7 is selected from the group consisting of hydrido, hydroxy, and alkyl;

R^{15} is selected from the group consisting of hydrido, hydroxy, halo, alkyl, and haloalkyl;

Ψ is selected from the group consisting of NH and NOH;

R^1 is selected from the group consisting of hydrido, alkyl, alkenyl, cyano, halo, haloalkyl, haloalkoxy, haloalkylthio, amino, aminoalkyl, alkylamino, amidino, hydroxy, hydroxyamino, alkoxy, hydroxyalkyl, alkoxyamino, thiol, and alkylthio;

R^2 is Z^0—Q;

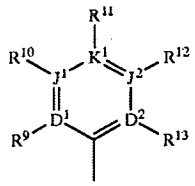
Z^0 is selected from the group consisting of covalent single bond, $(CR^{41}R^{42})_q$ wherein q is an integer selected from 1 through 3, $(CH(R^{41}))_g$—W^0—$(CH(R^{42}))_p$ wherein g and p are integers independently selected from 0 through 3 and W^0 is selected from the group consisting of O, S, C(O), S(O), N(R^{41}), and ON(R^{41}), and (CH(R^{41}))$_e$—W^{22}—$(CH(R^{42}))_h$ wherein e and h are integers independently selected from 0 through 1 and W^{22} is selected from the group consisting of CR^{41}=CR^{42}, 1,2-cyclopropyl, 1,2-cyclobutyl, 1,2-cyclohexyl, 1,3-cyclohexyl, 1,2-cyclopentyl, 1,3-cyclopentyl, 2,3-morpholinyl, 2,4-morpholinyl, 2,6-morpholinyl, 3,4-morpholinyl, 3,5-morpholinyl, 1,2-piperazinyl, 1,3-piperazinyl, 2,3-piperazinyl, 2,6-piperazinyl, 1,2-piperidinyl, 1,3-piperidinyl, 2,3-piperidinyl, 2,4-piperidinyl, 2,6-piperidinyl, 3,4-piperidinyl, 1,2-pyrrolidinyl, 1,3-pyrrolidinyl, 2,3-pyrrolidinyl, 2,4-pyrrolidinyl, 2,5-pyrrolidinyl, 3,4-pyrrolidinyl, 2,3-

tetrahydrofuranyl, 2,4-tetrahydrofuranyl, 2,5-tetrahydrofuranyl, and 3,4-tetrahydrofuranyl, with the proviso that Z is directly bonded to the pyrazinone ring;

R^{41} and R^{42} are independently selected from the group consisting of amidino, hydroxyamino, hydrido, hydroxy, amino, and alkyl;

Q^b is selected from the group consisting of hydrido, with the proviso that Z^0 is other than a covalent single bond, and the formula (II):

(II)



wherein D^1, D^2, J^1, J^2 and K^1 are independently selected from the group consisting of C, N, O, S and a covalent bond with the provisos that no more than one is a covalent bond, no more than one of D^1, D^2, J^1, J^2 and K^1 is O, no more than one of D^1, D^2, J^1, J^2 and K^1 is S, one of D^1, D^2, J^1, J^2 and K^1 must be a covalent bond when two of D^1, D^2, J^1, J^2 and K^1 are O and S, and no more than four of D^1, D^2, J^1, J^2 and K^1 are N, with the proviso that R^9, R^{10}, R^{11}, R^{12}, and R^{13} are each independently selected to maintain the tetravalent nature of carbon, trivalent nature of nitrogen, the divalent nature of sulfur, and the divalent nature of oxygen;

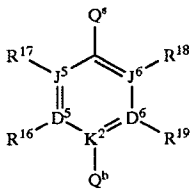
K is $(CR^{4a}R^{4b})_n$, wherein n is an integer selected from 1 through 2;

R^{4a} and R^{4b} are independently selected from the group consisting of halo, hydrido, hydroxyalkyl, alkyl, alkoxyalkyl, alkylthioalkyl, and haloalkyl;

E^0 is E^1, when K is $(CR^{4a}R^{4b})_n$, wherein E^1 is selected from the group consisting of a covalent single bond, C(O), C(S), C(O)N(R^7), (R^7)NC(O), $S(O)_2$, (R^7)NS(O)$_2$, and $S(O)_2N(R^7)$;

Y^0 is formula (IV):

(IV)



wherein

D^5, D^6, J^5, and J^6 are independently selected from the group consisting of C, N, O, S and a covalent bond with the provisos that no more than one is a covalent bond, K^2 is C, no more than one of D^5, D^5, J^5, and J^6 is O, no more than one of D^5, D^6, J^5, and J^6 is S, one of D^5, D^6, J^5, and J^6 must be a covalenthbond when two of D^5, D^6, and J^6 are O and S, and no more than four of D^5, D^6, J^5, and J^6 are N with the proviso that R^{16}, R^{17}, R^{18}, and R^{19} are each independently selected to maintain the tetravalent nature of carbon, trivalent nature of nitrogen, the divalent nature of sulfur, and the divalent nature of oxygen;

R^{16}, R^{17}, R^{18}, and R^{19} are independently selected from the group consisting of hydrido, amidino, guanidino, carboxy, haloalkylthio, alkoxy, hydroxy, amino, nitro, alkoxyamino, lower alkylamino, alkylthio, alkylsulfinyl, alkylsulfonyl, alkanoyl, haloalkanoyl, alkyl, alkenyl, halo, haloalkyl, haloalkoxy, hydroxyalkyl, alkylenylamino, haloalkoxyalkyl, carboalkoxy, and cyano;

Q^b is selected from the group consisting of $NR^{20}R^{21}$, aminoalkylenyl, Q^{be} wherein Q^{be} is hydrido, $N(R^{26})C(NR^{25})N(R^{23})(R^{24})$, and $C(NR^{25})NR^{23}R^{24}$, with the provisos that no more than one of R^{20} and R^{21} is hydroxy, amino, alkylamino, or dialkylamino at the same time and that no more than one of R^{23} and R^{24} is hydroxy, amino, alkylamino, or dialkylamino at the same time;

R^{20}, R^{21}, R^{23}, R^{24}, R^{25}, and R^{26} are independently selected from the group consisting of hydrido, alkyl, hydroxy, aminoalkylenyl, amino, dialkylamino, alkylamino, and hydroxyalkyl;

Q^s is selected from the group consisting of a single covalent bond, $(CR^{37}R^{38})_b$ wherein b is an integer selected from 1 through 4, and $(CH(R^{14}))_c$—W^1—$(CH(R^{15}))_d$ wherein c and d are integers independently selected from 1 through 3 and W^1 is selected from the group consisting of C(O)N(R^{14}), (R^{14})NC(O), S(O), $S(O)_2$, $S(O)_2N(R^{14})$, $N(R^{14})S(O)_2$, and N(R^{14}), with the provisos that R^{14} is selected from other than halo when directly bonded to N and that $(CR^{37}R^{38})_b$, and $(CH(R^{14}))_c$ are bonded to E^0;

R^{14} is selected from the group consisting of hydrido, halo, alkyl, and haloalkyl;

R^{37} and R^{38} are independently selected from the group consisting of hydrido, alkyl, and haloalkyl;

R^{38} is optionally selected from the group consisting of aroyl and heteroaroyl;

Y^0 is optionally Q^b—Q^{ss} wherein Q^{ss} is $(CH(R^{14}))_e$—W^2—$(CH(R^{15}))_h$, wherein e and h are integers independently selected from 1 through 2 and W^2 is CR^{4a}=CR^{4b} with the proviso that $(CH(R^{14}))_e$ is bonded to E^0;

Y^0 is optionally selected from the group consisting of Q^b—Q^{ssss} and Q^b—Q^{sssst} wherein Q^{ssss} is $(CH(R^{38}))_r$—$W^6$and Q^{sssst} is $(CH(R^{38}))_r$—W^6, r is an integer selected from 1 through 2, and W^5 and W^6 are independently selected from the group consisting of 1,4-indenyl, 1,5-indenyl, 1,6-indenyl, 1,7-indenyl, 2,7-indenyl, 2,6-indenyl, 2,5-indenyl, 2,4-indenyl, 3,4-indenyl, 3,5-indenyl, 3,6-indenyl, 3,7-indenyl, 2,4-benzofuranyl, 2,5-benzofuranyl, 2,6-benzofuranyl, 2,7-benzofuranyl, 3,4-benzofuranyl, 3,5-benzofuranyl, 3,6-benzofuranyl, 3,7-benzofuranyl, 2,4-benzothiophenyl, 2,5-benzothiophenyl, 2,6-benzothiophenyl, 2,7-benzothiophenyl, 3,4-benzothiophenyl, 3,5-benzothiophenyl, 3,6-benzothiophenyl, 3,7-benzothiophenyl, 2,7-imidazo(1,2-a)pyridinyl, 3,4-imidazo(1,2-a)pyridinyl, 3,5-imidazo(1,2-a)pyridinyl, 3,6-imidazo(1,2-a)pyridinyl, 3,7-imidazo(1,2-a)pyridinyl, 2,4-indolyl, 2,5-indolyl, 2,6-indolyl, 2,7-indolyl, 3,4-indolyl, 3,5-indolyl, 3,6-indolyl, 3,7-indolyl, 1,4-isoindolyl, 1,5-isoindolyl, 1,6-isoindolyl, 2,4-isoindolyl, 2,5-isoindolyl, 2,6-isoindolyl, 2,7-isoindolyl, 1,3-isoindolyl, 3,4indazolyl, 3,5-indazolyl, 3,6-indazolyl, 3,7-indazolyl, 2,4-benzoxazolyl, 2,5-benzoxazolyl, 2,6-benzoxazolyl, 2,7-benzoxazolyl, 3,4-benzisoxazolyl, 3,5-benzisoxazolyl, 3,6-benzisoxazolyl, 3,7-benzisoxazolyl, 1,4-naphthyl, 1,5-naphthyl, 1,6-naphthyl, 1,7-naphthyl, 1,8-naphthyl,

2,4-naphthyl, 2,5-naphthyl, 2,6-naphthyl, 2,7-naphthyl, 2,8-naphthyl, 2,4-quinolinyl, 2,5-quinolinyl, 2,6-quinolinyl, 2,7-quinolinyl, 2,8-quinolinyl, 3,4-quinolinyl, 3,5-quinolinyl, 3,6-quinolinyl, 3,7-quinolinyl, 3,8-quinolinyl, 4,5-quinolinyl, 4,6-quinolinyl, 4,7-quinolinyl, 4,8-quinolinyl, 1,4-isoquinolinyl, 1,5-isoquinolinyl, 1,6-isoquinolinyl, 1,7-isoquinolinyl, 1,8-isoquinolinyl, 3,4-isoquinolinyl, 3,5-isoquinolinyl, 3,6-isoquinolinyl, 3,7-isoquinolinyl, 3,8-isoquinolinyl, 4,5-isoquinolinyl, 4,6-isoquinolinyl, 4,7-isoquinolinyl, 4,8-isoquinolinyl, 3,4-cinnolinyl, 3,5-cinnolinyl, 3,6-cinnolinyl, 3,7-cinnolinyl, 3,8-cinnolinyl, 4,5-cinnolinyl, 4,6-cinnolinyl, 4,7-cinnolinyl, and 4,8-cinnolinyl, and each carbon and hyrido containing nitrogen member of the ring of the W^5 and of the ring of the W^6, other than the points of attachment of W^5 and W^6, is optionally substituted with one or more of the group consisting of R^9, R^{10}, R^{11}, and R^{12}, *with the provisos that* Q^b *is bonded to lowest* number substituent position of each W^5, Q^b is bonded to highest number substituent position of each W^6, and $(CH(R^{38}))_r$ is bonded to E^0.

In a more preferred embodiment of compounds of Formula I or a pharmaceutically acceptable salt thereof,

J is O;

B is selected from the group consisting of aryl and heteroaryl wherein a carbon adjacent to the carbon at the point of attachment is optionally substituted by R^{32}, the other carbon adjacent to the carbon at the point of attachment is optionally substituted by R^{36}, a carbon adjacent to R^{32} and two atoms from the carbon at the point of attachment is optionally substituted by R^{33}, a carbon adjacent to R^{36} and two atoms from the carbon at the point of attachment is optionally substituted by R^{35}, and any carbon adjacent to both R^{33} and R^{35} is optionally substituted by R^{34};

R^{32}, R^{33}, R^{34}, R^{35}, and R^{36} are independently selected from the group consisting of hydrido, acetamido, haloacetamido, amidino, guanidino, alkylenedioxy, haloalkylthio, alkanoyloxy, alkoxy, hydroxy, amino, *alkoxyamino, alkanoyl, haloalkanoyl, nitro,* lower alkylamino, alkylthio, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heterocyclyl, alkylsulfonamido, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, alkyl, alkenyl, halo, haloalkyl, haloalkenyl, haloalkoxy, hydroxyalkyl, alkylenylamino, carboalkoxy, carboxy, carboxamido, cyano, and Q^b;

B is optionally selected from the group consisting of hydrido, trialkylsilyl, C2–C8 alkyl, C3–C8 alkylenyl, C3–C8 alkenyl, C3–C8 alkynyl, and C2–C8 haloalkyl, wherein each member of group B is optionally substituted at any carbon up to and including 6 atoms from the point of attachment of B to A with one or more of the group consisting of R^{32}, R^{33}, R^{34}, R^{35}, and R^{36};

B is optionally selected from the group consisting of C3–C12 cycloalkyl and C4–C9 saturated heterocyclyl, wherein each ring carbon is optionally optionally substituted with R^{33}, a ring carbon other than the ring carbon at the point of attachment of B to A is optionally substituted with oxo provided that no more than one ring carbon is substituted by oxo at the same time, ring carbon and nitrogen atoms adjacent to the carbon atom at the point of attachment is optionally substituted with R^9 or R^{13}, a ring carbon or nitrogen atom adjacent to the R^9 position and two atoms from the point of attachment is optionally substituted with R^{10}, a ring carbon or nitrogen atom adjacent to the R^{13}position and two atoms from the point of attachment is optionally substituted with R^{12}, a ring carbon or nitrogen atom three atoms from the point of attachment and adjacent to the R^{10} position is optionally substituted with R^{11}, a ring carbon or nitrogen atom three atoms from the point of attachment and adjacent to the R^{12} position is optionally substituted with R^{33}, and a ring carbon or nitrogen atom four atoms from the point of attachment and adjacent to the R^{11} and R^{33} positions is optionally substituted with R^{34};

R^9, R^{10}, R^{11}, R^{12}, and R^{13} are independently selected from the group consisting of hydrido, acetamido, haloacetamido, alkoxyamino, alkanoyl, haloalkanoyl, amidino, guanidino, alkylenedioxy, haloalkylthio, alkoxy, hydroxy, amino, lower alkylamino, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylsulfonamido, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, alkyl, halo, haloalkyl, haloalkoxy, hydroxyalkyl, aminoalkyl, carboalkoxy, carboxyalkyl, carboxy, carboxamido, and cyano;

A is selected from the group consisting of single covalent bond and $(CH(R^{15}))_{pa}$—$(W^7)_{rr}$ wherein rr is an integer selected from 0 through 1, pa is an integer selected from 0 through 3, and W^7 is selected from the group consisting of O, S, C(O), $(R^7)NC(O)$, $(R^7)NC(S)$, and $N(R^7)$;

R^7 is selected from the group consisting of hydrido, hydroxy and alkyl;

R^{15} is selected from the group consisting of hydrido, hydroxy, halo, alkyl, and haloalkyl;

Ψ is NH;

R^1 is selected from the group consisting of hydrido, alkyl, cyano, halo, haloalkyl, haloalkoxy, amino, aminoalkyl, alkylamino, amidino, hydroxy, hydroxyamino, alkoxy, hydroxyalkyl, alkoxyamino, thiol, and alkylthio;

R^2 is Z^0—Q;

Z^0 is selected from the group consisting of covalent single bond and $(CR^{41}R^{42})_q$ wherein q is an integer selected from 1 through 2, $(CH(R^{41}))_g$—W^0—$(CH(R^{42}))_p$ wherein g and p are integers independently selected from 0 through 3 and W^0 is selected from the group consisting of O, S, and $N(R^{41})$, and $(CH(R^{41}))_e$—W^{22}—$(CH(R^{42}))_h$ wherein e and h are integers independently selected from 0 through 1 and W^{22} is selected from the group consisting of CR^{41}=CR^{42}, 1,2-cyclopropyl, 1,2-cyclobutyl, 1,2-cyclohexyl, 1,3-cyclohexyl, 1,2-cyclopentyl, 1,3-cyclopentyl, 2,3-morpholinyl, 2,4-morpholinyl, 2,6-morpholinyl, 3,4-morpholinyl, 3,5-morpholinyl, 1,2-piperazinyl, 1,3-piperazinyl, 2,3-piperazinyl, 2,6-piperazinyl, 1,2-piperidinyl, 1,3-piperidinyl, 2,3-piperidinyl, 2,4-piperidinyl, 2,6-piperidinyl, 3,4-piperidinyl, 1,2-pyrrolidinyl, 1,3-pyrrolidinyl, 2,3-pyrrolidinyl, 2,4-pyrrolidinyl, 2,5-pyrrolidinyl, 3,4-pyrrolidinyl, 2,3-tetrahydrofuranyl, 2,4-tetrahydrofuranyl, 2,5-tetrahydrofuranyl, and 3,4-tetrahydrofuranyl, with the proviso that Z^0 is directly bonded to the pyrazinone ring;

R^{41} and R^{42} are independently selected from the group consisting of hydrido, hydroxy, and amino,

Q is selected from the group consisting of hydrido, with the proviso that Z^0 is other than a covalent single bond, aryl, and heteroaryl, wherein a carbon adjacent to the carbon at the point of attachment is optionally substituted by R^9, the other carbon adjacent to the carbon at the point of attach-

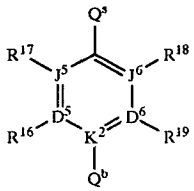
ment is optionally substituted by R^{13}, a carbon adjacent to R^9 and two atoms from the carbon at the point of attachment is optionally substituted by R^{10}, a carbon adjacent to R^{13} and two atoms from the carbon at the point of attachment is optionally substituted by R^{12}, and any carbon adjacent to both R^{10} and R^{12} is optionally substituted by R^{11};

K is CHR^{4a} wherein R^{4a} is selected from the group consisting of hydrido, hydroxyalkyl, alkyl, alkoxyalkyl, alkylthioalkyl, and haloalkyl;

E^0 is selected from the group consisting of a covalent single bond, C(O)N(H), (H)NC(O), $(R^7)NS(O)_2$, and $S(O)_2N(R^7)$;

Y^0 is formula (IV):

(IV)



wherein

D^5, D^6, J^5, and J^6 are independently selected from the group consisting of C, N, O, S and a covalent bond with the provisos that no more than one is a covalent bond, K^2 is C, no more than one of D^5, D^6, J^5, and J^6 is O, no more than one of D^5, D^6, J^5, and J^6 is S, one of D^5, D^6, J^5, and J^6 must be a covalent bond when two of D^5, D^6, J^5, and J^6 are O and S, and no more than four of D^5, D^6, J^5, and J^6 are N, with the provisos that R^{16}, R^{17}, R^{18}, and R^{19} are each independently selected to maintain the tetravalent nature of carbon, trivalent nature of nitrogen, the divalent nature of sulfur, and the divalent nature of oxygen;

R^{16}, R^{17}, R^{18}, and R^{19} are independently selected from the group consisting of hydrido, amidino, guanidino, carboxy, haloalkylthio, alkoxy, hydroxy, amino, alkoxyamino, lower alkylamino, alkylthio, alkylsulfinyl, alkylsulfonyl, alkanoyl, haloalkanoyl, alkyl, halo, haloalkyl, haloalkoxy, hydroxyalkyl, aminoalkyl, and cyano;

R^{16} and R^{19} are optionally Q^b with the proviso that no more than one of R^{16} and R^{19} is Q^b at the same time and that Q^b is Q^{be};

Q^b is selected from the group consisting of $NR^{20}R^{21}$, Q^{be} wherein Q^{be} is hydrido, $N(R^{26})C(NR^{25})N(R^{23})(R^{24})$, and $C(NR^{25})NR^{23}R^{24}$, with the provisos that no more than one of R^{20} and R^{21} is hydroxy, amino, alkylamino, or dialkylamino at the same time and that no more than one of R^{23} and R^{24} is hydroxy, amino, alkylamino, or dialkylamino at the same time;

R^{20}, R^{21}, R^{23}, R^{24}, R^{25}, and R^{26} are independently selected from the group consisting of hydrido, alkyl, hydroxy, amino, alkylamino and dialkylamino;

Q^s is selected from the group consisting of a single covalent bond, $(CR^{37}R^{38})_b$ wherein b is an integer selected from 1 through 4, and $(CH(R^{14}))_c—W^1—(CH(R^{15}))_d$ wherein c and d are integers independently selected from 1 through 3 and W^1 is selected from the group consisting of $C(O)N(R^{14})$, $(R^{14})NC(O)$, S(O), $S(O)_2$, $S(O)_2N(R^{14})$, $N(R^{14})S(O)_2$, and $N(R^{14})$, with the provisos that R^{14} is selected from other than halo when directly bonded to N and that $(CR^{37}R^{38})_b$, and $(CH(R^{14}))_c$ are bonded to E^0;

R^{14} is selected from the group consisting of hydrido, halo, alkyl, and haloalkyl;

R^{37} and R^{38} are independently selected from the group consisting of hydrido, alkyl, and haloalkyl;

R^{38} is optionally selected from the group consisting of aroyl and heteroaroyl;

Y^0 is optional $Q^b—Q^{ss}$ wherein Q^{ss} is $(CH(R^{14}))_e—W^2—(CH(R^{15}))_h$, wherein e and h are integers independently selected from 1 through 2 and W^2 is $CR^{4a}=CH$ with the proviso that $(CH(R^{14}))_e$ is bonded to E^0.

In an even more preferred embodiment of compounds of Formula I or a pharmaceutically acceptable salt thereof,

J is O;

B is selected from the group consisting of aryl and heteroaryl wherein a carbon adjacent to the carbon at the point of attachment is optionally substituted by R^{32}, the other carbon adjacent to the carbon at the point of attachment is optionally substituted by R^{36}, a carbon adjacent to R^{32} and two atoms from the carbon at the point of attachment is optionally substituted by R^{33}, a carbon adjacent to R^{36} and two atoms from the carbon at the point of attachment is optionally substituted by R^{35}, and any carbon adjacent to both R^{33} and R^{35} is optionally substituted by R^{34};

R^{32}, R^{33}, R^{34}, R^{35}, and R^{36} are independently selected from the group consisting of hydrido, acetamido, haloacetamido, amidino, guanidino, alkoxy, hydroxy, amino, alkoxyamino, lower alkylamino, alkylthio, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, alkyl, halo, haloalkyl, haloalkoxy, hydroxyalkyl, carboalkoxy, carboxy, carboxamido, cyano, and Q^b;

A is selected from the group consisting of single covalent bond and $(CH(R^{15}))_{pa}—(W^7)_{rr}$ wherein rr is an integer selected from 0 through 1, pa is an integer selected from 0 through 3, and W^7 is selected from the group consisting of $(R^7)NC(O)$ and $N(R^7)$;

R^7 is selected from the group consisting of hydrido, hydroxy and alkyl;

R^{15} is selected from the group consisting of hydrido, halo, alkyl, and haloalkyl;

Ψ is NH;

R^1 is selected from the group consisting of hydrido, alkyl, cyano, haloalkyl, and halo;

R^2 is $Z^0—Q$;

Z^0 is selected from the group consisting of a covalent single bond and CH_2;

Q is selected from the group consisting of aryl and heteroaryl wherein a carbon adjacent to the carbon at the point of attachment is optionally substituted by R^9, the other carbon adjacent to the carbon at the point of attachment is optionally substituted by R^{13}, a carbon adjacent to R^9 and two atoms from the carbon at the point of attachment is optionally substituted by R^{10}, a carbon adjacent to R^{13} and two atoms from the carbon at the point of attachment is optionally substituted by R^{12}, and any carbon adjacent to both R^{10} and R^{12} is optionally substituted by R^{11};

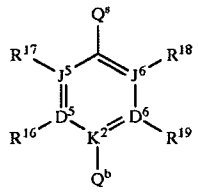
R^9, R^{11}, and R^{13} are independently selected from the group consisting of hydrido, hydroxy, amino, amidino, guanidino, lower alkylamino, alkylthio, alkylsulfonamido, alkylsulfinyl, alkylsulfonyl, amidosulfonyl, monoalkyl amidosulfonyl, alkyl, alkoxy, halo, haloalkyl, haloalkoxy, hydroxyalkyl, carboxy, carboxamido, and cyano;

R^{10} and R^{12} are independently selected from the group consisting of hydrido, acetamido, haloacetamido, amidino, guanidino, alkyl, alkoxy, hydroxy, amino, alkoxyamino, lower alkylamino, alkylsulfonamido, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, hydroxyalkyl, aminoalkyl, carboalkoxy, carboxy, carboxyalkyl, amidocarbonyl, halo, haloalkyl, and cyano;

K is CH_2;

E^0 is C(O)N(H);

Y^0 is formula (IV):



(IV)

wherein

D^5, D^6, J^5 and J^6 are independently selected from the group consisting of C, N, O, S and a covalent bond with the provisos that no more than one is a covalent bond, K^2 is C, no more than one of D^5, D^6, J^5, and J^6 is optionally O, no more than one of D^5, D^6, J^5, and J^6 is optionally S, one of D^5, D^6, J^6, and J^6 must be acovalent bond when two of D^5, D^5, J^5, and J^6 are O and S, and no more than four of D^5, D^6, J^5, and J^6 are N;

R^{16}, R^{17}, R^{18}, and R^{19} are independently selected from the group consisting of hydrido, amidino, guanidino, carboxy, haloalkylthio, alkoxy, hydroxy, amino, lower alkylamino, alkylthio, alkylsulfinyl, alkylsulfonyl, alkanoyl, haloalkanoyl, alkyl, halo, haloalkyl, haloalkoxy, hydroxyalkyl, aminoalkyl, and cyano;

R^{16} and R^{19} are optionally Q^b with the proviso that no more than one of R^{16} and R^{19} is Q^b at the same time and that Q^b is Q^{be};

Q^b is selected from the group consisting of $NR^{20}R^{21}$, Q^{be} wherein Q^{be} is hydrido, and $C(NR^{25})NR^{23}R^{24}$, with the provisos that no more than one of R^{20} and R^{21} is hydroxy at the same time and that no more than one of R^{23} and R^{24} is hydroxy at the same time;

R^{20}, R^{21}, R^{23}, R^{24}, and R^{25} are independently selected from the group consisting of hydrido, alkyl, and hydroxy;

Q^s is selected from the group consisting of a single covalent bond, CH_2, and CH_2CH_2.

In another even more preferred embodiment of compounds of Formula I or a pharmaceutically acceptable salt thereof,

J is O;

B is optionally selected from the group consisting of hydrido, C2–C8 alkyl, C3–C8 alkenyl, C3–C8 alkynyl, and C2–C8 haloalkyl, wherein each member of group B is optionally substituted at any carbon up to and including 6 atoms from the point of attachment of B to A with one or more of the group consisting of R^{32}, R^{33}, R^{34}, R^{35}, and R^{36};

R^{32}, R^{33}, R^{34}, R^{36}, and R^{36} are independently selected from the group consisting of hydrido, acetamido, haloacetamido, amidino, guanidino, alkoxy, hydroxy, amino, alkoxyamino, lower alkylamino, alkylthio, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, alkyl, halo, haloalkyl, haloalkoxy, hydroxyalkyl, carboalkoxy, carboxy, carboxamido, cyano, and Q^b;

A is selected from the group consisting of single covalent bond and $(CH(R^{15}))_{pa}$—$(W^7)_{rr}$ wherein rr is an integer selected from 0 through 1, pa is an integer selected from 0 through 3, and W^7 is selected from the group consisting of $(R^7)NC(O)$ and $N(R^7)$;

R^7 is selected from the group consisting of hydrido, hydroxy and alkyl;

R^{15} is selected from the group consisting of hydrido, halo, alkyl, and haloalkyl;

Ψ is NH;

R^1 is selected from the group consisting of hydrido, alkyl, cyano, haloalkyl, and halo;

R^2 is Z^0—Q;

Z^0 is selected from the group consisting of covalent single bond and CH_2;

Q is selected from the group consisting of aryl and heteroaryl wherein a carbon adjacent to the carbon at the point of attachment is optionally substituted by R^9, the other carbon adjacent to the carbon at the point of attachment is optionally substituted by R^{13}, a carbon adjacent to R^9 and two atoms from the carbon at the point of attachment is optionally substituted by R^{10}, a carbon adjacent to R^{13} and two atoms from the carbon at the point of attachment is optionally substituted by R^{12}, and any carbon adjacent to both R^{10} and R^{12} is optionally substituted by R^{11};

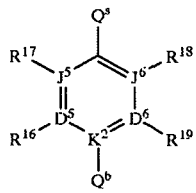
R^9, R^{11}, and R^{13} are independently selected from the group consisting of hydrido, hydroxy, amino, amidino, guanidino, lower alkylamino, alkylthio, alkylsulfonamido, alkylsulfinyl, alkylsulfonyl, amidosulfonyl, monoalkyl amidosulfonyl, alkyl, alkoxy, halo, haloalkyl, haloalkoxy, hydroxyalkyl, carboxy, carboxamido, and cyano;

R^{10} and R^{12} are independently selected from the group consisting of hydrido, acetamido, haloacetamido, amidino, guanidino, alkyl, alkoxy, hydroxy, amino, alkoxyamino, lower alkylamino, alkylsulfonamido, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, hydroxyalkyl, alkylenylamino, carboalkoxy, carboxy, carboxyalkyl, amidocarbonyl, halo, haloalkyl, and cyano;

K is CH_2;

E^0 is C(O)N(H);

Y^0 is formula (IV):



(IV)

wherein

D^5, D^6, J^5, and J^6 are independently selected from the group consisting of C, N, O, S and a covalent bond with the provisos that no more than one is a covalent bond, K^2 is C, no more than one of D^5, D^6, J^5, and

J^6 is O, no more than one of D^5, D^6, J^5 and J^6 is S, one of D^5, D^6, J^5, and J^6 must be a covalent bond when two of D^5, D^6, J^5, and J^6 are O and S, and no more than four of D^5, D^6, J^5, and J^6 are N, with the provisos that R^{16}, R^{17}, R^{18}, and R^{19} are each independently selected to maintain the tetravalent nature of carbon, trivalent nature of nitrogen, the divalent nature of sulfur, and the divalent nature of oxygen;

R^{16}, R^{17}, R^{18}, and R^{19} are independently selected from the group consisting of hydrido, amidino, guanidino, carboxy, haloalkylthio, alkoxy, hydroxy, amino, lower alkylamino, alkylthio, alkylsulfinyl, alkylsulfonyl, alkanoyl, haloalkanoyl, alkyl, halo, haloalkyl, haloalkoxy, hydroxyalkyl, alkylenylamino, and cyano;

R^{16} and R^{19} are optionally Q^b with the proviso that no more than one of R^{16} and R^{19} is Q^b at the same time and that Q^b is Q^{be};

Q^b is selected from the group consisting of $NR^{20}R^{21}$, Q^{be} wherein Q^{be} is hydrido, $C(NR^{25})NR^{23}R^{24}$, and $N(R^{26})C(NR^{25})N(R^{23})(R^{24})$, with the provisos that no more than one of R^{20} and R^{21} is hydroxy at the same time and that no more than one of R^{23} and R^{24} is hydroxy at the same time;

R^{20}, R^{21}, R^{23}, R^{24}, R^{25}, and R^{26} are independently selected from the group consisting of hydrido, alkyl, and hydroxy;

Q^s is selected from the group consisting of a single covalent bond, CH_2, and CH_2CH_2.

In still another even more preferred embodiment of compounds of Formula I or a pharmaceutically acceptable salt thereof,

J is O;

B is optionally selected from the group consisting of C3–C7 cycloalkyl and C4–C6 saturated heterocyclyl, wherein each ring carbon is optionally substituted with R^{33}, a ring carbon other than the ring carbon at the point of attachment of B to A is optionally substituted with oxo provided that no more than one ring carbon is substituted by oxo at the same time, ring carbon and nitrogen atoms adjacent to the carbon atom at the point of attachment is optionally substituted with R^9 or R^{13}, a ring carbon or nitrogen atom adjacent to the R^9 position and two atoms from the point of attachment is optionally substituted with R^{10}, a ring carbon or nitrogen atom adjacent to the R^{13} position and two atoms from the point of attachment is optionally substituted with R^{12}, a ring carbon or nitrogen atom three atoms from the point of attachment and adjacent to the R^{10} position is optionally substituted with R^{11}, a ring carbon or nitrogen atom three atoms from the point of attachment and adjacent to the R^{12} position is optionally substituted with R^{23}, and a ring carbon or nitrogen atom four atoms from the point of attachment and adjacent to the R^{11} and R^{33} positions is optionally substituted with R^{34};

R^9, R^{11}, and R^{13} are independently selected from the group consisting of hydrido, hydroxy, amino, amidino, guanidino, lower alkylamino, alkylthio, alkylsulfonamido, alkylsulfinyl, alkylsulfonyl, amidosulfonyl, monoalkyl amidosulfonyl, alkyl, alkoxy, halo, haloalkyl, haloalkoxy, hydroxyalkyl, carboxy, carboxamido, and cyano;

R^{10} and R^{12} are independently selected from the group consisting of hydrido, acetamido, haloacetamido, amidino, guanidino, alkyl, alkoxy, hydroxy, amino, alkoxyamino, lower alkylamino, alkylsulfonamido, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, hydroxyalkyl, alkylenylamino, carboalkoxy, carboxy, carboxyalkyl, amidocarbonyl, halo, haloalkyl, and cyano;

R^{33} and R^{34} are independently selected from the group consisting of hydrido, acetamido, haloacetamido, amidino, guanidino, alkoxy, hydroxy, amino, alkoxyamino, lower alkylamino, alkylthio, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, alkyl, halo, haloalkyl, haloalkoxy, hydroxyalkyl, carboalkoxy, carboxy, carboxamido, cyano, and Q^b;

A is selected from the group consisting of single covalent bond and $(CH(R^{15}))_{rr}$—$(W^7)_{pa}$, wherein rr is an integer selected from 0 through 1, pa is an integer selected from 0 through 3, and W^7 is selected from the group consisting of $(R^7)NC(O)$ and $N(R^7)$;

R^7 is selected from the group consisting of hydrido, hydroxy and alkyl;

R^{15} is selected from the group consisting of hydrido, halo, alkyl and haloalkyl;

Ψ is NH;

R^1 is selected from the group consisting of hydrido, alkyl, cyano, haloalkyl, and halo;

R^2 is Z^0—Q;

Z^0 is selected from the group consisting of covalent single bond and CH_2;

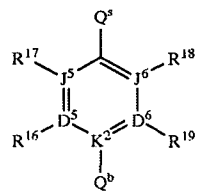
Q is selected from the group consisting of aryl and heteroaryl wherein a carbon adjacent to the carbon at the point of attachment is optionally substituted by R^9, the other carbon adjacent to the carbon at the point of attachment is optionally substituted by R^{13}, a carbon adjacent to R^9 and two atoms from the carbon at the point of attachment is optionally substituted by R^{10}, a carbon adjacent to R^{13} and two atoms from the carbon at the point of attachment is optionally substituted by R^{12}, and any carbon adjacent to both R^{10} and R^{12} is optionally substituted by R^{11};

K is CH_2;

E^0 is C(O)N(H);

Y^0 is formula (IV):

(IV)



wherein

D^5, D^6, J^5, and J^6 are independently selected from the group consisting of C, N, O, S and a covalent bond with the provisos that no more than one is a covalent bond, K^2 is C, no more than one of D^5, D^6, J^5, and J^6 is O, no more than one of D^5, D^6, J^5, and J^6 is S, one of D^5, D^6, J^5 and J^6 must be a covalent bond when two of D^5, D^6, J^5, and J^6 are O and S, and no more than four of D^5, D^6, J^5, and J^6 are N, with the provisos that R^{16}, R^{17}, R^{18}, and R^{19} are each independently selected to maintain the tetravalent nature of carbon, trivalent nature of nitrogen, the divalent nature of sulfur, and the divalent nature of oxygen;

R^{16}, R^{17}, R^{18}, and R^{19} are independently selected from the group consisting of hydrido, amidino, guanidino, carboxy, haloalkylthio, alkoxy, hydroxy, amino, lower alkylamino, alkylthio, alkylsulfinyl, alkylsulfonyl, alkanoyl, haloalkanoyl, alkyl, halo, haloalkyl, haloalkoxy, hydroxyalkyl, alkylenylamino, and cyano;

R^{16} and R^{19} are optionally Q^b with the proviso that no more than one of R^{16} and R^{19} is Q^b at the same time and that Q^b is Q^{be};

Q^b is selected from the group consisting of $NR^{20}R^{21}$, Q^{be} wherein Q^{be} is hydrido, and $C(NR^{25})NR^{23}R^{24}$, with the provisos that no more than one of R^{20} and R^{21} is hydroxy at the same time and that no more than one of R^{23} and R^{24} is hydroxy at the same time,

R^{20}, R^{21}, R^{23}, R^{24}, and R^{25} are independently selected from the group consisting of hydrido, alkyl, and hydroxy;

Q^s is selected from the group consisting of a single covalent bond, CH_2, and CH_2CH_2.

In a most preferred embodiment of compounds of Formula I or a pharmaceutically acceptable salt thereof,

J is O;

B is selected from the group consisting of aryl and heteroaryl wherein a carbon adjacent to the carbon at the point of attachment is optionally substituted by R^{32}, the other carbon adjacent to the carbon at the point of attachment is optionally substituted by R^{36}, a carbon adjacent to R^{32} and two atoms from the carbon at the point of attachment is optionally substituted by R^{33}, a carbon adjacent to R^{36} and two atoms from the carbon at the point of attachment is optionally substituted by R^{35}, and any carbon adjacent to both R^{33} and R^{35} is optionally substituted by R^{34};

R^{32}, R^{33}, R^{34}, R^{35}, and R^{36} are independently selected from the group consisting of hydrido, acetamido, haloacetamido, amidino, guanidino, alkoxy, hydroxy, amino, alkoxyamino, lower alkylamino, alkylthio, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, alkyl, halo, haloalkyl, haloalkoxy, hydroxyalkyl, carboalkoxy, carboxy, carboxamido, cyano, and Q^b;

A is selected from the group consisting of single covalent bond and $(CH(R^{15}))_{pa}$—$(W^7)_{rr}$ wherein rr is an integer selected from 0 through 1, pa is an integer selected from 0 through 3, and W^7 is $N(R^7)$;

R^7 is selected from the group consisting of hydrido and alkyl;

R^{15} is selected from the group consisting of hydrido, halo, alkyl, and haloalkyl;

Ψ is NH;

R^1 is selected from the group consisting of hydrido, cyano, haloalkyl, and halo;

R^2 is Z^0—Q;

Z^0 is a covalent single bond;

Q is selected from the group consisting of aryl and heteroaryl wherein a carbon adjacent to the carbon at the point of attachment is optionally substituted by R^9, the other carbon adjacent to the carbon at the point of attachment is optionally substituted by R^{13}, a carbon adjacent to R^9 and two atoms from the carbon at the point of attachment is optionally substituted by R^{10}, a carbon adjacent to R^{13} and two atoms from the carbon at the point of attachment is optionally substituted by R^{12}, and any carbon adjacent to both R^{10} and R^{12} is optionally substituted by R^{11};

R^9, R^{11}, and R^{13} are independently selected from the group consisting of hydrido, hydroxy, amino, amidino, guanidino, lower alkylamino, alkylthio, alkoxy, alkylsulfinyl, alkylsulfonyl, amidosulfonyl, monoalkyl amidosulfonyl, alkyl, halo, haloalkyl, haloalkoxy, hydroxyalkyl, carboxy, carboxamido, and cyano;

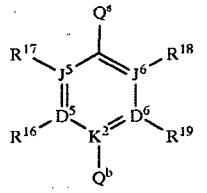
R^{10} and R^{12} are independently selected from the group consistingof hydrido, acetamido, haloacetamido, amidino, guanidino, alkyl, alkoxy, alkoxyamino, aminoalkyl, hydroxy, amino, lower alkylamino, alkylsulfonamido, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, hydroxyalkyl, aminoalkyl, halo, haloalkyl, carboalkoxy, carboxy, carboxyalkyl, carboxyamido, and cyano;

K is CH_2;

E^0 is C(O)N(H);

Y^0 is formula (IV):

(IV)



wherein

D^5,D^6, J^5 and J^6 are independently selected from the group consisting of C, N, O, S and a covalent bond with the provisos that no more than one is a covalent bond, K^2 is C, no more than one of D^5, D^6, J^5 and J^6 is O, no more than one of D^5, D^6, J^5, and J^6 is S, one of D^5, D^6, J^5, and J^6 must be a covalent bond when two of D^5, D^6, J^5 and J^6 are O and S, and no more than four of D^5, D^6, J^5, and J^6 are N;

R^{16}, R^{17}, R^{18}, and R^{19} are independently selected from the group consisting of hydrido, amidino, guanidino, carboxy, haloalkylthio, alkoxy, hydroxy, amino, lower alkylamino, alkylthio, alkylsulfinyl, alkylsulfonyl, alkanoyl, haloalkanoyl, alkyl, halo, haloalkyl, haloalkoxy, hydroxyalkyl, aminoalkyl, and cyano;

R^{16} and R^{19} are optionally Q^b with the proviso that no more than one of R^{16} and R^{19} is Q^b at the same time and that Q^b is Q^{be};

Q^b is selected from the group consisting of $NR^{20}R^{21}$, Q^{be} wherein Q^{be} is hydrido, and $C(NR^{25})NR^{23}R^{24}$;

R^{20}, R^{21}, R^{23}, R^{24}, and R^{25} are independently selected from the group consisting of hydrido and alkyl;

Q^s is CH_2.

In another most preferred embodiment of compounds of Formula I or a pharmaceutically acceptable salt thereof,

J is O;

B is optionally selected from the group consisting of hydrido, C2–C8 alkyl, C3–C8 alkenyl, C3–C8 alkynyl, and C2–C8 haloalkyl, wherein each member of group B is optionally substituted at any carbon up to and including 6 atoms from the point of attachment of B to A with one or more of the group consisting of R^{32}, R^{33}, R^{34}, R^{35}, and R^{36};

R^{32}, R^{33}, R^{34}, R^{35}, and R^{36} are independently selected from the group consisting of hydrido, acetamido, haloacetamido, amidino, guanidino, alkoxy, hydroxy, amino, alkoxyamino, lower alkylamino, alkylthio,

amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, alkyl, halo, haloalkyl, haloalkoxy, hydroxyalkyl, carboalkoxy, carboxy, carboxamido, cyano,and Q^b;

A is selected from the group consisting of single covalent bond and $(CH(R^{15}))_{pa}$—$(W^7)_{rr}$ wherein rr is an integer selected from 0 through 1, pa is an integer selected from 0 through 3, and W^7 is $N(R^7)$;

R^7 is selected from the group consisting of hydrido and alkyl;

R^{15} is selected from the group consisting of hydrido, halo, alkyl, and haloalkyl;

Ψ is NH;

R^1 is selected from the group consisting of hydrido, cyano, haloalkyl, and halo;

R^2 is Z^0—Q;

Z^0 is a covalent single bond;

Q is selected from the group consisting of aryl and heteroaryl wherein a carbon adjacent to the carbon at the point of attachment is optionally substituted by R^9, the other carbon adjacent to the carbon at the point of attachment is optionally substituted by R^{13}, a carbon adjacent to R and two atoms from the carbon at the point of attachment is optionally substituted by R^{10}, a carbon adjacent to R^{13} and two atoms from the carbon at the point of attachment is optionally substituted by R^{12}, and any carbon adjacent to both R^{12} and R^{12} is optionally substituted by R^{11};

R^9, R^{11}, and R^{13} are independently selected from the group consisting of hydrido, hydroxy, amino, amidino, guanidino, lower alkylamino, alkylthio, alkoxy, alkylsulfinyl, alkylsulfonyl, amidosulfonyl, monoalkyl amidosulfonyl, alkyl, halo, haloalkyl, haloalkoxy, hydroxyalkyl, carboxy, carboxamido, and cyano;

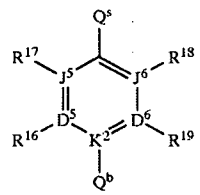
R^{10} and R^{12} are independently selected from the group consisting of hydrido, acetamido, haloacetamido, amidino, guanidino, alkyl, alkoxy, alkoxyamino, aminoalkyl, hydroxy, amino, lower alkylamino, alkylsulfonamido, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, hydroxyalkyl, aminoalkyl, halo, haloalkyl, carboalkoxy, carboxy, carboxyalkyl, carboxyamido, and cyano;

K is CH_2;

E^0 is C(O)N(H);

Y^0 is formula (IV):

(IV)



wherein

D^5, D^6, J^5, and J^6 are independently selected from the group consisting of C, N, O, S and a covalent bond with the provisos that no more than one is a covalent bond, K^2 is C, no more than one of D^5, D^6, J^5, and J^6 is O, no more than one of D^5, D^6, J^5, and J^6 is S, one of D^5, D^6, J^5 and J^6 must be a covalent bond when two of D^5, D^6, J^5, and J^6 are O and S, and no more than four of D^5, D^6, J^5, and J^6 are N, with the provisos that R^{16}, R^{17}, R^{18}, and R^{19} are each independently selected to maintain the tetravalent nature of carbon, trivalent nature of nitrogen, the divalent nature of sulfur, and the divalent nature of oxygen;

R^{16}, R^{17}, R^{18}, and R^{19} are independently selected from the group consisting of hydrido, amidino, guanidino, carboxy, haloalkylthio, alkoxy, hydroxy, amino, lower alkylamino, alkylthio, alkylsulfinyl, alkylsulfonyl, alkanoyl, haloalkanoyl, alkyl, halo, haloalkyl, haloalkoxy, hydroxyalkyl, aminoalkyl, and cyano;

R^{16} and R^{19} are optionally Q^b with the proviso that no more than one of R^{16} and R^{19} is Q^b at the same time and that Q^b is Q^{be};

Q^b is selected from the group consisting of $NR^{20}R^{21}$, Q^{be} wherein Q^{be} is hydrido, $N(R^{26})C(NR^{25})N(R^{23})(R^{24})$, and $C(NR^{25})NR^{23}R^{24}$;

R^{20}, R^{21}, R^{23}, R^{24}, R^{25}, and R^{26} are independently selected from the group consisting of hydrido and alkyl;

Q^s is CH_2.

In still another most preferred embodiment of compounds of Formula I or a pharmaceutically acceptable salt thereof,

J is O;

B is optionally selected from the group consisting of C3–C7 cycloalkyl and C4–C6 saturated heterocyclyl, wherein each ring carbon is optionally substituted with R^{33}, a ring carbon other than the ring carbon at the point of attachment of B to A is optionally substituted with oxo provided that no more than one ring carbon is substituted by oxo at the same time, ring carbon and nitrogen atoms adjacent to the carbon atom at the point of attachment is optionally substituted with R^9 or R^{13}, a ring carbon or nitrogen atom adjacent to the R^9 position and two atoms from the point of attachment is optionally substituted with R^{10}, a ring carbon or nitrogen atom adjacent to the R^{13} position and two atoms from the point of attachment is optionally substituted with R^{12}, a ring carbon or nitrogen atom three atoms from the point of attachment and adjacent to the R^{10} position is optionally substituted with R^{11}, a ring carbon or nitrogen atom three atoms from the point of attachment and adjacent to the R^{12} position is optionally substituted with R^{33}, and a ring carbon or nitrogen atom four atoms from the point of attachment and adjacent to the R^{11} and R^{33} positions is optionally substituted with R^{34};

R^9, R^{11}, and R^{13} are independently selected from the group consisting of hydrido, hydroxy, amino, amidino, guanidino, lower alkylamino, alkylthio, alkoxy, alkylsulfinyl, alkylsulfonyl, amidosulfonyl, monoalkyl amidosulfonyl, alkyl, halo, haloalkyl, haloalkoxy, hydroxyalkyl, carboxy, carboxamido, and cyano;

R^{10} and R^{12} are independently selected from the group consisting of hydrido, acetamido, haloacetamido, amidino, guanidino, alkyl, alkoxy, alkoxyamino, aminoalkyl, hydroxy, amino, lower alkylamino, alkylsulfonamido, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, hydroxyalkyl, aminoalkyl, halo, haloalkyl, carboalkoxy, carboxy, carboxyalkyl, carboxyamido, and cyano;

R^{33} and R^{34} are independently selected from the group consisting of hydrido, amidino, guanidino, alkoxy, hydroxy, amino, alkoxyamino, lower alkylamino, alkylthio, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, alkyl, halo, haloalkyl,

haloalkoxy, hydroxyalkyl, carboalkoxy, carboxy, carboxamido, and cyano;

R^{33} is optionally Q^b;

A is selected from the group consisting of single covalent bond and $(CH(R^{15}))_{pa}$—$(W^7)_{rr}$ wherein rr is an integer selected from 0 through 1, pa is an integer selected from 0 through 3, and W^7 is $N(R^7)$;

R^7 is selected from the group consisting of hydrido, hydroxy and alkyl;

R^{15} is selected from the group consisting of hydrido, halo, alkyl, and haloalkyl;

Ψ is NH;

R^1 is selected from the group consisting of hydrido, cyano, haloalkyl, and halo;

R^2 is Z^0—Q;

Z^0 is a covalent single bond;

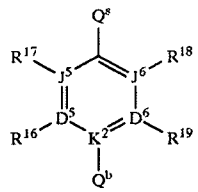
Q is selected from the group consisting of aryl and heteroaryl wherein a carbon adjacent to the carbon at the point of attachment is optionally substituted by R^9, the other carbon adjacent to the carbon at the point of attachment is optionally substituted by R^{13}, a carbon adjacent to R^9 and two atoms from the carbon at the point of attachment is optionally substituted by R^{10}, a carbon adjacent to R^{13} and two atoms from the carbon at the point of attachment is optionally substituted by R^{12}, and any carbon adjacent to both R^{10} and R^{12} is optionally substituted by R^{11};

K is CH_2;

E^0 is C(O)N(H);

Y^0 is formula (IV):

(IV)



wherein

D^5, D^6, J^5, and J^6 are independently selected from the group consisting of C, N, O, S and a covalent bond with the provisos that no more than one is a covalent bond, K^2 is C, no more than one of D^5, D^6, J^5, and J^6 is O, no more than one of D^5, D^6, J^5, and J^6 is S, one of D^5, D^6, J^5, and J^6 must be a covalent bond when two of D^5, D^6, J^5, and J^6 are O and S, and no more than four of D^5, D^6, J^5, and J^6 are N. with the provisos that R^{16}, R^{17}, R^{18}, and R^{19} are each independently selected to maintain the tetravalent nature of carbon, trivalent nature of nitrogen, the divalent nature of sulfur, and the divalent nature of oxygen;

R^{16}, R^{17}, R^{18}, and R^{19} are independently selected from the group consisting of hydrido, amidino, guanidino, carboxy, haloalkylthio, alkoxy, hydroxy, amino, lower alkylamino, alkylthio, alkylsulfinyl, alkylsulfonyl, alkanoyl, haloalkanoyl, alkyl, halo, haloalkyl, haloalkoxy, hydroxyalkyl, alkylenylamino, and cyano;

R^{16} and R^{19} are optionally Q^b with the proviso that no more than one of R^{16} and R^{19} is Q^b at the same time and that Q^b is Q^{be};

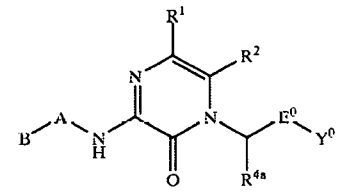
Q^b is selected from the group consisting of $NR^{20}R^{21}$, Q^{be} wherein Q^{be} is hydrido, and $C(NR^{25})NR^{23}R^{24}$;

R^{20}, R^{21}, R^{23}, R^{24}, and R^{25} are independently selected from the group consisting of hydrido and alkyl;

Q^s is CH_2.

In a preferred specific embodiment of Formula I, compounds have the Formula I-S:

(I-S)



or a pharmaceutically acceptable salt thereof, wherein;

B is selected from the group consisting of phenyl, 2-thienyl, 3-thienyl, 2-furyl, 3-furyl, 2-pyrrolyl, 3-pyrrolyl, 2-imidazolyl, 4-imidazolyl, 3-pyrazolyl, 4-pyrazolyl, 1,2,4-triazol-3-yl, 1,2,4-triazol-5-yl, 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl, 1,3,4-oxadiazol-3-yl, 1,3,4-oxadiazol-5-yl, 3-isothiazolyl, 5-isothiazolyl, 2-oxazolyl, 2-thiazolyl, 3-isoxazolyl, 5-isoxazolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrazinyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 3-pyridazinyl, 4-pyridazinyl, 1,3,5-triazin-2-yl, 1,2,4-triazin-3-yl, 1,2,4-triazin-5-yl, 1,2,4-triazin-6-yl, 1,2,3-triazin-4-yl, and 1,2,3-triazin-5-yl,, wherein a carbon adjacent to the carbon at the point of attachment is optionally substituted by R^{32}, the other carbon adjacent to the carbon at the point of attachment is optionally substituted by R^{36}, a carbon adjacent to R^{32} and two atoms from the carbon at the point of attachment is optionally substituted by R^{33}, a carbon adjacent to R^{36} and two atoms from the carbon at the point of attachment is optionally substituted by R^{35}, and any carbon adjacent to both R^{33} and R^{35} is optionally substituted by R^{34};

R^{32}, R^{33}, R^{34}, R^{35}, and R^{36} are independently selected from the group consisting of hydrido, amidino, guanidino, carboxy, methyl, ethyl, isopropyl, propyl, methoxy, ethoxy, isopropoxy, propoxy, hydroxy, amino, methoxyamino, ethoxyamino, acetamido, trifluoroacetamido, nitro, aminomethyl, 1-aminoethyl, 2-aminoethyl, N-methylamino, dimethylamino, N-ethylamino, methylthio, ethylthio, isopropylthio, trifluoromethylthio, trifluoromethyl, pentafluoroethyl, 2,2,2-trifluoroethyl, 2,2,3,3,3-pentafluoropropyl, trifluoromethoxy, 1,1,2,2-tetrafluoroethoxy, fluoro, chloro, bromo, amidosulfonyl, N-methylamidosulfonyl, N,N-dimethylamidosulfonyl, acetyl, propanoyl, trifluoroacetyl, pentafluoropropanoyl, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 2,2,2-trifluoro-1-hydroxyethyl, 2,2,2-trifluoro-1-trifluoromethyl-1-hydroxyethyl, carboxymethyl, methoxycarbonyl, ethoxycarbonyl, amidocarbonyl, N-methylamidocarbonyl, N,N-dimethylamidocarbonyl, cyano, and Q^b;

B is selected from the group consisting of hydrido, trimethylsilyl, ethyl, 2-propenyl, 2-propynyl, propyl, isopropyl, butyl, 2-butenyl, 3-butenyl, 2-butynyl, sec-butyl, tert-butyl, isobutyl, 2-methylpropenyl, 1-pentyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 2-pentynyl, 3-pentynyl, 2-pentyl, 1-methyl-2-butenyl, 1-methyl-3-butenyl, 1-methyl-2-butynyl, 3-pentyl, 1-ethyl-2-

propenyl, 2-methylbutyl, 2-methyl-2-butenyl, 2-methyl-3-butenyl, 2-methyl-3-butynyl, 3-methylbutyl, 3-methyl-2-butenyl, 3-methyl-3-butenyl, 1-hexyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, 2-hexyl, 1-methyl-2-pentenyl, 1-methyl-3-pentenyl, 1-methyl-4-pentenyl, 1-methyl-2-pentynyl, 1-methyl-3-pentynyl, 3-hexyl, 1-ethyl-2-butenyl, 1-ethyl-3-butenyl, 1-propyl-2-propenyl, 1-ethyl-2-butynyl, 1-heptyl, 2-heptenyl, 3-heptenyl, 4-heptenyl, 5-heptenyl, 6-heptenyl, 2-heptynyl, 3-heptynyl, 4-heptynyl, 5-heptynyl, 2-heptyl, 1-methyl-2-hexenyl, 1-methyl-3-hexenyl, 1-methy-4-hexenyl, 1-methyl-5-hexenyl, 1-methyl-2-hexynyl, 1-methyl-3-hexynyl, 1-methyl-4-hexynyl, 3-heptyl, 1-ethyl-2-pentonyl, 1-ethyl-3-pentenyl, 1-ethyl-4-pentenyl, 1-butyl-2-propenyl, 1-ethyl-2-pentynyl, 1-ethyl-3-pentynyl, 1-octyl, 2-octenyl, 3-octenyl, 4-octenyl, 5-octenyl, 6-octenyl, 7-octenyl, 2-octynyl, 3-octynyl, 4-octynyl, 5-octynyl, 6-octynyl, 2-octyl, 1-methyl-2-heptenyl, 1-methyl-3-heptenyl, 1-methyl-4-heptenyl, 1-methyl-5-heptenyl, 1-methyl-6-heptenyl, 1-methyl-2-heptynyl, 1-methyl-3-heptynyl, 1-methyl-4-heptenyl, 1-methyl-5-heptenyl, 1-methyl-6-heptenyl, 1-methyl-2-heptenyl, 1-methyl-3-heptynyl, 1-methyl-4-heptynyl, 1-methyl-5-heptynyl, 3-octyl, 1-ethyl-2-hexenyl, 1-ethyl-3-hexenyl, 1-ethyl-4-hexenyl, 1-ethyl-2-hexynyl, 1-ethyl-3-hexynyl, 1-ethyl-4-hexynyl, 1-ethyl-5-hexenyl, 1-pentyl-2-propenyl, 4-octyl, 1-propyl-2-pentenyl, 1-propyl-3-pentenyl, 1-propyl-4-pentenyl, 1-butyl-2-butenyl, 1-propyl-2-pentynyl, 1-propyl-3-pentynyl, 1-butyl-2-butynyl, 1-butyl-3-butenyl, 2,2,2-trifluoroethyl, 2,2-difluoropropyl, 4-trifluoromethyl-5,5,5-trifluoropentyl, 4-trifluoromethylpentyl, 5,5,6,6,6-pentafluorohexyl, and 3,3,3-trifluoropropyl, wherein each member of group B is optionally substituted at any carbon up to and including 5 atoms from the point of attachment of B to A with one or more of the group consisting of R^{32}, R^{33}, R^{34}, R^{35}, and R^{36};

B is optionally selected from the group consisting of cyclopropyl, cyclobutyl, oxetan-2-yl, oxetan-3-yl, azetidin-1-yl, azetidin-2-yl, azetidin-3-yl, thiaetan-2-yl, thiaetan-3-yl, cyclopentyl, cyclohexyl, adamantyl, norbornyl, 3-trifluoromethylnorbornyl, 7-oxabicyclo[2.2.1]heptan-2-yl, bicyclo[3.1.0]hexan-6-yl, cycloheptyl, cyclooctyl, 2-morpholinyl, 3-morpholinyl, 4-morpholinyl, 1-piperazinyl, 2-piperazinyl, 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-piperidinyl, 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 2-dioxanyl, 4H-2-pyranyl, 4H-3-pyranyl, 4H-4-pyranyl, 4H-pyran-4-one-2-yl, 4H-pyran-4-one-3-yl, 2-tetrahydrofuranyl, 3-tetrahydrofuranyl, 2-tetrahydropyranyl, 3-tetrahydropyranyl, 4-tetrahydropyranyl, 2-tetrahydrothienyl, and 3-tetrahydrothienyl, wherein each ring carbon is optionally substituted with R^{33}, a ring carbon and nitrogen atoms adjacent to the carbon atom at the point of attachment is optionally substituted with R^9 or R^{13}, a ring carbon or nitrogen atom adjacent to the R^9 position and two atoms from the point of attachment is optionally substituted with R^{10}, and a ring carbon or nitrogen atom adjacent to the R^{13} position and two atoms from the point of attachment is optionally substituted with R^{12};

R^9, R^{10}, R^{11}, R^{12}, and R^{13} are independently selected from the group consisting of hydrido, amidino, guanidino, carboxy, carboxymethyl, methyl, ethyl, isopropyl, propyl, methoxy, ethoxy, isopropoxy, propoxy, hydroxy, amino, methoxyamino, ethoxyamino, acetamido, trifluoroacetamido, nitro, aminomethyl, 1-aminoethyl, 2-aminoethyl, N-methylamino, dimethylamino, N-ethylamino, methylthio, ethylthio, isopropylthio, trifluoromethylthio, trifluoromethyl, pentafluoroethyl, 2,2,2-trifluoroethyl, 2,2,3,3,3-pentafluoropropyl, trifluoromethoxy, 1,1,2,2-tetrafluoroethoxy, fluoro, chloro, bromo, methanesulfonamido, amidosulfonyl, N-methylamidosulfonyl, N,N-dimethylamidosulfonyl, acetyl, propanoyl, trifluoroacetyl, pentafluoropropanoyl, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 2,2,2-trifluoro-1-hydroxyethyl, 2,2,2-trifluoro-1-trifluoromethyl-1-hydroxyethyl, carboxymethyl, methoxycarbonyl, ethoxycarbonyl, amidocarbonyl, N-methylamidocarbonyl, N,N-dimethylamidocarbonyl, and cyano;

A is selected from the group consisting of single covalent bond, O, S, NH, $N(CH_3)$, N(OH), C(O), CH_2, CH_3CH, CF_3CH, NHC(O), $N(CH_3)C(O)$, C(O)NH, C(O)N(CH_3), $CF_3CC(O)$, $C(O)CCH_3$, $C(O)CCF_3$, $CH_2C(O)$, $(O)CCH_2$, CH_2CH_2, $CH_2CH_2CH_2$, CH_3CHCH_2, CF_3CHCH_2, $CH_3CC(O)CH_2$, $CF_3CC(O)CH_2$, $CH_2C(O)CCH_3$, $CH_2C(O)CCF_3$, $CH_2CH_2C(O)$, and $CH_2(O)CCH_2$;

A is optionally selected from the group consisting of $CH_2N(CH_3)$, $CH_2N(CH_2CH_3)$, $CH_2CH_2N(CH_3)$, and $CH_2CH_2N(CH_2CH_3)$ with the proviso that B is hydrido;

R^1 is selected from the group consisting of hydrido, cyano, methyl, ethyl, propyl, trifluoromethyl, pentafluoroethyl, 2,2,2-trifluoroethyl, 2,2,3,3,3-pentafluoropropyl, trifluoromethoxy, 1,1,2,2-tetrafluoroethoxy, fluoro, chloro, and bromo;

R^2 is Z^0—Q;

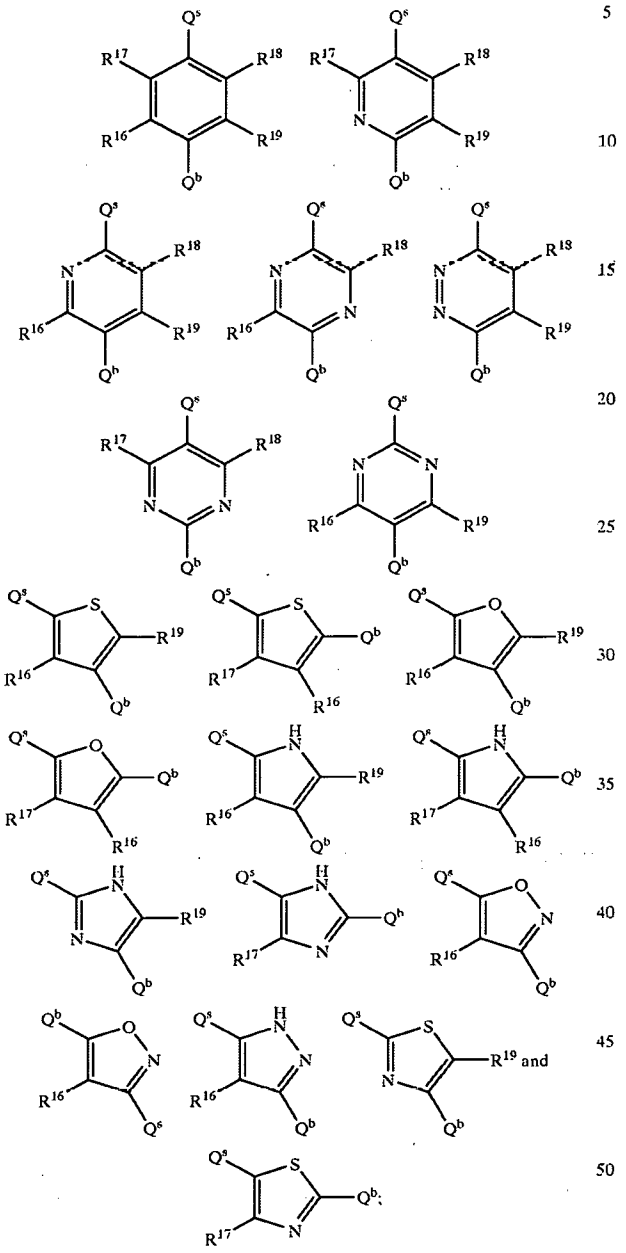
Z^0 is selected from the group consisting of covalent single bond, CH_2, CH_2CH_2, CH(OH), $CH(NH_2)$, $CH_2CH(OH)$, CH_2CHNH_2, $CH(OH)CH_2$, and $CH(NH_2)CH_2$;

Q is selected from the group consisting of phenyl, 2-thienyl, 3-thienyl, 2-furyl, 3-furyl, 2-pyrrolyl, 3-pyrrolyl, 2-imidazolyl, 4-imidazolyl, 3-pyrazolyl, 4-pyrazolyl, 1,2,4-triazol-3-yl, 1,2,4-triazol-5-yl, 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl, 1,3,4-oxadiazol-3-yl, 1,3,4-oxadiazol-5-yl, 3-isothiazolyl, 5-isothiazolyl, 2-oxazolyl, 2-thiazolyl, 3-isoxazolyl, 5-isoxazolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrazinyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 3-pyridazinyl, 4-pyridazinyl, 1,3,5-triazin-2-yl, 1,2,4-triazin-3-yl, 1,2,4-triazin-5-yl, 1,2,4-triazin-6-yl, 1,2,3-triazin-4-yl, and 1,2,3-triazin-5-yl, wherein a carbon adjacent to the carbon at the point of attachment is optionally substituted by R^9, the other carbon adjacent to the carbon at the point of attachment is optionally substituted by R^{13}, a carbon adjacent to R^9 and two atoms from the carbon at the point of attachment is optionally substituted by R^{10}, a carbon adjacent to R^{13} and two atoms from the carbon at the point of attachment is optionally substituted by R^{12}, and any carbon adjacent to both R^{10} and R^{12} is optionally substituted by R^{11};

K is CHR^{4a} wherein R^{4a} is selected from the group consisting of methyl, ethyl, propyl, isopropyl, hydroxymethyl, 1-hydroxyethyl, methoxymethyl, trifluoromethyl, pentafluoroethyl, 2,2,2-trifluoromethyl, methylthiomethyl, and hydrido;

E^0 is a covalent single bond, C(O)N(H), (H)NC(O), and $S(O)_2N(H)$;

Y^0 is selected from the group of formulas consisting of:



R^{16}, R^{17}, R^{18}, and R^{19} are independently selected from the group consisting of hydrido, methyl, ethyl, isopropyl, propyl, amidino, guanidino, carboxy, methoxy, ethoxy, isopropoxy, propoxy, hydroxy, amino, methoxyamino, ethoxyamino, aminomethyl, 1-aminoethyl, 2-aminoethyl, N-N-methylamino, dimethylamino, N-ethylamnino, methylthio, ethylthio, isopropylthio, trifluoromethylthio, methylsulfinyl, ethylsulfinyl, methylsulfonyl, ethylsulfonyl, trifluoromethyl, pentafluoroethyl, 2,2,2-trifluoroethyl, 2,2,3,3,3-pentafluoropropyl, trifluoromethoxy, 1,1,2,2-tetrafluoroethoxy, fluoro, chloro, bromo, amidosulfonyl, N-methylamidosulfonyl, N,N-dimethylamidosulfonyl, acetyl, propanoyl, trifluoroacetyl, pentafluoropropanoyl, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 2,2,2-trifluoro-1-hydroxyethyl, and cyano;

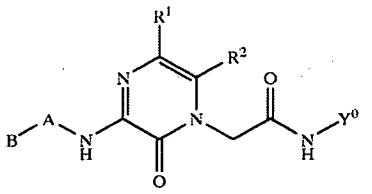
R^{16} and R^{19} are optionally Q^b with the proviso that no more than one of R^{16} and R^{19} is Q^b at the same time and that Q^b is Q^{be};

Q^b is selected from the group consisting of $NR^{20}R^{21}$, Q^{be} wherein Q^{be} is hydrido, $C(NR^{25})NR^{23}R^{24}$ and $N(R^{26})C(NR^{25})N(R^{23})(R^{24})$, with the proviso that no more than one of R^{20} and R^{21} is hydroxy, N-methylamino, and N,N-dimethylamino at the same time and that no more than one of R^{23} and R^{24} is hydroxy, N-methylamino, and N,N-dimethylamino at the same time;

R^{20}, R^{21}, R^{23}, R^{24}, R^{25}, and R^{26} are independently selected from the group consisting of hydrido, methyl, ethyl, propyl, butyl, isopropyl, hydroxy, 2-aminoethyl, 2-(N-methylamino)ethyl, and 2-(N,N-dimethylamino)ethyl;

Q^s is selected from the group consisting of a single covalent bond, CH_2, CH_2CH_2, CH_3CH, CF_3CH, CH_3CHCH_2, CF_3CHCH_2, $CH_2(CH_3)CH$, CH=CH, CF=CH, $C(CH_3)$=CH, CH=$CHCH_2$, CF=$CHCH_2$, $C(CH_3)$=$CHCH_2$, CH_2CH=CH, CH_2CF=CH, $CH_2C(CH_3)$=CH, CH_2CH=$CHCH_2$, CH_2CF=$CHCH_2$, $CH_2C(CH_3)$=$CHCH_2$, CH_2CH=$CHCH_2CH_2$, CH_2CF=$CHCH_2CH_2$, and $CH_2C(CH_3)$=$CHCH_2CH_2$.

In a more preferred specific embodiment of Formula I, compounds have the Formula I-MPS wherein B is an aromatic:



(I-MPS wherein B is aromatic)

or a pharmaceutically acceptable salt thereof, wherein;

B is selected from the group consisting of phenyl, 2-thienyl, 3-thienyl, 2-furyl, 3-furyl, 2-pyrrolyl, 3-pyrrolyl, 2-imidazolyl, 4-imidazolyl, 3-pyrazolyl, 4-pyrazolyl, 2-thiazolyl, 3-isoxazolyl, 5-isoxazolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrazinyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 3-pyridazinyl, 4-pyridazinyl, and 1,3,5-triazin-2-yl, wherein a carbon adjacent to the carbon at the point of attachment is optionally substituted by R^{32}, the other carbon adjacent to the carbon at the point of attachment is optionally substituted by R^{36}, a carbon adjacent to R^{32} and two atoms from the carbon at the point of attachment is optionally substituted by R^{33}, a carbon adjacent to R^{36} and two atoms from the carbon at the point of attachment is optionally substituted by R^{35}, and any carbon adjacent to both R^{33} and R^{35} is optionally substituted by R^{34};

R^{32}, R^{33}, R^{34}, R^{35}, and R^{36} are independently selected from the group consisting of hydrido, amidino, guanidino, carboxy, methoxy, ethoxy, isopropoxy, propoxy, hydroxy, amino, methoxyamino,

ethoxyamino, acetamido, trifluoroacetamido, N-methylamino, dimethylamino, N-ethylamino, methylthio, ethylthio, isopropylthio, trifluoromethyl, pentafluoroethyl, 2,2,2-trifluoroethyl, 2,2,3,3,3-pentafluoropropyl, trifluoromethoxy, 1,1,2,2-tetrafluoroethoxy, fluoro, chloro, bromo, amidosulfonyl, N-methylamidosulfonyl, N,N-dimethylamidosulfonyl, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 2,2,2-trifluoro-1-hydroxyethyl, methoxycarbonyl, ethoxycarbonyl, amidocarbonyl, N-methylamidocarbonyl, N,N-dimethylamidocarbonyl, cyano, and Q^b;

A is selected from the group consisting of single covalent bond, NH, $N(CH_3)$, N(OH), CH_2, CH_3CH, CF_3CH, NHC(O), $N(CH_3)C(O)$, C(O)NH, $C(O)N(CH_3)$, CH_2CH_2, $CH_2CH_2CH_2$, CH_3CHCH_2, and CF_3CHCH_2;

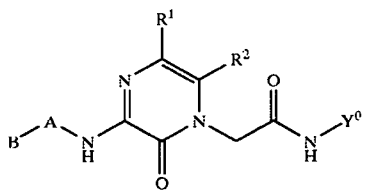
Q^b is selected from the group consisting of $NR^{20}R^{21}$, Q^{be} wherein Q^{be} is hydrido, and $C(NR^{25})NR^{23}R^{24}$, with the provisos that no more than one of R^{20} and R^{21} is hydroxy at the same time and that no more than one of R^{23} and R^{24} is hydroxy at the same time;

R^{20}, R^{21}, R^{23}, R^{24}, and R^{25} are independently selected from the group consisting of hydrido, methyl, ethyl, propyl, butyl, isopropyl, and hydroxy;

Q^s is selected from the group consisting of a single covalent bond, CH_2, and CH_2CH_2.

In another more preferred specific embodiment of Formula I, compounds have the Formula I-MPS wherein B is a non-cyclic substituent:

(I-MPS



wherein B is a non-cyclic substituent)

or a pharmaceutically acceptable salt thereof, wherein;

B is selected from the group consisting of hydrido, ethyl, 2-propenyl, 2-propynyl, propyl, isopropyl, butyl, 2-butenyl, 3-butenyl, 2-butynyl, sec-butyl, tert-butyl, isobutyl, 2-methylpropenyl, 1-pentyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 2-pentynyl, 3-pentynyl, 2-pentyl, 1-methyl-2-butenyl, 1-methyl-3-butenyl, 1-methyl-2-butynyl, 3-pentyl, 1-ethyl-2-propenyl, 2-methylbutyl, 2-methyl-2-butenyl, 2-methyl-3-butenyl, 2-methyl-3-butynyl, 3-methylbutyl, 3-methyl-2-butenyl, 3-methyl-3-butenyl, 1-hexyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, 2-hexyl, 1-methyl-2-pentenyl, 1-methyl-3-pentenyl, 1-methyl-4-pentenyl, 1-methyl-2-pentynyl, 1-methyl-3-pentynyl, 3-hexyl, 1-ethyl-2-butenyl, 1-ethyl-3-butenyl, 1-propyl-2-propenyl, 1-ethyl-2-butynyl, 1-heptyl, 2-heptenyl, 3-heptenyl, 4-heptenyl, 5-heptenyl, 6-heptenyl, 2-heptynyl, 3-heptynyl, 4-heptynyl, 5-heptynyl, 2-heptyl, 1-methyl-2-hexenyl, 1-methyl-3-hexenyl, 1-methyl-4-hexenyl, 1-methyl-5-hexenyl, 1-methyl-2-hexynyl, 1-methyl-3-hexynyl, 1-methyl-4-hexynyl, 3-heptyl, 1-ethyl-2-pentenyl, 1-ethyl-3-pentenyl, 1-ethyl-4-pentenyl, 1-butyl-2-propenyl, 1-ethyl-2-pentynyl, 1-ethyl-3-pentynyl, 2,2,2-trifluoroethyl, 2,2-difluoropropyl, 4-trifluoromethyl-5,5,5-trifluoropentyl, 4-trifluoromethylpentyl, 5,5,6,6,6-pentafluorohexyl, and 3,3,3-trifluoropropyl, wherein each member of group B is optionally substituted at any carbon up to and including 5 atoms from the point of attachment of B to A with one or more of the group consisting of R^{32}, R^{33}, R^{34}, and R^{36};

R^{32}, R^{33}, R^{34}, R^{35}, and R^{36} are independently selected from the group consisting of hydrido, amidino, guanidino, carboxy, methoxy, ethoxy, isopropoxy, propoxy, hydroxy, amino, methoxyamino, ethoxyamino, acetamido, trifluoroacetamido, N-methylamino, dimethylamino, N-ethylamino, methylthio, ethylthio, isopropylthio, trifluoromethyl, pentafluoroethyl, 2,2,2-trifluoroethyl, 2,2,3,3,3-pentafluoropropyl, trifluoromethoxy, 1,1,2,2-tetrafluoroethoxy, fluoro, chloro, bromo, amidosulfonyl, N-methylamidosulfonyl, N,N-dimethylamidosulfonyl, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 2,2,2-trifluoro-1-hydroxyethyl, methoxycarbonyl, ethoxycarbonyl, amidocarbonyl, N-methylamidocarbonyl, N,N-dimethylamidocarbonyl, cyano, and Q^b;

A is selected from the group consisting of single covalent bond, NH, $N(CH_3)$, N(OH), CH_2, CH_3CH, CF_3CH, NHC(O), $N(CH_3)C(O)$, C(O)NH, $C(O)N(CH_3)$, CH_2CH_2, $CH_2CH_2CH_2$, CH_3CHCH_2, and CF_3CHCH_2;

A is optionally selected from the group consisting of $CH_2N(CH_3)$, $CH_2N(CH_2CH_3)$, $CH_2CH_2N(CH_3)$, and $CH_2CH_2N(CH_2CH_3)$ with the proviso that B is hydrido;

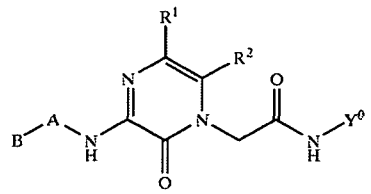
Q^b is selected from the group consisting of $NR^{20}R^{21}$, Q^{be}, wherein Q^{be} is hydrido, $C(NR^{25})N^{23}R^{24}$, and $N(R^{26})C(NR^{25})N(R^{23})(R^{24})$, with the provisos that no more than one of R^{20} and R^{21} is hydroxy at the same time and that no more than one of R^{23} and R^{24} is hydroxy at the same time;

R^{20}, R^{21}, R^{23}, R^{24}, R^{25}, and R^{26} are independently selected from the group consisting of hydrido, methyl, ethyl, propyl, butyl, isopropyl, and hydroxy;

Q^s is selected from the group consisting of a single covalent bond, CH_2, and CH_2CH_2.

In still another more preferred specific embodiment of Formula I, compounds have the Formula I-MPS wherein B is a non-aromatic cyclic substituent:

(I-MPS



wherein B is a non-aromatic cyclic substituent)

or a pharmaceutically acceptable salt thereof, wherein;

B is optionally selected from the group consisting of cyclopropyl, cyclobutyl, oxetan-3-yl, azetidin-1-yl, azetidin-2-yl, azetidin-3-yl, thiaetan-3-yl, cyclopentyl, cyclohexyl, norbornyl, 7-oxabicyclo[2.2.1]heptan-2-yl, bicyclo[3.1.0]hexan-6-yl, cycloheptyl, 2-morpholinyl, 3-morpholinyl, 4-morpholinyl, 1-piperazinyl, 2-piperazinyl, 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-piperidinyl, 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 2-dioxanyl, 4H-2-

pyranyl, 4H-3-pyranyl, 4H-4-pyranyl, 4H-pyran-4-one-2-yl, 4H-pyran-4-one-3-yl, 2-tetrahydrofuranyl, 3-tetrahydrofuranyl, 2-tetrahydropyranyl, 3-tetrahydropyranyl, 4-tetrahydropyranyl, 2-tetrahydrothienyl, and 3-tetrahydrothienyl, wherein each ring carbon is optionally substituted with R^{33}, a ring carbon and nitrogen atoms adjacent to the carbon atom at the point of attachment is optionally substituted with R^9 or R^{13}, a ring carbon or nitrogen atom adjacent to the R^9 position and two atoms from the point of attachment is optionally substituted with R^{10}, and a ring carbon or nitrogen atom adjacent to the R^{13} position and two atoms from the point of attachment is optionally substituted with R^{12};

A is selected from the group consisting of single covalent bond, NH, $N(CH_3)$, N(OH), CH_2, CH_3CH, CF_3CH, NHC(O), $N(CH_3)C(O)$, C(O)NH, $C(O)N(CH_3)$, CH_2CH_2, $CH_2CH_2CH_2$, CH_3CHCH_2, and CF_3CHCH_2;

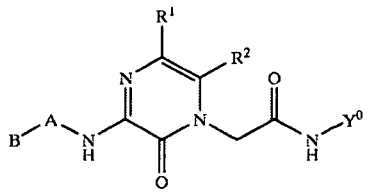
R^{33} and R^{34} are independently selected from the group consisting of hydrido, amidino, guanidino, carboxy, methoxy, ethoxy, isopropoxy, propoxy, hydroxy, amino, methoxyamino, ethoxyamino, acetamido, trifluoroacetamido, N-methylamino, dimethylamino, N-ethylamino, methylthio, ethylthio, isopropylthio, trifluoromethyl, pentafluoroethyl, 2,2,2-trifluoroethyl, 2,2,3,3,3-pentafluoropropyl, trifluoromethoxy, 1,1,2,2-tetrafluoroethoxy, fluoro, chloro, bromo, amnidosulfonyl, N-methylamidosulfonyl, N,N-dimethylamidosulfonyl, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 2,2,2-trifluoro-1-hydroxyethyl, methoxycarbonyl, ethoxycarbonyl, amidocarbonyl, N-methylamidocarbonyl, N,N-dimethylamidocarbonyl, cyano, and Q^b;

Q^b is selected from the group consisting of $NR^{20}R^{21}$, Q^{be} wherein Q is hydrido, and $C(NR^{25})NR^{23}R^{24}$, with the provisos that no more than one of R^{20} and R^{21} is hydroxy at the same time and that no more than one of R^{23} and R^{24} is hydroxy at the same time;

R^{20}, R^{21}, R^{23}, R^{24}, and R^{25} are independently selected from the group consisting of hydrido, methyl, ethyl, propyl, butyl, isopropyl, and hydroxy;

Q^e is selected from the group consisting of a single covalent bond, CH_2, and CH_2CH_2.

The more preferred specific embodiment (I-MPS) compounds of the present invention having the Formula:



or a pharmaceutically acceptable salt thereof, have common structural units, wherein;

R^1 is selected from the group consisting of hydrido, methyl, ethyl, propyl, trifluoromethyl, pentafluoroethyl, 2,2,2-trifluoroethyl, 2,2,3,3,3-pentafluoropropyl, fluoro, chloro, and bromo;

R^2 is Z^0—Q;

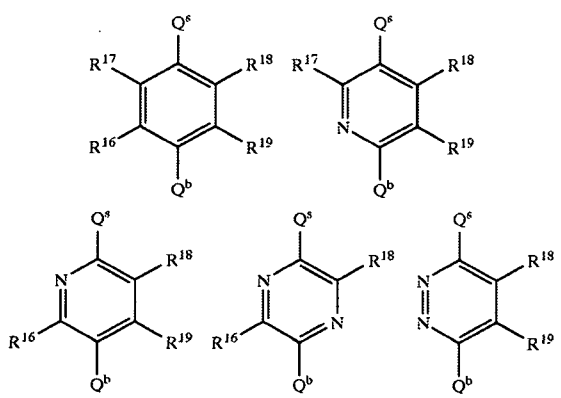
Z^0 is selected from the group consisting of covalent single bond and CH_2;

Q is selected from the group consisting of phenyl, 2-thienyl, 3-thienyl, 2-furyl, 3-furyl, 2-pyrrolyl, 3-pyrrolyl, 2-imidazolyl, 4-imidazolyl, 3-pyrazolyl, 4-pyrazolyl, 2-thiazolyl, 3-isoxazolyl, 5-isoxazolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrazinyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 3-pyridazinyl, 4-pyridazinyl, and 1,3,5-triazin-2-yl, wherein a carbon adjacent to the carbon at the point of attachment is optionally substituted by R^9, the other carbon adjacent to the carbon at the point of attachment is optionally substituted by R^{13}, a carbon adjacent to R^9 and two atoms from the carbon at the point of attachment is optionally substituted by R^{10}, a carbon adjacent to R^{13} and two atoms from the carbon at the point of attachment is optionally substituted by R^{12}, and any carbon adjacent to both R^{10} and R^{12} is optionally substituted by R^{11};

R^9, R^{11}, and R^{13} are independently selected from the group consisting of hydrido, amidino, guanidino, carboxy, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, isopropoxy, propoxy, hydroxy, amino, N-methylamino, N,N-dimethylamino, N-ethylamino, methylthio, ethylthio, isopropylthio, trifluoromethyl, pentafluoroethyl, 2,2,2-trifluoroethyl, 2,2,3,3,3-pentafluoropropyl, trifluoromethoxy, 1,1,2,2-tetrafluoroethoxy, fluoro, chloro, bromo, methanesulfonamido, amidosulfonyl, N-methylamidosulfonyl, N,N-dimethylamidosulfonyl, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 2,2,2-trifluoro-1-hydroxyethyl, amidocarbonyl, N-methylamidocarbonyl, N,N-dimethylamidocarbonyl, and cyano;

R^{10} and R^{12} are independently selected from the group consisting of hydrido, amidino, guanidino, carboxy, carboxymethyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, isopropoxy, propoxy, hydroxy, amino, methoxyamino, ethoxyamino, acetamido, trifluoroacetamido, aminomethyl, 1-aminoethyl, 2-aminoethyl, N-methylamino, dimethylamino, N-ethylamino, methanesulfonamido, amidosulfonyl, N-methylamidosulfonyl, N,N-dimethylamidosulfonyl, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 2,2,2-trifluoro-1-hydroxyethyl, methoxycarbonyl, ethoxycarbonyl, amidocarbonyl, N-methylamidocarbonyl, N,N-dimethylamidocarbonyl, fluoro, chloro, bromo, and cyano;

Y^0 is selected from the group of formulas consisting of:



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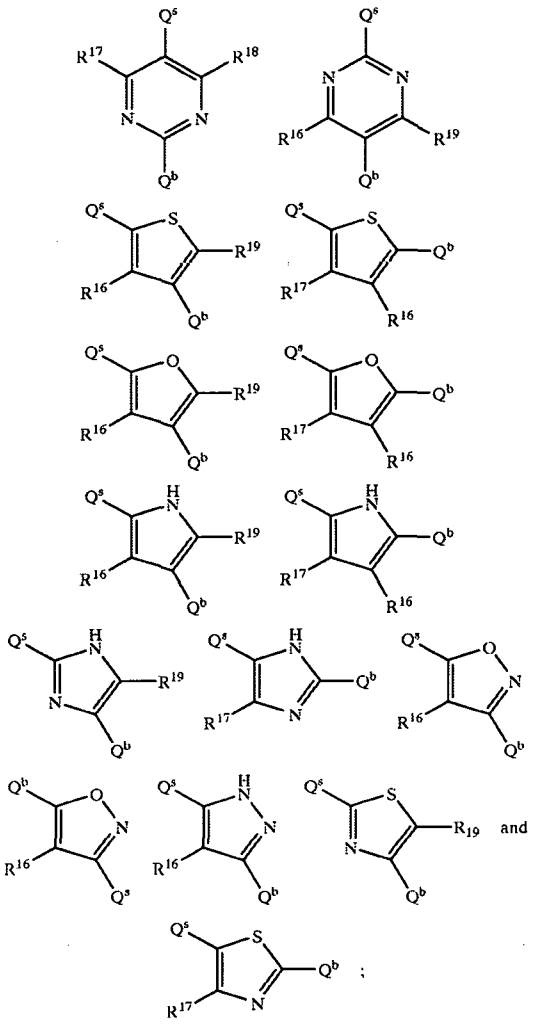
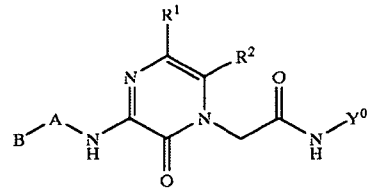


R^{16}, R^{17}, R^{18}, and R^{19} are independently selected from the group consisting of hydrido, methyl, ethyl, isopropyl, propyl, carboxy, amidino, guanidino, methoxy, ethoxy, isopropoxy, propoxy, hydroxy, amino, aminomethyl, 1-aminoethyl, 2-aminoethyl, N-methylamino, dimethylamino, N-ethylamino, methylthio, ethylthio, isopropylthio, trifluoromethylthio, methylsulfinyl, ethylsulfinyl, methylsulfonyl, ethylsulfonyl, trifluoromethyl, pentafluoroethyl, 2,2,2-trifluoroethyl, 2,2,3,3,3-pentafluoropropyl, trifluoromethoxy, 1,1,2,2-tetrafluoroethoxy, fluoro, chloro, bromo, amidosulfonyl, N-methylamidosulfonyl, N,N-dimethylamidosulfonyl, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 2,2,2-trifluoro-1-hydroxyethyl, and cyano;

R^{16} and R^{19} are optionally Q^b with the proviso that no more than one of R^{16} and R^{19} is Q^b at the same time and that Q^b is Q^{be}.

In a most preferred specific embodiment of Formula I, compounds have the Formula I-EMPS wherein B is an aromatic:



(I-EMPS wherein B is aromatic)

or a pharmaceutically acceptable salt thereof, wherein;

B is selected from the group consisting of phenyl, 2-thienyl, 3-thienyl, 2-furyl, 3-furyl, 2-pyrrolyl, 3-pyrrolyl, 2-imidazolyl, 4-imidazolyl, 3-pyrazolyl, 4-pyrazolyl, 2-thiazolyl, 3-isoxazolyl, and 5-isoxazolyl, wherein a carbon adjacent to the carbon at the point of attachment is optionally substituted by R^{32}, the other carbon adjacent to the carbon at the point of attachment is optionally substituted by R^{36}, a carbon adjacent to R^{32} and two atoms from the carbon at the point of attachment is optionally substituted by R^{33}, a carbon adjacent to R^{36} and two atoms from the carbon at the point of attachment is optionally substituted by R^{35}, and any carbon adjacent to both R^{33} and R^{35} is optionally substituted by R^{34};

R^{32}, R^{33}, R^{34}, R^{35}, and R^{36} are independently selected from the group consisting of hydrido, amidino, guanidino, methyl, ethyl, methoxy, ethoxy, hydroxy, amino, N-methylamino, dimethylamino, methylthio, ethylthio, trifluoromethyl, pentafluoroethyl, 2,2,2-trifluoroethyl, fluoro, chloro, bromo, amidosulfonyl, N-methylamidosulfonyl, hydroxymethyl, amidocarbonyl, carboxy, cyano, and Q^b;

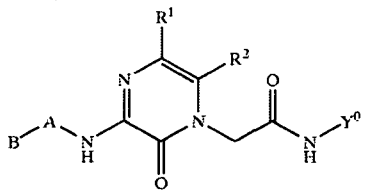
A is selected from the group consisting of single covalent bond, NH, $N(CH_3)$, CH_2, CH_3CH, and CH_2CH_2;

Q^b is selected from the group consisting of $N^{20}R^{21}$ and $C(NR^{25})NR^{23}R^{24}$, with the proviso that said Q^b group is bonded directly to a carbon atom;

R^{20}, R^{21}, R^{23}, R^{24}, and R^{25} are independently selected from the group consisting of hydrido, methyl, and ethyl;

Q^s is CH_2.

In another most preferred specific embodiment of Formula I, compounds have the Formula I-EMPS wherein B is a non-cyclic substituent:



(I-EMPS wherein B is a non-cyclic substituent)

or a pharmaceutically acceptable salt thereof, wherein;

B is selected from the group consisting of hydrido, ethyl, 2-propenyl, 2-propynyl, propyl, isopropyl, butyl, 2-butenyl, 2-butynyl, sec-butyl, tert-butyl, isobutyl, 2-methylpropenyl, 1-pentyl, 2-pentenyl, 3-pentenyl, 2-pentynyl, 3-pentynyl, 2-pentyl, 3-pentyl, 2-methylbutyl, 2-methyl-2-butenyl, 3-methylbutyl, 3-methyl-2-butenyl, 1-hexyl, 2-hexenyl, 3-hexenyl,

4-hexenyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, 2-hexyl, 1-methyl-2-pentenyl, 1-methyl-3-pentenyl, 1-methyl-2-pentynyl, 1-methyl-3-pentynyl, 3-hexyl, 1-ethyl-2-butenyl, 1-heptyl, 2-heptenyl, 3-heptenyl, 4-heptenyl, 5-heptenyl, 2-heptynyl, 3-heptynyl, 4-heptynyl, 5-heptynyl, 2-heptyl, 1-methyl-2-hexenyl, 1-methyl-3-hexenyl, 1-methyl-4-hexenyl, 1-methyl-2-hexynyl, 1-methyl-3-hexynyl, 1-methyl-4-hexynyl, 3-heptyl, 1-ethyl-2-pentenyl, 1-ethyl-3-pentenyl, 1-ethyl-2-pentynyl, 1-ethyl-3-pentynyl, 2,2,2-trifluoroethyl, 2,2-difluoropropyl, 4-trifluoromethyl-5,5,5-trifluoropentyl, 4-trifluoromethylpentyl, 5,5,6,6,6-pentafluorohexyl, and 3,3,3-trifluoropropyl, wherein each member of group B is optionally substituted at any carbon up to and including 5 atoms from the point of attachment of B to A with one or more of the group consisting of R^{32}, R^{33}, R^{34}, R^{35}, and R^{36};

R^{32}, R^{33}, R^{34}, R^{35}, and R^{36} are independently selected from the group consisting of hydrido, amidino, guanidino, methyl, ethyl, methoxy, ethoxy, hydroxy, amino, N-methylamino, dimethylamino, methylthio, ethylthio, trifluoromethyl, pentafluoroethyl, 2,2,2-trifluoroethyl, fluoro, chloro, bromo, amidosulfonyl, N-methylamidosulfonyl, hydroxymethyl, amidocarbonyl, carboxy, cyano, and Q^b;

A is selected from the group consisting of single covalent bond, NH, $N(CH_3)$, CH_2, CH_3CH, and CH_2CH_2;

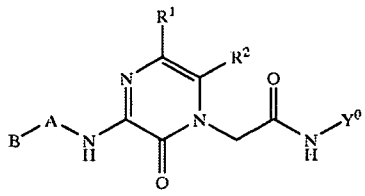
A is optionally selected from the group consisting of $CH_2N(CH_3)$, $CH_2N(CH_2CH_3)$, $CH_2CH_2N(CH_3)$, and $CH_2CH_2N(CH_2CH_3)$ with the proviso that B is hydrido;

Q^b is selected from the group consisting of $NR^{20}R^{21}$, $C(NR^{25})NR^{23}R^{24}$, and $N(R^{26})C(NR^{25})N(R^{23})(R^{24})$, with the proviso that said Q^b group is bonded directly to a carbon atom;

R^{20}, R^{21}, R^{23}, R^{24}, R^{25}, and R^{26} are independently selected from the group consisting of hydrido, methyl, and ethyl;

Q^s is CH_2.

In still another most preferred specific embodiment of Formula I, compounds have the Formula I-EMPS wherein B is a non-aromatic cyclic substituent:



(I-EMPS wherein B is a non-aromatic cyclic substituent) or a pharmaceutically acceptable salt thereof, wherein;

B is optionally selected from the group consisting of cyclopropyl, cyclobutyl, oxetan-3-yl, azetidin-3-yl, thiaetan-3-yl, cyclopentyl, cyclohexyl, 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 2-tetrahydrofuranyl, 3-tetrahydrofuranyl, 2-tetrahydrothienyl, and 3-tetrahydrothienyl, wherein each ring carbon is optionally substituted with R^{33}, a ring carbon and nitrogen atoms adjacent to the carbon atom at the point of attachment is optionally substituted with R^9 or R^{13}, a ring carbon or nitrogen atom adjacent to the R^9 position and two atoms from the point of attachment is optionally substituted with R^{10}, and a ring carbon or nitrogen atom adjacent to the R^{13} position and two atoms from the point of attachment is optionally substituted with R^{12};

R^{33} are independently selected from the group consisting of hydrido, amidino, guanidino, methyl, ethyl, methoxy, ethoxy, hydroxy, carboxy, amino, N-methylamino, dimethylamino, methylthio, ethylthio, trifluoromethyl, pentafluoroethyl, 2,2,2-trifluoroethyl, fluoro, chloro, bromo, amidosulfonyl, N-methylamidosulfonyl, hydroxymethyl, amidocarbonyl, cyano, and Q^b;

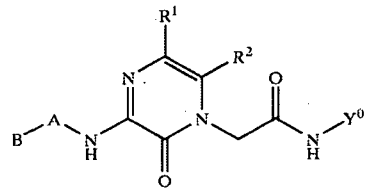
A is selected from the group consisting of single covalent bond, NH, $N(CH_3)$, CH_2, CH_3CH, and CH_2CH_2;

Q^b is selected from the group consisting of $NR^{20}R^{21}$ and $C(NR^{25})NR^{23}R^{24}$, with the proviso that said Q^b group is bonded directly to a carbon atom;

R^{20}, R^{21}, R^{23}, R^{24}, and R^{25} are independently selected from the group consisting of hydrido, methyl, and ethyl;

Q^s is CH_2.

The most preferred specific embodiment (I-EMPS) compounds of the present invention having the Formula:



or a pharmaceutically acceptable salt thereof, have common structural units, wherein;

R^1 is selected from the group consisting of hydrido, trifluoromethyl, pentafluoroethyl, fluoro, and chloro;

R^2 is Z^0—Q;

Z^0 is a covalent single bond;

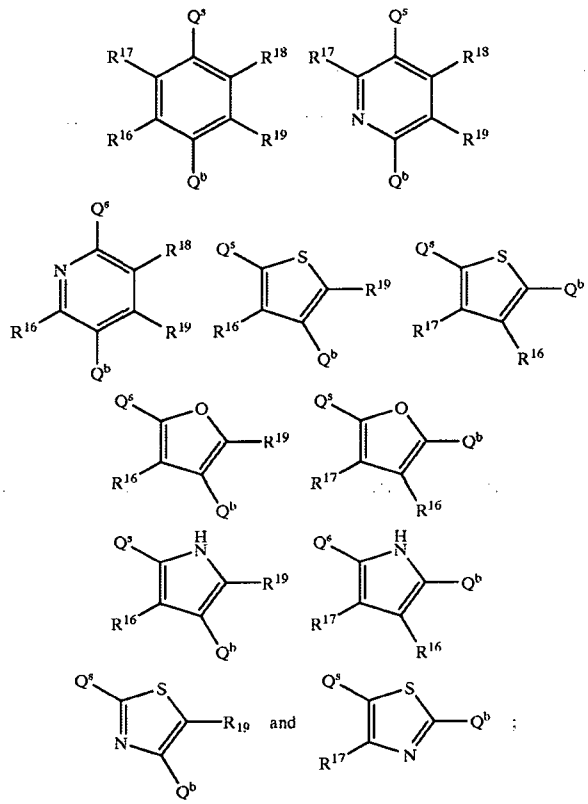
Q is selected from the group consisting of phenyl, 2-thienyl, 2-furyl, 2-pyrrolyl, 2-imidazolyl, 2-thiazolyl, 3-isoxazolyl, 2-pyridyl, and 3-pyridyl, wherein a carbon adjacent to the carbon at the point of attachment is optionally substituted by R^9, the other carbon adjacent to the carbon at the point of attachment is optionally substituted by R^{13}, a carbon adjacent to R^9 and two atoms from the carbon at the point of attachment is optionally substituted by R^{10}, a carbon adjacent to R^{13} and two atoms from the carbon at the point of attachment is optionally substituted by R^{12}, and any carbon adjacent to both R^{10} and R^{12} is optionally substituted by R^{11};

R^9, R^{11}, and R^{13} are independently selected from the group consisting of hydrido, methyl, ethyl, methoxy, ethoxy, hydroxy, amino, N-methylamino, N,N-dimethylamino, methylthio, trifluoromethyl, pentafluoroethyl, 2,2,2-trifluoroethyl, fluoro, chloro, bromo, amidosulfonyl, N-methylamidosulfonyl, N,N-dimethylamidosulfonyl, hydroxymethyl, 1-hydroxyethyl, amidocarbonyl, N-methylamidocarbonyl, carboxy, and cyano;

R^{10} and R^{12} are independently selected from the group consisting of hydrido, amidino, amidocarbonyl, N-methylamidocarbonyl, guanidino, methyl, ethyl, methoxy, ethoxy, hydroxy, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, carboxy,

carboxymethyl, amino, acetamido, trifluoromethyl, pentafluoroethyl, 2,2,2-trifluoroethyl, trifluoroacetamido, aminomethyl, N-methylamino, dimethylamino, amidosulfonyl, N-methylamidosulfonyl, N,N-dimethylamidosulfonyl, methoxycarbonyl, fluoro, chloro, bromo, and cyano;

Y^0 is selected from the group of formulas consisting of:



R^{16}, R^{17}, R^{18}, and R^{19} are independently selected from the group consisting of hydrido, methyl, ethyl, amidino, guanidino, methoxy, hydroxy, amino, aminomethyl, 1-aminoethyl, 2-aminoethyl, N-methylamino, dimethylamino, methylthio, ethylthio, trifluoromethylthio, methylsulfinyl, methylsulfonyl, trifluoromethyl, pentafluoroethyl, 2,2,2-trifluoroethyl, trifluoromethoxy, fluoro, chloro, amidosulfonyl, N-methylamidosulfonyl, hydroxymethyl, carboxy, and cyano.

The compounds of this invention can be used in anticoagulant therapy for the treatment and prevention of a variety of thrombotic conditions including coronary artery and cerebrovascular disease. The compounds of this invention can be used to inhibit serine protease associated with the coagulation cascade and factors II, VII, VIII, IX, X, XI, or XII. The compounds of the invention can inhibit the formation of blood platelet aggregates, inhibit the formation of fibrin, inhibit thrombus formation. and inhibiting embolus formation in a mammal, in blood, in blood products, and in mammalian organs. The compounds also can be used for treating or preventing unstable angina, refractory angina, myocardial infarction, transient ischemic attacks, atrial fibrillation, thrombotic stroke, embolic stroke, deep vein thrombosis, disseminated intravascular coagulation, ocular build up of fibrin, and reocclusion or restenosis of recanalized vessels in a mammal. The compounds can also be used in prophylactic treatment of subjects who are at risk of developing such disorders. The compounds can be used to lower the risk of atherosclerosis. The compounds of Formula (I) would also be useful in prevention of cerebral vascular accident (CVA) or stroke.

Besides being useful for human treatment, these compounds are also useful for veterinary treatment of companion animals, exotic animals and farm animals, including mammals, rodents, and the like. More preferred animals include horses, dogs, and cats.

In yet another embodiment of the present invention, the novel compounds are selected from the compounds set forth in Examples 1 through Example 109 and Tables 1 through Table 7.

The use of generic terms in the description of the compounds are herein defined for clarity.

Standard single letter elemental symbols are used to represent specific types of atoms unless otherwise defined. The symbol "C" represents a carbon atom. The symbol "O" represents an oxygen atom. The symbol "N" represents a nitrogen atom. The symbol "P" represents a phosphorus atom. The symbol "S" represents a sulfur atom. The symbol "H" represents a hydrido atom. Double letter elemental symbols are used as defined for the elements of the periodical table (i.e., Cl represents chlorine, Se represents selenium, etc.).

As utilized herein, the term "alkyl", either alone or within other terms such as "haloalkyl" and "alkylthio", means an acyclic alkyl radical containing from 1 to about 10, preferably from 3 to about 8 carbon atoms and more preferably 3 to about 6 carbon atoms. Said alkyl radicals may be optionally substituted with groups as defined below. Examples of such radicals include methyl, ethyl, chloroethyl, hydroxyethyl, n-propyl, oxopropyl, isopropyl, n-butyl, cyanobutyl, isobutyl, sec-butyl, tert-butyl, pentyl, aminopentyl, iso-amyl, hexyl, octyl and the like.

The term "alkenyl" refers to an unsaturated, acyclic hydrocarbon radical in so much as it contains at least one double bond. Such alkenyl radicals contain from about 2 to about 10 carbon atoms, preferably from about 3 to about 8 carbon atoms and more preferably 3 to about 6 carbon atoms. Said alkenyl radicals may be optionally substituted with groups as defined below. Examples of suitable alkenyl radicals include propenyl, 2-chloropropenyl, buten-1-yl, isobutenyl, penten-1-yl, 2-2-methylbuten-1-yl, 3-methylbuten-1-yl, hexen-1-yl, 3-hydroxyhexen-1-yl, hepten-1-yl, and octen-1-yl, and the like.

The term "alkynyl" refers to an unsaturated, acyclic hydrocarbon radical in so much as it contains one or more triple bonds, such radicals containing about 2 to about 10 carbon atoms, preferably having from about 3 to about 8 carbon atoms and more preferably having 3 to about 6 carbon atoms. Said alkynyl radicals may be optionally substituted with groups as defined below. Examples of suitable alkynyl radicals include ethynyl, propynyl, hydroxypropynyl, butyn-1-yl, butyn-2-yl, pentyn-1-yl, pentyn-2-yl, 4-methoxypentyn-2-yl, 3-methylbutyn-1-yl. hexyn-1-yl, hexyn-2-yl, hexyn-3-yl, 3,3-dimethylbutyn-1-yl radicals and the like.

The term "hydrido" denotes a single hydrogen atom (H). This hydrido radical may be attached, for example, to an oxygen atom to form a "hydroxyl" radical, one hydrido radical may be attached to a carbon atom to form a "methine" radical —CH=, or two hydrido radicals may be attached to a carbon atom to form a "methylene" (—CH_2—) radical.

The term "carbon" radical denotes a carbon atom without any covalent bonds and capable of forming four covalent bonds.

The term "cyano" radical denotes a carbon radical having three of four covalent bonds shared by a nitrogen atom.

The term "hydroxyalkyl" embraces radicals wherein any one or more of the alkyl carbon atoms is substituted with a hydroxyl as defined above. Specifically embraced are monohydroxyalkyl, dihydroxyalkyl and polyhydroxyalkyl radicals.

The term "alkanoyl" embraces radicals wherein one or more of the terminal alkyl carbon atoms are substituted with one or more carbonyl radicals as defined below. Specifically embraced are monocarbonylalkyl and dicarbonylalkyl radicals. Examples of monocarbonylalkyl radicals include formyl, acetyl, and pentanoyl. Examples of dicarbonylalkyl radicals include oxalyl, malonyl, and succinyl.

The term "alkylene" radical denotes linear or branched radicals having from 1 to about 10 carbon atoms and having attachment points for two or more covalent bonds. Examples of such radicals are methylene, ethylene, methylethylene, and isopropylidene.

The term "alkenylene" radical denotes linear or branched radicals having from 2 to about 10 carbon atoms, at least one double bond, and having attachment points for two or more covalent bonds. Examples of such radicals are 1,1-vinylidene (CH_2=C), 1,2-vinylidene (—CH=CH—), and 1,4-butadienyl (—CH=CH—CH=CH—).

The term "halo" means halogens such as fluorine, chlorine, bromine or iodine atoms.

The term "haloalkyl" embraces radicals wherein any one or more of the alkyl carbon atoms is substituted with halo as defined above. Specifically embraced are monohaloalkyl, dihaloalkyl and polyhaloalkyl radicals. A monohaloalkyl radical, for one example, may have either a bromo, chloro or a fluoro atom within the radical. Dihalo radicals may have two or more of the same halo atoms or a combination of different halo radicals and polyhaloalkyl radicals may have more than two of the same halo atoms or a combination of different halo radicals. More preferred haloalkyl radicals are "lower haloalkyl" radicals having one to about six carbon atoms. Examples of such haloalkyl radicals include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, trifluoroethyl, pentafluoroethyl, heptafluoropropyl, difluorocloromethyl, dichiorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl.

The term "hydroxyhaloalkyl" embraces radicals wherein any one or more of the haloalkyl carbon atoms is substituted with hydroxy as defined above. Examples of "hydroxyhaloalkyl" radicals include hexafluorohydroxypropyl.

The term "haloalkylene radical" denotes alkylene radicals wherein any one or more of the alkylene carbon atoms is substituted with halo as defined above. Dihalo alkylene radicals may have two or more of the same halo atoms or a combination of different halo radicals and polyhaloalkylene radicals may have more than two of the same halo atoms or a combination of different halo radicals. More preferred haloalkylene radicals are "lower haloalkylene" radicals having one to about six carbon atoms. Examples of "haloalkylene" radicals include difluoromethylene, tetrafluoroethylene, tetrachloroethylene, alkyl substituted monofluoromethylene, and aryl substituted trifluoromethylene.

The term "haloalkenyl" denotes linear or branched radicals having from 1 to about 10 carbon atoms and having one or more double bonds wherein any one or more of the alkenyl carbon atoms is substituted with halo as defined above. Dihaloalkenyl radicals may have two or more of the same halo atoms or a combination of different halo radicals and polyhaloalkenyl radicals may have more than two of the same halo atoms or a combination of different halo radicals.

The terms "alkoxy" and "alkoxyalkyl" embrace linear or branched oxy-containing radicals each having alkyl portions of one to about ten carbon atoms, such as methoxy radical. The term "alkoxyalkyl" also embraces alkyl radicals having one or more alkoxy radicals attached to the alkyl radical, that is, to form monoalkoxyalkyl and dialkoxyalkyl radicals. More preferred alkoxy radicals are "lower alkoxy" radicals having one to six carbon atoms. Examples of such radicals include methoxy, ethoxy, propoxy, butoxy, isopropoxy and tert-butoxy alkyls. The "alkoxy" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide "haloalkoxy" and "haloalkoxyalkyl" radicals. Examples of such haloalkoxy radicals include fluoromethoxy, chloromethoxy, trifluoromethoxy, difluoromethoxy, trifluoroethoxy, fluoroethoxy, tetrafluoroethoxy, pentafluoroethoxy, and fluoropropoxy. Examples of such haloalkoxyalkyl radicals include fluoromethoxymethyl, chloromethoxyethyl, trifluoromethoxymethyl, difluoromethoxyethyl, and trifluoroethoxymethyl.

The terms "alkenyloxy" and "alkenyloxyalkyl" embrace linear or branched oxy-containing radicals each having alkenyl portions of two to about ten carbon atoms, such as ethenyloxy or propenyloxy radical. The term "alkenyloxyalkyl" also embraces alkenyl radicals having one or more alkenyloxy radicals attached to the alkyl radical, that is, to form monoalkenyloxyalkyl and dialkenyloxyalkyl radicals. More preferred alkenyloxy radicals are "lower alkenyloxy" radicals having two to six carbon atoms. Examples of such radicals include ethenyloxy, propenyloxy, butenyloxy, and isopropenyloxy alkyls. The "alkenyloxy" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide "haloalkenyloxy" radicals. Examples of such radicals include trifluoroethenyloxy, fluoroethenyloxy, difluoroethenyhloxy, and fluoropropenyloxy.

The term "haloalkoxyalkyl" also embraces alkyl radicals having one or more haloalkoxy radicals attached to the alkyl radical, that is, to form monohaloalkoxyalkyl and dihaloalkoxyalkyl radicals. The term "haloalkenyloxy" also embraces oxygen radicals having one or more haloalkenyloxy radicals attached to the oxygen radical, that is, to form monohaloalkenyloxy and dihaloalkenyloxy radicals. The term "haloalkenyloxyalkyl" also embraces alkyl radicals having one or more haloalkenyloxy radicals attached to the alkyl radical, that is, to form monohaloalkenyloxyalkyl and dihaloalkenyloxyalkyl radicals.

The term "alkylenedioxy" radicals denotes alkylene radicals having at least two oxygens bonded to a single alkylene group. Examples of "alkylenedioxy" radicals include methylenedioxy, ethylenedioxy, alkylsubstituted methylenedioxy, and arylsubstituted methylenedioxy. The term "haloalkylenedioxy" radicals denotes haloalkylene radicals having at least two oxy groups bonded to a single haloalkyl group. Examples of "haloalkylenedioxy" radicals include difluoromethylenedioxy, tetrafluoroethylenedioxy, tetrachloroethylenedioxy, alkylsubstituted monofluoromethylenedioxy, and arylsubstituted monofluoromethylenedioxy.

The term "aryl", alone or in combination, means a carbocyclic aromatic system containing one, two or three rings wherein such rings may be attached together in a pendant manner or may be fused. The term "fused" means that a second ring is present (ie, attached or formed) by having two adjacent atoms in common (ie, shared) with the first ring.

The term "fused" is equivalent to the term "condensed". The term "aryl" embraces aromatic radicals such as phenyl, naphthyl, tetrahydronaphthyl, indane and biphenyl.

The term "perhaloaryl" embraces aromatic radicals such as phenyl, naphthyl, tetrahydronaphthyl, indane and biphenyl wherein the aryl radical is substituted with 3 or more halo radicals as defined below.

The term "heterocyclyl" embraces saturated and partially saturated heteroatom-containing ring-shaped radicals having from 4 through 15 ring members, herein referred to as "C4–C15 heterocyclyl", selected from carbon, nitrogen, sulfur and oxygen, wherein at least one ring atom is a heteroatom. Heterocyclyl radicals may contain one, two or three rings wherein such rings may be attached in a pendant manner or may be fused. Examples of saturated heterocyclic radicals include saturated 3 to 6-membered heteromonocylic group containing 1 to 4 nitrogen atoms [e.g. pyrrolidinyl, imidazolidinyl, piperidino, piperazinyl, etc.]; saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms [e.g. morpholinyl, etc.]; saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms [e.g., thiazolidinyl, etc.]. Examples of partially saturated heterocyclyl radicals include dihydrothiophene, dihydropyran, dihydrofuran and dihydrothiazole. Non-limiting examples of heterocyclic radicals include 2-pyrrolinyl, 3-pyrrolinyl, pyrrolindinyl, 1,3-dioxolanyl, 2H-pyranyl, 4H-pyranyl, piperidinyl, 1,4-dioxanyl, morpholinyl, 1,4-dithianyl, thiomorpholinyl, and the like.

The term "heteroaryl" embraces fully unsaturated heteroatom-containing ring-shaped aromatic radicals having from 4 through 15 ring members selected from carbon, nitrogen, sulfur and oxygen, wherein at least one ring atom is a heteroatom. Heteroaryl radicals may contain one, two or three rings wherein such rings may be attached in a pendant manner or may be fused. Examples of "heteroaryl" radicals, include unsaturated 5 to 6 membered heteromonocyclyl group containing 1 to 4 nitrogen atoms, for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl [e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.] tetrazolyl [e.g. 1H-tetrazolyl, 2H-tetrazolyl, etc.], etc.; unsaturated condensed heterocyclic group containing 1 to 5 nitrogen atoms, for example, indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, tetrazolopyridazinyl [e.g., tetrazolo [1,5-b]pyridazinyl, etc.], etc.; unsaturated 3 to 6-membered heteromonocyclic group containing an oxygen atom, for example, pyranyl, 2-furyl, 3-furyl, etc.: unsaturated 5 to 6-membered heteromonocyclic group containing a sulfur atom, for example, 2-thienyl, 3-thienyl, etc.; unsaturated 5- to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, oxazolyl, isoxazolyl, oxadiazolyl [e.g., 1,2,4oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,-oxadiazolyl, etc.] etc.; unsaturated condensed heterocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms [e.g. benzoxazolyl, benzoxadiazolyl, etc.]; unsaturated 5 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, for example, thiazolyl, thiadiazolyl [e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, etc.] etc.; unsaturated condensed heterocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms [e.g., benzothiazolyl, benzothiadiazolyl, etc.] and the like. The term also embraces radicals where heterocyclic radicals are fused with aryl radicals. Examples of such fused bicyclic radicals include benzofuran, benzothiophene, and the like.

Said "heterocyclyl" group may have 1 to 3 substituents as defined below. Preferred heterocyclic radicals include five to twelve membered fused or unfused radicals. Non-limiting examples of heteroaryl radicals include pyrrolyl, pyridinyl, pyridyloxy, pyrazolyl, triazolyl, pyrimidinyl, pyridazinyl, oxazolyl, thiazolyl, imidazolyl, indolyl, thiophenyl, furanyl, tetrazolyl, 2-imidazolinyl, imidazolidinyl, 2-pyrazolinyl, pyrazolidinyl, isoxazolyl, isothiazolyl, 1,2,3-oxadiazolyl, 1,2,3-triazolyl, 1,3,4-thiadiazolyl, pyrazinyl, piperazinyl, 1,3,5-triazinyl, 1,3,5-trithianyl, benzo(b)thiophenyl, benzimidazoyl, quinolinyl, tetraazolyl, and the like.

The term "sulfonyl", whether used alone or linked to other terms such as alkylsulfonyl, denotes respectively divalent radicals —SO_2—. "Alkylsulfonyl", embraces alkyl radicals attached to a sulfonyl radical, where alkyl is defined as above. "Alkylsulfonylalkyl", embraces alkylsulfonyl radicals attached to an alkyl radical, where alkyl is defined as above. "Haloalkylsulfonyl", embraces haloalkyl radicals attached to a sulfonyl radical, where haloalkyl is defined as above. "Haloalkylsulfonylalkyl", embraces haloalkylsulfonyl radicals attached to an alkyl radical, where alkyl is defined as above. The term "aminosulfonyl" denotes an amino radical attached to a sulfonyl radical.

The term "sulfinyl", whether used alone or linked to other terms such as alkylsulfinyl, denotes respectively divalent radicals —S(O)—. "Alkylsulfinyl", embraces alkyl radicals attached to a sulfinyl radical, where alkyl is defined as above. "Alkylsulfinylalkyl", embraces alkylsulfinyl radicals attached to an alkyl radical, where alkyl is defined as above. "Haloalkylsulfinyl", embraces haloalkyl radicals attached to a sulfinyl radical, where haloalkyl is defined as above. "Haloalkylsulfonylalkyl", embraces haloalkylsulfinyl radicals attached to an alkyl radical, where alkyl is defined as above.

The term "aralkyl" embraces aryl-substituted alkyl radicals. Preferable aralkyl radicals are "lower aralkyl" radicals having aryl radicals attached to alkyl radicals having one to six carbon atoms. Examples of such radicals include benzyl, diphenylmethyl, triphenylmethyl, phenylethyl and diphenylethyl. The terms benzyl and phenylmethyl are interchangeable.

The term "heteroaralkyl" embraces heteroaryl-substituted alkyl radicals wherein the heteroaralkyl radical may be additionally substituted with three or more substituents as defined above for aralkyl radicals. The term "perhaloaralkyl" embraces aryl-substituted alkyl radicals wherein the aralkyl radical is substituted with three or more halo radicals as defined above.

The term "aralkylsulfinyl", embraces aralkyl radicals attached to a sulfinyl radical, where aralkyl is defined as above. "Aralkylsulfinylalkyl", embraces aralkylsulfinyl radicals attached to an alkyl radical, where alkyl is defined as above.

The term "aralkylsulfonyl", embraces aralkyl radicals attached to a sulfonyl radical, where aralkyl is defined as above. "Aralkylsulfonylalkyl", embraces aralkylsulfonyl radicals attached to an alkyl radical, where alkyl is defined as above.

The term "cycloalkyl" embraces radicals having three to 15 carbon atoms. More preferred cycloalkyl radicals are "lower cycloalkyl" radicals having three to seven carbon atoms. Examples include radicals such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. The term cycloalkyl embraces radicals having seven to 15 carbon atoms and having two to four rings. Exmaples incude radicals such as norbornyl (i.e., bicyclo[2.2.1]heptyl) and adamantyl. The term "cycloalkylalkyl" embraces

cycloalkyl-substituted alkyl radicals. Preferable cycloalkylalkyl radicals are "lower cycloalkylalkyl" radicals having cycloalkyl radicals attached to alkyl radicals having one to six carbon atoms. Examples of such radicals include cyclohexylhexyl. The term "cycloalkenyl" embraces radicals having three to ten carbon atoms and one or more carbon-carbon double bonds. Preferred cycloalkenyl radicals are "lower cycloalkenyl" radicals having three to seven carbon atoms. Examples include radicals such as cyclobutenyl, cyclopentenyl, cyclohexenyl and cycloheptenyl. The term "halocycloalkyl" embraces radicals wherein any one or more of the cycloalkyl carbon atoms is substituted with halo as defined above. Specifically embraced are monohalocycloalkyl, dihalocycloalkyl and polyhalocycloalkyl radicals. A monohalocycloalkyl radical, for one example, may have either a bromo, chloro or a fluoro atom within the radical. Dihalo radicals may have two or more of the same halo atoms or a combination of different halo radicals and polyhalocycloalkyl radicals may have more than two of the same halo atoms or a combination of different halo radicals. More preferred halocycloalkyl radicals are "lower halocycloalkyl" radicals having three to about eight carbon atoms. Examples of such halocycloalkyl radicals include fluorocyclopropyl, difluorocyclobutyl, trifluorocyclopentyl, tetrafluorocyclohexyl, and dichlorocyclopropyl. The term "halocycloalkenyl" embraces radicals wherein any one or more of the cycloalkenyl carbon atoms is substituted with halo as defined above. Specifically embraced are monohalocycloalkenyl, dihalocycloalkenyl and polyhalocycloalkenyl radicals.

The term "cycloalkoxy" embraces cycloalkyl radicals attached to an oxy radical. Examples of such radicals includes cyclohexoxy and cyclopentoxy. The term "cycloalkoxyalkyl" also embraces alkyl radicals having one or more cycloalkoxy radicals attached to the alkyl radical, that is, to form monocycloalkoxyalkyl and dicycloalkoxyalkyl radicals. Examples of such radicals include cyclohexoxyethyl. The "cycloalkoxy" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide "halocycloalkoxy" and "halocycloalkoxyalkyl" radicals.

The term "cycloalkylalkoxy" embraces cycloalkyl radicals attached to an alkoxy radical. Examples of such radicals includes cyclohexylmethoxy and cyclopentylmethoxy.

The term "cycloalkenyloxy" embraces cycloalkenyl radicals attached to an oxy radical. Examples of such radicals includes cyclohexenyloxy and cyclopentenyloxy. The term "cycloalkenyloxyalkyl" also embraces alkyl radicals having one or more cycloalkenyloxy radicals attached to the alkyl radical, that is, to form monocycloalkenyloxyalkyl and dicycloalkenyloxyalkyl radicals. Examples of such radicals include cyclohexenyloxyethyl. The "cycloalkenyloxy" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide "halocycloalkenyloxy" and "halocycloalkenyloxyalkyl" radicals.

The term "cycloalkylenedioxy" radicals denotes cycloalkylene radicals having at least two oxygens bonded to a single cycloalkylene group. Examples of "alkylenedioxy" radicals include 1,2-dioxycyclohexylene.

The term "cycloalkylsulfinyl", embraces cycloalkyl radicals attached to a sulfinyl radical, where cycloalkyl is defined as above. "Cycloalkylsulfinylalkyl", embraces cycloalkylsulfinyl radicals attached to an alkyl radical, where alkyl is defined as above. The term "Cycloalkylsulfonyl", embraces cycloalkyl radicals attached to a sulfonyl radical, where cycloalkyl is defined as above. "Cycloalkylsulfonylalkyl", embraces cycloalkylsulfonyl radicals attached to an alkyl radical, where alkyl is defined as above.

The term "cycloalkylalkanoyl" embraces radicals wherein one or more of the cycloalkyl carbon atoms are substituted with one or more carbonyl radicals as defined below. Specifically embraced are monocarbonylcycloalkyl and dicarbonylcycloalkyl radicals. Examples of monocarbonylcycloalkyl radicals include cyclohexylcarbonyl, cyclohexylacetyl, and cyclopentylcarbonyl. Examples of dicarbonylcycloalkyl radicals include 1,2-dicarbonylcyclohexane.

The term "alkylthio" embraces radicals containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to a divalent sulfur atom. More preferred alkylthio radicals are "lower alkylthio" radicals having one to six carbon atoms. An example of "lower alkylthio" is methylthio (CH_3—S—). The "alkylthio" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide "haloalkylthio" radicals. Examples of such radicals include fluoromethylthio, chloromethylthio, trifluoromethylthio, difluoromethylthio, trifluoroethylthio, fluoroethylthio, tetrafluoroethylthio, pentafluoroethylthio, and fluoropropylthio.

The term "alkyl aryl amino" embraces radicals containing a linear or branched alkyl radical, of one to ten carbon atoms, and one aryl radical both attached to an amino radical. Examples include N-methyl-4-methoxyaniline, N-ethyl-4-methoxyaniline, and N-methyl-4-trifluoromethoxyaniline.

The terms alkylamino denotes "monoalkylamino" and "dialkylamino" containing one or two alkyl radicals, respectively, attached to an amino radical.

The terms arylamino denotes "monoarylamino" and "diarylamino" containing one or two aryl radicals, respectively, attached to an amino radical. Examples of such radicals include N-phenylamino and N-naphthylamino.

The term "aralkylamino", embraces aralkyl radicals attached to an amino radical, where aralkyl is defined as above. The term aralkylamino denotes "monoaralkylamino" and "diaralkylamino" containing one or two aralkyl radicals, respectively, attached to an amino radical. The term aralkylamino further denotes "monoaralkyl monoalkylamino" containing one aralkyl radical and one alkyl radical attached to an amino radical.

The term "arylsulfinyl" embraces radicals containing an aryl radical, as defined above, attached to a divalent S(O) atom. The term "arylsulfinylalkyl" denotes arylsulfinyl radicals attached to a linear or branched alkyl radical, of one to ten carbon atoms.

The term "arylsulfonyl", embraces aryl radicals attached to a sulfonyl radical, where aryl is defined as above. "arylsulfonylalkyl", embraces arylsulfonyl radicals attached to an alkyl radical, where alkyl is defined as above. The term "heteroarylsulfinyl" embraces radicals containing an heteroaryl radical, as defined above, attached to a divalent S(O) atom. The term "heteroarylsulfinylalkyl" denotes heteroarylsulfinyl radicals attached to a linear or branched alkyl radical, of one to ten carbon atoms. The term "Heteroarylsulfonyl", embraces heteroaryl radicals attached to a sulfonyl radical, where heteroaryl is defined as above. "Heteroarylsulfonylalkyl", embraces heteroarylsulfonyl radicals attached to an alkyl radical, where alkyl is defined as above.

The term "aryloxy" embraces aryl radicals, as defined above, attached to an oxygen atom. Examples of such radicals include phenoxy, 4-chloro-3-ethylphenoxy, 4-chloro-3-methylphenoxy, 3-chloro-4-ethylphenoxy, 3,4-dichlorophenoxy, 4-methylphenoxy, 3-trifluoromethoxyphenoxy, 3-trifluoromethylphenoxy,

4-fluorophenoxy, 3,4-dimethylphenoxy, 5-bromo-2-fluorophenoxy, 4-bromo-3-fluorophenoxy, 4-fluoro-3-methylphenoxy, 5,6,7,8-tetrahydronaphthyloxy, 3-isopropylphenoxy, 3-cyclopropylphenoxy, 3-ethylphenoxy, 3-pentafluoroethylphenoxy, 3-(1,1,2,2-tetrafluoroethoxy)-phenoxy, and 4-tert-butylphenoxy.

The term "aroyl" embraces aryl radicals, as defined above, attached to an carbonyl radical as defined above. Examples of such radicals include benzoyl and toluoyl.

The term "aralkanoyl" embraces aralkyl radicals, as defined herein, attached to an carbonyl radical as defined above. Examples of such radicals include, for example, phenylacetyl.

The term "aralkoxy" embraces oxy-containing aralkyl radicals attached through an oxygen atom to other radicals. More preferred aralkoxy radicals are "lower aralkoxy" radicals having phenyl radicals attached to lower alkoxy radical as described above. Examples of such radicals include benzyloxy, 1-phenylethoxy, 3-trifluoromethoxybenzyloxy, 3-trifluoromethylbenzyloxy, 3,5-difluorobenyloxy, 3-bromobenzyloxy, 4-propylbenzyloxy, 2-fluoro-3-trifluoromethylbenzyloxy, and 2-phenylethoxy.

The term "aryloxyalkyl" embraces aryloxy radicals, as defined above, attached to an alkyl group. Examples of such radicals include phenoxymethyl.

The term "haloaryloxyalkyl" embraces aryloxyalkyl radicals, as defined above, wherein one to five halo radicals are attached to an aryloxy group.

The term "heteroaroyl" embraces heteroaryl radicals, as defined above, attached to an carbonyl radical as defined above. Examples of such radicals include furoyl and nicotinyl.

The term "heteroaralkanoyl" embraces heteroaralkyl radicals, as defined herein, attached to an carbonyl radical as defined above. Examples of such radicals include, for example, pyridylacetyl and furylbutyryl.

The term "heteroaralkoxy" embraces oxy-containing heteroaralkyl radicals attached through an oxygen atom to other radicals. More preferred heteroaralkoxy radicals are "lower heteroaralkoxy" radicals having heteroaryl radicals attached to lower alkoxy radical as described above.

The term "haloheteroaryloxyalkyl" embraces heteroaryloxyalkyl radicals, as defined above, wherein one to four halo radicals are attached to an heteroaryloxy group.

The term "heteroarylamino" embraces heterocyclyl radicals, as defined above, attached to an amino group. Examples of such radicals include pyridylamino.

The term "heteroarylaminoalkyl" embraces heteroarylamino radicals, as defined above, attached to an alkyl group. Examples of such radicals include pyridylmethylamino.

The term "heteroaryloxy" embraces heterocyclyl radicals, as defined above, attached to an oxy group. Examples of such radicals include 2-thiophenyloxy, 2-pyrimidyloxy, 2-pyridyloxy, 3-pyridyloxy, and 4-pyridyloxy.

The term "heteroaryloxyalkyl" embraces heteroaryloxy radicals, as defined above, attached to an alkyl group. Examples of such radicals include 2-pyridyloxymethyl, 3-pyridyloxyethyl, and 4-pyridyloxymethyl.

The term "arylthio" embraces aryl radicals, as defined above, attached to an sulfur atom. Examples of such radicals include phenylthio.

The term "arylthioalkyl" embraces arylthio radicals, as defined above, attached to an alkyl group. Examples of such radicals include phenylthiomethyl.

The term "alkylthioalkyl" embraces alkylthio radicals, as defined above, attached to an alkyl group. Examples of such radicals include methylthiomethyl. The term "alkoxyalkyl" embraces alkoxy radicals, as defined above, attached to an alkyl group. Examples of such radicals include methoxymethyl.

The term "carbonyl" denotes a carbon radical having two of the four covalent bonds shared with an oxygen atom. The term "carboxy" embraces a hydroxyl radical, as defined above, attached to one of two unshared bonds in a carbonyl group. The term "carboxamide" embraces amino, monoalkylamino, dialkylamino, monocycloalkylamino, alkylcycloalkylamino, and dicycloalkylamino radicals, attached to one of two unshared bonds in a carbonyl group. The term "carboxamidoalkyl" embraces carboxamide radicals, as defined above, attached to an alkyl group. The term "carboxyalkyl" embraces a carboxy radical, as defined above, attached to an alkyl group. The term "carboalkoxy" embraces alkoxy radicals, as defined above, attached to one of two unshared bonds in a carbonyl group. The term "carboaralkoxy" embraces aralkoxy radicals, as defined above, attached to one of two unshared bonds in a carbonyl group. The term "monocarboalkoxyalkyl" embraces one carboalkoxy radical, as defined above, attached to an alkyl group. The term "dicarboalkoxyalkyl" embraces two carboalkoxy radicals, as defined above, attached to an alkylene group. The term "monocyanoalkyl" embraces one cyano radical, as defined above, attached to an alkyl group. The term "dicyanoalkylene" embraces two cyano radicals, as defined above, attached to an alkyl group. The term "carboalkoxycyanoalkyl" embraces one cyano radical, as defined above, attached to an carboalkoxyalkyl group.

The term "acyl", alone or in combination, means a carbonyl or thionocarbonyl group bonded to a radical selected from, for example, hydrido, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, alkoxyalkyl, haloalkoxy, aryl, heterocyclyl, heteroaryl, alkylsulfinylalkyl, alkylsulfonylalkyl, aralkyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, alkylthio, arylthio, amino, alkylamino, dialkylamino, aralkoxy, arylthio, and alkylthioalkyl. Examples of "acyl" are formyl, acetyl, benzoyl, trifluoroacetyl, phthaloyl, malonyl, nicotinyl, and the like. The term "haloalkanoyl" embraces one or more halo radicals, as defined herein, attached to an alkanoyl radical as defined above. Examples of such radicals include, for example, chloroacetyl, trifluoroacetyl, bromopropanoyl, and heptafluorobutanoyl.

The term "phosphono" embraces a pentavalent phosphorus attached with two covalent bonds to an oxygen radical. The term "dialkoxyphosphono" denotes two alkoxy radicals, as defined above, attached to a phosphono radical with two covalent bonds. The term "diaralkoxyphosphono" denotes two aralkoxy radicals, as defined above, attached to a phosphono radical with two covalent bonds. The term "dialkoxyphosphonoalkyl" denotes dialkoxyphosphono radicals, as defined above, attached to an alkyl radical. The term "diaralkoxyphosphonoalkyl" denotes diaralkoxyphosphono radicals, as defined above, attached to an alkyl radical.

The term "amino" denotes a nitrogen atom containing two substituents such as hydrido, hydroxy or alkyl and having one covalent bond available for bonding to a single atom such as carbon. Examples of such amino radicals include, for example, $-NH_2$, $-NHCH_3$, $-NHOH$, and $-NHOCH_3$. The term "imino" denotes a nitrogen atom containing one substituent such as hydrido, hydroxy or alkyl and having two covalent bonds available for bonding to a single atom such as carbon. Examples of such imino radicals include, for example, $=NH$, $=NCH_3$, $=NOH$, and $=NOCH_3$. The term "imino carbonyl" denotes a carbon

radical having two of the four covalent bond sites shared with an imino group. Examples of such imino carbonyl radicals include, for example, C=NH, C=NCH$_3$, C=NOH, and C=NOCH$_3$. The term "amidino" embraces a substituted or unsubstituted amino group bonded to one of two available bonds of an iminocarbonyl radical. Examples of such amidino radicals include, for example, NH$_2$—C=NH, NH$_2$—C—NCH$_3$, NH$_2$=C=NOCH$_3$ and CH$_3$NH—C=NOH. The term "guanidino" denotes an amidino group bonded to an amino group as defined above where said amino group can be bonded to a third group. Examples of such guanidino radicals include, for example, NH$_2$—C(NH)—NH—, NH$_2$—C(NCH$_3$)—NH—, NH$_2$—C(NOCH$_3$)—NH—, and CH$_3$NH—C(NOH)—NH—.

The term "sulfonium" denotes a positively charged trivalent sulfur atom where said sulfur is substituted with three carbon based groups such as alkyl, alkenyl, aralkyl, or aryl. The term "dialkyl sulfonium" denotes a sulfonium group where said sulfur is substituted with two alkyl groups. Examples of such dialkylsulfonium radicals include, for example, (CH$_3$)$_2$S$^+$—. The term "dialkyl sulfonium alkyl" denotes a dialkyl sulfonium group where said group is bonded to one bond of an alkylene group as defined above. Examples of such dialkylsulfoniumalkyl radicals include (CH$_3$)$_2$S$^+$—CH$_2$CH$_2$—.

The term "phosphonium" denotes a positively charged tetravalent phosphorus atom where said phosphorus is substituted with four carbon based groups such as alkyl, alkenyl, aralkyl, or aryl. The term "trialkyl phosphonium" denotes a phosphonium group where said phosphorus is substituted with three alkyl groups. Examples of such trialkylphosphonium radicals include, for example, (CH$_3$)$_3$P$^+$—.

Said "alkyl", "alkenyl", "alkynyl", "alkanoyl", "alkylene", "alkenylene", "hydroxyalkyl", "haloalkyl", "haloalkylene", "haloalkenyl", "alkoxy", "alkenyloxy", "alkenyloxyalkyl", "alkoxyalkyl", "aryl", "perhaloaryl", "haloalkoxy", "haloalkoxyalkyl", "haloalkenyloxy", "haloalkenyloxyalkyl", "alkylenedioxy", "haloalkylenedioxy", "heterocyclyl", "heteroaryl", "hydroxyhaloalkyl", "alkylsulfonyl", "haloalkylsulfonyl", "alkylsulfonylalkyl", "haloalkylsulfonylalkyl", "alkylsulfinyl", "alkylsulfinylalkyl", "haloalkylsulfinylalkyl", "aralkyl", "heteroaralkyl", "perhaloaralkyl", "aralkylsulfonyl", "aralkylsulfonylalkyl", "aralkylsulfinyl", "aralkylsulfinylalkyl", "cycloalkyl", "cycloalkylalkanoyl", "cycloalkylalkyl", "cycloalkenyl", "halocycloalkyl", "halocycloalkenyl", "cycloalkylsulfinyl", "cycloalkylsulfinylalkyl", "cycloalkylsulfonyl", "cycloalkylsulfonylalkyl", "cycloalkoxy", "cycloalkoxyalkyl", "cycloalkylalkoxy", "cycloalkenyloxy", "cycloalkenyloxyalkyl", "cycloalkylenedioxy", "halocycloalkoxy", "halocycloalkoxyalkyl", "halocycloalkenyloxy", "halocycloalkenyloxyalkyl", "alkylthio", "haloalkylthio", "alkylsulfinyl", "amino", "oxy", "thio", "alkylamino", "arylamino", "aralkylamino", "arylsulfinyl", "arylsulfinylalkyl", "arylsulfonyl", "arylsulfonylalkyl", "heteroarylsulfinyl", "heteroarylsulfinylalkyl", "heteroarylsulfonyl", "heteroarylsulfonylalkyl", "heteroarylamino", "heteroarylaminoalkyl", "heteroaryloxy", "heteroaryloxylalkyl", "aryloxy", "aroyl", "aralkanoyl", "aralkoxy", "aryloxyalkyl", "haloaryloxyalkyl", "heteroaroyl", "heteroaralkanoyl", "heteroaralkoxy", "heteroaralkoxyalkyl", "arylthio", "arylthioalkyl", "alkoxyalkyl", "acyl", "amidino", "guanidino", "dialkylsulfonium", "trialkylphosphonium", and "dialkylsulfoniumalkyl" groups defined above may optionally have 1 or more non-hydrido substituents such as amidino, guanidino, dialkylsulfonium, trialkylphosphonium, dialkylsulfoniumalkyl, perhaloaralkyl, aralkylsulfonyl, aralkylsulfonylalkyl, aralkylsulfinyl, aralkylsulfinylalkyl, halocycloalkyl, halocycloalkenyl, cycloalkylsulfinyl, cycloalkylsulfinylalkyl, cycloalkylsulfonyl, cycloalkylsulfonylalkyl, heteroarylamino, N-heteroarylamino-N-alkylamino, heteroarylaminoalkyl, heteroaryloxy, heteroaryloxylalkyl, haloalkylthio, alkanoyloxy, alkoxy, alkoxyalkyl, haloalkoxylalkyl, heteroaralkoxy, cycloalkoxy, cycloalkenyloxy, cycloalkoxyalkyl, cycloalkylalkoxy, cycloalkenyloxyalkyl, cycloalkylenedioxy, halocycloalkoxy, halocycloalkoxyalkyl, halocycloalkenyloxy, halocycloalkenyloxyalkyl, hydroxy, amino, thio, nitro, lower alkylamino, alkylthio, alkylthioalkyl, arylamino, aralkylamino, arylthio, arylthioalkyl, heteroaralkoxyalkyl, alkylsulfinyl, alkylsulfinylalkyl, arylsulfinylalkyl, arylsulfonylalkyl, heteroarylsulfinylalkyl, heteroarylsulfonylalkyl, alkylsulfonyl, alkylsulfonylalkyl, haloalkylsulfinylalkyl, haloalkylsulfonylalkyl, alkylsulfonamido, alkylaminosulfonyl, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, monoarylamidosulfonyl, arylsulfonamido, diarylamidosulfonyl, monoalkyl monoaryl amidosulfonyl, arylsulfinyl, arylsulfonyl, heteroarylthio, heteroarylsulfinyl, heteroarylsulfonyl, alkanoyl, alkenoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, haloalkanoyl, alkyl, alkenyl, alkynyl, alkenyloxy, alkenyloxyalky, alkylenedioxy, haloalkylenedioxy, cycloalkyl, cycloalkylalkanoyl, cycloalkenyl, lower cycloalkylalkyl, lower cycloalkenylalkyl, halo, haloalkyl, haloalkenyl, haloalkoxy, hydroxyhaloalkyl, hydroxyaralkyl, hydroxyalkyl, aminoalkyl, hydoxyheteroaralkyl, haloalkoxyalkyl, aryl, aralkyl, aryloxy, aralkoxy, aryloxyalkyl, saturated heterocyclyl, partially saturated heterocyclyl, heteroaryl, heteroaryloxy, heteroaryloxyalkyl, arylalkyl, heteroarylalkyl, arylalkenyl, heteroarylalkenyl, carboxyalkyl, carboalkoxy, alkoxycarbonyl, carboaralkoxy. carboxamido, carboxamidoalkyl, cyano, carbohaloalkoxy, phosphono, phosphonoalkyl, diaralkoxyphosphono, and diaralkoxyphosphonoalkyl.

The term "spacer" can include a covalent bond and a linear moiety having a backbone of 1 to 7 contiguous atoms. The spacer may have 1 to 7 atoms of a univalent or multi-valent chain. Univalent chains may be constituted by a radical selected from =C(H)—, =C(R^{2a})—, —O—, —S—, —S(O)—, —S(O)$_2$—, —NH—, —N(R^{2a})—, —N=, —CH(OH)—, =C(OH)—, —CH(OR^{2a})—, =C(OR^{2a})—, and —C(O)— wherein R^{2a} is selected from alkyl, alkenyl, alkynyl, aryl, heteroaryl, aralkyl, aryloxyalkyl, alkoxyalkyl, alkylthioalkyl, arylthioalkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, haloalkenyl, haloalkoxyalkyl, perhaloaralkyl, heteroarylalkyl, heteroaryloxyalkyl, heteroarylthioalkyl, and heteroarylalkenyl. Multi-valent chains may consist of a straight chain of 1 or 2 or 3 or 4 or 5 or 6 or 7 atoms or a straight chain of 1 or 2 or 3 or 4 or 5 or 6 atoms with a side chain. The chain may be constituted of one or more radicals selected from: lower alkylene, lower alkenyl, —O—, —O—CH$_2$—, —S—CH$_2$—, —CH$_2$CH$_2$—, ethenyl, —CH=CH(OH)—, —OCH$_2$O—, —O(CH$_2$)$_2$O—, —NHCH$_2$—, —OCH(R^{2a})O—, —O(CH$_2$CHR^{2a})O—, —OCF$_2$O—, —(CF$_2$)$_2$O—, —S—, —S(O)—, —S(O)$_2$—, —N(H)—, —N(H)O—, —N(R^{2a})O—, —N(R^{2a})—, —C(O)—, —C(O)NH—,

—C(O)NR^{2a}—, —N═, —OCH$_2$—, —SCH$_2$—, S(O)CH$_2$—, —CH$_2$C(O)—, —CH(OH)—, ═C(OH)—, —CH(OR^{2a})—, ═C(OR^{2a})—, S(O)$_2$CH$_2$—, and —NR^{2a}CH$_2$— and many other radicals defined above or generally known or ascertained by one of skill-in-the art. Side chains may include substituents such as 1 or more non-hydrido substituents such as amidino, guanidino, dialkylsulfonium, trialkylphosphonium, dialkylsulfoniumalkyl, perhaloaralkyl, aralkylsulfonyl, aralkylsulfonylalkyl, aralkylsulfinyl, aralkylsulfinylalkyl, halocycloalkyl, halocycloalkenyl, cycloalkylsulfinyl, cycloalkylsulfinylalkyl, cycloalkylsulfonyl, cycloalkylsulfonylalkyl, heteroarylaminno, N-heteroarylamino-N-alkylamino, heteroarylaminoalkyl, heteroaryloxy, heteroaryloxylalkyl, haloalkylthio, alkanoyloxy, alkoxy, alkoxyalkyl, haloalkoxylalkyl, heteroaralkoxy, cycloalkoxy, cycloalkenyloxy, cycloalkoxyalkyl, cycloalkylalkoxy, cycloalkenyloxyalkyl, cycloalkylenedioxy, halocycloalkoxy, halocycloalkoxyalkyl, halocycloalkenyloxy, halocycloalkenyloxyalkyl, hydroxy, amino, thio, nitro, lower alkylamino, alkylthio, alkylthioalkyl, arylamino, aralkylamino, arylthio, arylthioalkyl, heteroaralkoxyalkyl, alkylsulfinyl, alkylsulfinylalkyl, arylsulfinylalkyl, arylsulfonylalkyl, heteroarylsulfinylalkyl, heteroarylsulfonylalkyl, alkylsulfonyl, alkylsulfonylalkyl, haloalkylsulfinylalkyl, haloalkylsulfonylalkyl, alkylsulfonamindo, alkylaminosulfonyl, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, monoarylamidosulfonyl, arylsulfonamido, diarylamidosulfonyl, monoalkyl monoaryl amidosulfonyl, arylsulfinyl, arylsulfonyl, heteroarylthio, heteroarylsulfinyl, heteroarylsulfonyl, alkanoyl, alkenoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, haloalkanoyl, alkyl, alkenyl, alkynyl, alkenyloxy, alkenyloxyalky, alkylenedioxy, haloalkylenedioxy, cycloalkyl, cycloalkenyl, lower cycloalkylalkyl, lower cycloalkenylalkyl, halo, haloalkyl, haloalkenyl, haloalkoxy, hydroxyhaloalkyl, hydroxyaralkyl, hydroxyalkyl, aminoalkyl, hydoxyheteroaralkyl, haloalkoxyalkyl, aryl, aralkyl, aryloxy, aralkoxy, aryloxyalkyl, saturated heterocyclyl, partially saturated heterocyclyl, heteroaryl, heteroaryloxy, heteroaryloxyalkyl, arylalkyl, heteroarylalkyl, arylalkenyl, heteroarylalkenyl, carboxyalkyl, carboalkoxy, carboaralkoxy, carboxamido, carboxamidoalkyl, cyano, carbohaloalkoxy, phosphono, phosphonoalkyl, diaralkoxyphosphono, and diaralkoxyphosphonoalkyl.

Compounds of the present invention can exist in tautomeric, geometric or stereoisomeric forms. The present invention contemplates all such compounds, including cis- and trans-geometric isomers, E- and Z-geometric isomers, R- and S-enantiomers, diastereomers, d-isomers, 1-isomers, the racemic mixtures thereof and other mixtures thereof, as falling within the scope of the invention. Pharmaceutically acceptable sales of such tautomeric, geometric or stereoisomeric forms are also included within the invention.

The terms "cis" and "trans" denote a form of geometric isomerism in which two carbon atoms connected by a double bond will each have a hydrogen atom on the same side of the double bond ("cis") or on opposite sides of the double bond ("trans").

Some of the compounds described contain alkenyl groups, and are meant to include both cis and trans or "E" and "Z" geometric forms.

Some of the compounds described contain one or more stereocenters and are meant to include R, S, and mixtures of R and S forms for each stereocenter present.

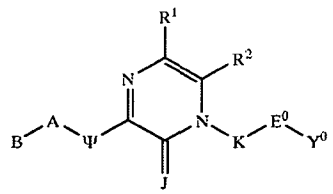
Some of the compounds described herein may contain one or more ketonic or aldehydic carbonyl groups or combinations thereof alone or as part of a heterocyclic ring system. Such carbonyl groups may exist in part or principally in the "keto" form and in part or principally as one or more "enol" forms of each aldehyde and ketone group present. Compounds of the present invention having aldehydic or ketonic carbonyl groups are meant to include both "keto" and "enol" tautomeric forms.

Some of the compounds described herein may contain one or more amide carbonyl groups or combinations thereof alone or as part of a heterocyclic ring system. Such carbonyl groups may exist in part or principally in the "keto" form and in part or principally as one or more "enol" forms of each amide group present. Compounds of the present invention having amidic carbonyl groups are meant to include both "keto" and "enol" tautomeric forms. Said amide carbonyl groups may be both oxo (C═O) and thiono (C═S) in type.

Some of the compounds described herein may contain one or more imine or enamine groups or combinations thereof. Such groups may exist in part or principally in the "imine" form and in part or principally as one or more "enamine" forms of each group present. Compounds of the present invention having said imine or enamine groups are meant to include both "imine" and "enamine" tautomeric forms.

The present invention also comprises a treatment and prophylaxis in anticoagulant therapy for the treatment and prevention of a variety of thrombotic conditions including coronary artery and cerebrovascular disease in a subject, comprising administering to the subject having such disorder a therapeutically-effective amount of a compound of Formula (I):

(I)



or a pharmaceutically-acceptable salt thereof.

As a further embodiment, compounds of the present invention of Formula (I) or a pharmaceutically-acceptable salt thereof as defined above, comprise a treatment and prophylaxis of coronary artery disease, cerebrovascular disease and other coagulation cascade related disorders in a subject, comprising administering to the subject having such disorder a therapeutically-effective amount of compounds of formula (I) of the present invention or a pharmaceutically-acceptable salt thereof.

Compounds of the present invention of Formula (I) or a pharmaceutically-acceptable salt thereof can also be used whenever inhibition of blood coagulation is required such as to prevent coagulation of stored whole blood and to prevent coagulation in other biological samples for testing or storage. Thus coagulation inhibitors of the present inhibition can be added to or contacted with stored whole blood and any medium containing or suspected of containing plasma coagulation factors and in which it is desired that blood coagulation be inhibited, e.g. when contacting the mammal's blood with material selected from the group consisting of vascular grafts, stents, orthopedic prothesis, cardiac prosthesis, and extracorporeal circulation systems.

Compounds of Formula (I) are capable of inhibiting activity of serine proteases related to the coagulation

cascade, and thus could be used in the manufacture of a medicament, a method for the prophylactic or therapeutic treatment of diseases mediated by coagulation cascade serine proteases, such as inhibiting the formation of blood platelet aggregates, inhibiting the formation of fibrin, inhibiting thrombus formation, and inhibiting embolus formation in a mammal, in blood, in blood products, and in mammalian organs. The compounds also can be used for treating or preventing unstable angina, refractory angina, myocardial infarction, transient ischemic attacks, atrial fibrillation, thrombotic stroke, embolic stroke, deep vein thrombosis, disseminated intravascular coagulation, ocular build up of fibrin, and reocclusion or restenosis of recanalized vessels in a mammal. The compounds also can be used to study the mechanism of action of coagulation cascade serine proteases to enable the design of better inhibitors and development of better assay methods. The compounds of Formula (I) would be also useful in prevention of cerebral vascular accident (CVA) or stroke.

Also included in the family of compounds of Formula (I) are the pharmaceutically-acceptable salts thereof. The term "pharmaceutically-acceptable salt" embraces salts commonly used to form alkali metal salts and to form addition salts of free acids or free bases. The nature of the salt is not critical, provided that it is pharmaceutically acceptable. Suitable pharmaceutically-acceptable acid addition salts of compounds of Formula (I) may be prepared from inorganic acid or from an organic acid. Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulfuric and phosphoric acid. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic and sulfonic classes of organic acids, examples of which are formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucoronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, salicylic, p-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethylsulfonic, benzenesulfonic, sulfanilic, stearic, cyclohexylaminosulfonic, algenic, galacturonic acid. Suitable pharmaceutically-acceptable base addition salts of compounds of Formula (I) include metallic salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc or organic salts made from N,N'-dibenzylethyleneldiamine, choline, chloroprocaine, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procain. All of these salts may be prepared by conventional means from the corresponding compound of Formula (I) by reacting, for example, the appropriate acid or base with the compound of Formula (I).

The present invention also comprises a pharmaceutical composition comprising a therapeutically-effective amount of a compound of Formulas (I) in association with at least one pharmaceutically-acceptable carrier, adjuvant or diluent. Pharmaceutical compositions of the present invention can comprise the active compounds of Formula (I) in association with one or more non-toxic, pharmaceutically-acceptable carriers and/or diluents and/or adjuvants (collectively referred to herein as "carrier" materials) and, if desired, other active ingredients. The active compounds of the present invention may be administered by any suitable route, preferably in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment intended.

The active compounds and composition may, for example, be administered orally, intravascularly, intraperitoneally, subcutaneously, intramuscularly, ocularly, or topically. For treating ocular build up of fibrin, the compounds may be administered intraocularly or topically as well as orally or parenterally.

The compounds can be administered in the form of a depot injection or implant preparation which may be formulated in such a manner as to permit a sustained release of the active ingredient. The active ingredient can be compressed into pellets or small cylinders and implanted subcutaneously or intramusculary as depot injections or implants. Implants may employ inert materials such as biodegradable polymers or synthetic silicones, for example, Silastic, silicone rubber or other silicon containing polymers.

The compounds can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

The compounds may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxy-propyl-methacrylamide-phenol, polyhydroxyethyl-aspartamide-phenol, or ployethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, the compounds may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross linked or amphitpathic block copolymers of hydrogels.

For oral administration, the pharmaceutical composition may be in the form of, for example, tablets, capsules (each of which includes sustained release or timed release formulations), pills, powders, granules, elixers, tinctures, suspensions, liquids including syrups, and emulsions. The pharmaceutical composition is preferably made in the form of a dosage unit containing a particular amount of the active ingredient. Examples of such dosage units are tablets or capsules. The active ingredient may also be administered by injection as a composition wherein, for example, saline, dextrose or water may be used as a suitable carrier.

The amount of therapeutically active compounds which are administered and the dosage regimen for treating a disease condition with the compounds and/or compositions of this invention depends on a variety of factors, including the age, weight, sex and medical condition of the subject, the severity of the disease, the route and frequency of administration, and the particular compound employed, and thus may vary widely.

The pharmaceutical compositions may contain active ingredients in the range of about 0.1 to 2000 mg, and preferably in the range of about 0.5 to 500 mg. A daily dose of about 0.01 to 100 mg/kg body weight, and preferably between about 0.5 and about 20 mg/kg body weight, may be appropriate. The daily dose can be administered in one to four doses per day.

The compounds may be formulated in topical ointment or cream, or as a suppository, containing the active ingredients in a total amount of, for example, 0.075 to 30% w/w, preferably 0.2 to 20% w/w and most preferably 0.4 to 15% w/w. When formulated in an ointment, the active ingredients may be employed with either paraffinic or a water-miscible ointment base.

Alternatively, the active ingredients may be formulated in a cream with an oil-in-water cream base. If desired, the aqueous phase of the cream base may include, for example at least 30% w/w of a polyhydric alcohol such as propylene glycol, butane-1,3-diol, mannitol, sorbitol, glycerol, polyethylene glycol and mixtures thereof. The topical formulation may desirably include a compound which enhances absorption or penetration of the active ingredient through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethylsulfoxide and related analogs. The compounds of this invention can also be administered by a transdermal device. Preferably topical administration will be accomplished using a patch either of the reservoir and porous membrane type or of a solid matrix variety. In either case, the active agent is delivered continuously from the reservoir or microcapsules through a membrane into the active agent permeable adhesive, which is in contact with the skin or mucosa of the recipient. If the active agent is absorbed through the skin, a controlled and predetermined flow of the active agent is administered to the recipient. In the case of microcapsules, the encapsulating agent may also function as the membrane.

The oily phase of the emulsions of this invention may be constituted from known ingredients in a known manner. While the phase may comprise merely an emulsifier, it may comprise a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabilizer. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s) make-up the so-called emulsifying wax, and the wax together with the oil and fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations. Emulsifiers and emulsion stabilizers suitable for use in the formulation of the present invention include Tween 60, Span 80, cetostearyl alcohol, myristyl alcohol, glyceryl monostearate, and sodium lauryl sulfate, among others.

The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties, since the solubility of the active compound in most oils likely to be used in pharmaceutical emulsion formulations is very low. Thus, the cream should preferably be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as diisoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters may be used. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils can be used.

For therapeutic purposes, the active compounds of the present invention are ordinarily combined with one or more adjuvants appropriate to the indicated route of administration. If administered per os, the compounds may be admixed with lactose, sucrose, starch powder, cellulose esters of alkanoic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets may contain a controlled-release formulation as may be provided in a dispersion of active compound in hydroxypropylmethyl cellulose. Formulations for parenteral administration may be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions may be prepared from sterile powders or granules having one or more of the carriers or diluents mentioned for use in the formulations for oral administration. The compounds may be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art.

In practicing the methods of the present invention for the treatment and prevention of a variety of thrombotic conditions including coronary artery and cerebrovascular disease, the compounds and pharmaceutical compositions of the present invention are administered alone or in combination with one another, or in combination with other therapeutics or in vivo diagnostic agents. The coagulation cascade inhibitors of the present invention can also be coadministered with suitable anti-platelet agreggation agents, including, but not limited to ticlopidine or clopidrogel, fibrinogen receptor antagonists (e.g. to treat or prevent unstable angina or to prevent reocculsion after angioplasty and restenosis), anticoagulants such as aspirin, warfarin or heparins, thrombolytic agents such as plasminogen activators or streptokinase to achieve synergistic effects in the treatment of various pathologies, lipid lowering agents including antihypercholesterolemics (e.g. HMG CoA reductase inhibitors such as mevastatin, lovastatin, simvastatin, pravastatin, and fluvastatin, HMG CoA synthatase inhibitors, etc.), antidiabetic drugs, or other cardiovascular agents (loop diuretics, thiazide type diuretics, nitrates, aldosterone antagonistics (i.e., spironolactone and epoxymexlerenone), angiotensin converting enzyme (e.g. ACE) inhibitors, angiotensin II receptor antagonists, beta-blockers, antiarrythmics, anti-hypertension agents, and calcium channel blockers) to treat or prevent atheriosclerosis. For example, patients suffering from coronary artery disease, and patients subjected to angioplasty procedures, would benefit from coadministration of fibrinogen receptor antagonists and coagulation cascade inhibitors of the present invention. Also, coagulation cascade inhibitors could enhance the efficiency of tissue plasminogen activator-mediated thrombolytic reperfusion.

Typical doses of coagulation cascade inhibitors of the present invention with other suitable anti-platelet agents, anticoagulation agents, cardiovascular therapeutic agents, or thrombolytic agents may be the same as those doses of coagulation cascade inhibitors administered without coadministration of additional anti-platelet agents, anticoagulation agents, cardiovascular therapeutic agents, or thrombolytic agents, or may be substantially less than those doses of coagulation cascade inhibitors administered without coadministration of additional anti-platelet agents, anticoagulation agents, cardiovascular therapeutic agents, or thrombolytic agents, depending on a patient's therapeutic needs.

All mentioned references are incorporated by reference as if here written.

Although this invention has been described with respect to specific embodiments, the details of these embodiments are not to be construed as limitations. The following examples are provided to illustrate the present invention and are not intended to limit the scope thereof. Without further elaboration, it is believed that one skilled in the art can, using the preceding descriptions, utilize the present invention to its fullest extent. Therefore the following preferred specific embodiments are to be construed as merely illus-

trative and not limitative of the remainder of the disclosure in any way whatsoever. Compounds containing multiple variations of the structural modifications illustrated in the schemes or the following Examples are also contemplated. Those skilled in the art will readily understand that known variations of the conditions and processes of the following preparative procedures can be used to prepare these compounds.

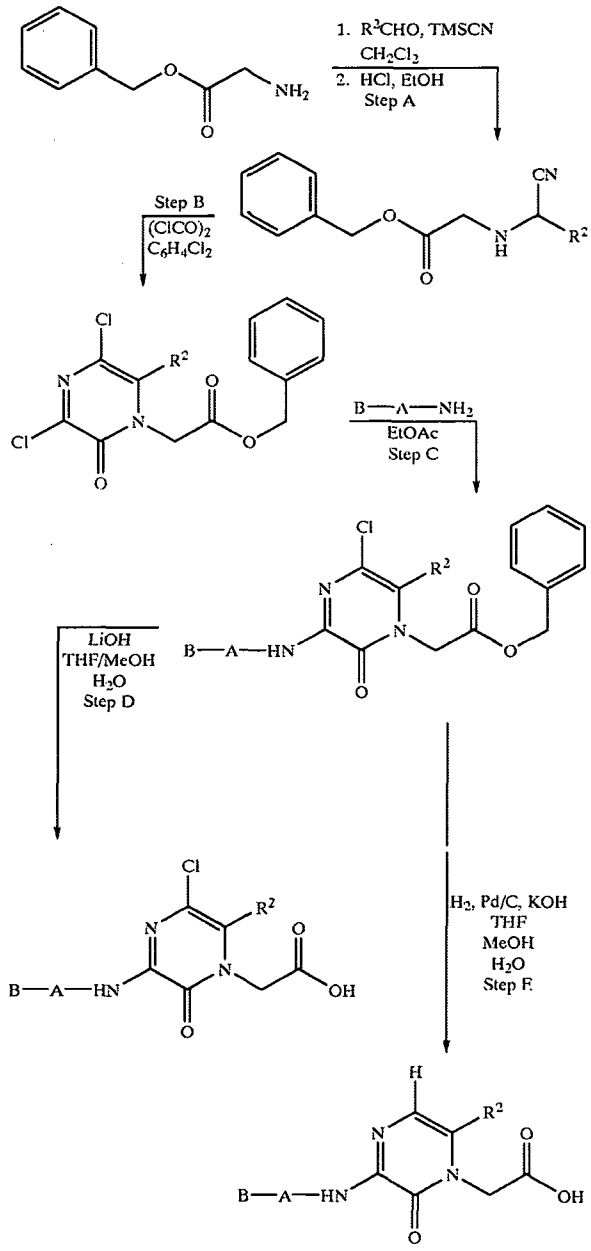
One skilled in the art may use these generic methods to prepare the following specific examples, which have been or may be properly characterized by ^1H NMR, mass spectrometry, elemental composition, and similar procedures. These compounds also may be formed in vivo. The following examples contain detailed descriptions of the methods of preparation of compounds of Formula (I). These detailed descriptions fall within the scope and are presented for illustrative purposes only and are not intended as a restriction on the scope of the invention. All parts are by weight and temperatures are Degrees centigrade unless otherwise indicated.

The following general synthetic sequences are useful in making the present invention. Abbreviations used in the schemes and tables include: "AA" represents amino acids, "AcCN" represents acetonitrile, "AcOH" represents acetic acid, "BINAP" represents 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, "BnOH" represents benzyl alcohol, "BnCHO" represents 2-phenylethanal, "$BnSO_2Cl$" represents benzylsulfonyl chloride, "Boc" represents tert-butyloxycarbonyl, "BOP" represents benzotriazol-1-yl-oxy-tris-(dimethylamino), "bu" represents butyl, "dba" represents dibenzylidene-acetone, "DCC" represents 1,3-dicyclohexylcarbodiimide, "DCM" represents dichloromethane or methylene chloride, "DIBAH" or "DIBAL" represents diisobutylaluminum hydride, "DMF" represents dimethylformamide, "DMSO" represents dimethylsulfoxide, "DPPA" represents diphenylphosphoryl azide", "EDC" represents 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride, "Ex. No." represents Example Number, "Fmoc" represents 9-fluorenylmethoxycarbonyl, "HOBt" represents hydroxybenzoltriazole", "LDA" represents lithium diisopropylamide, "MW" represents molecular weight, "NMM" represents N-methylmorpholine, "Ph" represents phenyl or aryl, "PHTH" represents a phthaloyl group, "pnZ" represents 4-nitrobenzyloxycarbonyl, "PTC" represents a phase transfer catalyst, "py" represents pyridine, "RNH_2" represents a primary organic amine, "p-TsOH" represents paratoluenesulfonic acid, "TBAF" represents tetrabutylammonium fluoride, "TBTU" represents 2-(1H-benzotriozole-1-yl)-1,1,3,3-tetramethyl uronium tetrafluoroborate, "TEA" represents triethylamine, "TFA" represents trifluoroacetic acid, "THF" represents tetrahydrofuran, "TMS" represents trimethylsilyl, "TMSCN" represents trimethylsilyl cyanide, and "Cbz" or "Z" represents benzyloxycarbonyl.

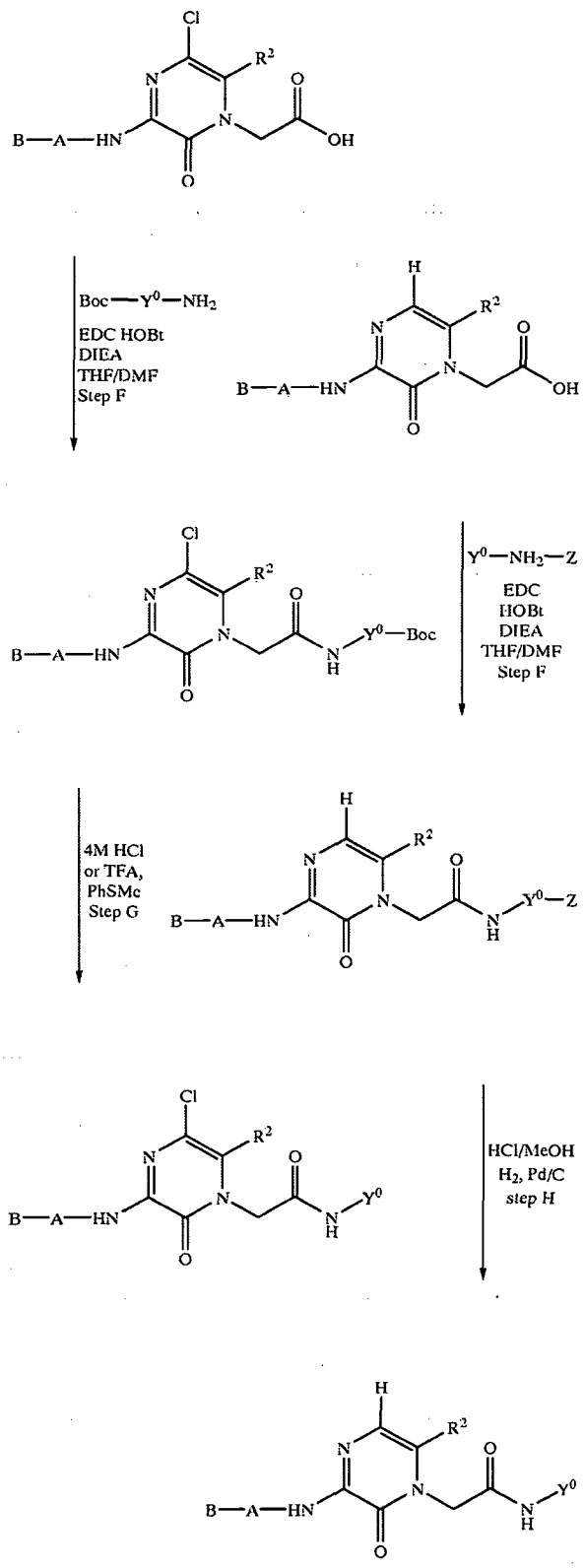
GENERAL SYNTHETIC PROCEDURES AND SPECIFIC EXAMPLES

The compounds of the present invention can be synthesized, for example, according to the following procedures and Schemes given below. The general synthetic approach to substituted pyrazinones is shown in Schemes 1 and 2 below. Treatment of benzyl glycine under Strecker reaction conditions followed by cyclocondensation with oxalyl chloride provides the pyrazinone heterocyclic core with an acetic acid ester at N-1. Heating a solution of the pyrazinone in ethyl acetate in the presence of excess amine results in the nucleophilic displacement of the C-3 chlorine atom by the amine. Stirring the substituted pyrazinone in the presence of lithium hydroxide results in the unmasking of the acid functional group. Alternatively, treatment of the pyrazinone with potassium hydroxide and catalytic palladium on carbon under an atmosphere of hydrogen results in the reductive dechlorination of the C-5 chlorine atom as well as the unmasking of the acid functional group. These acids are then coupled under standard peptide coupling conditions with various amines. These amines are typically multifunctional, and are introduced in a protected form. Removal of these protecting groups in any of several ways provides the compounds for screening. These synthetic schemes are exemplified in specific examples disclosed herein.

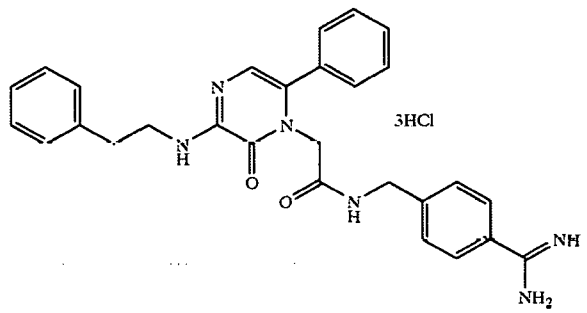
SCHEME 1
General Pyrazinone Synthesis



Scheme 2
General Pyrazinone Synthesis (Continued)



Example 1



A solution of benzyl glycine hydrochloride (78.00 g,386.8 mmol) in 1.2 L ethyl acetate was washed with brine and saturated Na_2CO_3 (1:1, 3×1 L). The organic solution was dried ($MgSO_4$), filtered, and concentrated. The resulting light yellow oil was placed on the high vacuum for approximately 15 minutes to remove residual solvent. The yellow oil was then diluted with 137.0 mL dichloromethane (2.82 M) and added benzaldehyde (39.30 mL, 386.6 mmol) slowly by syringe at room temperature. The reaction becomes slightly exothermic and turbid. The mixture was then added trimethylsilyl nitrile (51.60 mL, 386.9 mmol) drop wise via syringe over a 10 minute period, upon which a slight exotherm occurs and the reaction becomes clear and golden brown in color. The reaction was stirred for 4 hours at room temperature. The reaction mixture was then concentrated under reduced pressure . The resulting brown oil was diluted with ethyl acetate (500.0 mL), washed with brine (3×150 mL), dried ($MgSO_4$), and concentrated to leave a yellow oil. The oil was diluted ethyl acetate (80 mL) and added 9.9 M HCl (406.4 mmol) in ethanol (prepared by addition of 28.90 mL acetyl chloride to 41.0 mL cold ethanol). Upon which a white precipitate forms exothermically. The precipitate was collected by filtration, washed with ethyl ether, and dried which gave pure benzyl-N-(1-cyanobenzyl)glycine hydrochloride (EX-1A) in 35% yield: ^1H NMR (300 MHz, DMSO) δ9.13–9.00 (br s, 1H) 7.68–7.60 (m, 2H), 7.55–7.32 (m, 8H) 5.70 (s, 1H), 5.19 (s, 2H), 3.81 (d, J=5.4 Hz, 1H); ^{13}C NMR (75 MHz, DMSO) d 168.6, 136.1, 130.7, 129.78, 129.49, 129.17, 128.99, 128.92, 127.10, 67.3, 51.7, 47.1; HRMS (ES) calcd for $C_{17}H_{17}N_2O_2$ 281.1290, found 281.1311.

A suspension of benzyl-N-(1-cyanobenzyl)glycine hydrochloride (EX-1A) (42.90 g, 135.4 mmol) in 135.0 mL dry 1,2-dichlorobenzene (1.0 M) was added to oxalyl chloride (47.50 mL, 544.5 mmol) with stirring at room temperature. The resulting light brown suspension was heated to 100° C. for approximately 18 hours. Upon heating to mixture 100° C., the mixture became homogeneous and dark brown in color with gaseous HCl being evolved. The reaction was allowed to cool to room temperature and the volatiles were removed under reduced pressure. The remaining solution was passed through a silica gel column (1 L hexane flush, followed by 2 L 50% ethyl acetate/hexanes). Concentration of the solution gave a dark brown solid. The crude product was purified by MPLC (2 L hexane flush to 25% ethyl acetate/hexanes) to gave pure 1-Benzyloxycarbonylmethyl-3,5-dichloro-6-phenylpyrazinone (EX-1B) in 60% yield as a yellow solid: ^1H NMR (300 MHz, $CDCl_3$) δ7.58–7.37 (m, 6H), 7.31–7.26 (m, 4H), 5.18 (s, 2H), 4.53 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ166.4, 152.4, 146.0, 138.3, 134.9, 131.1, 130.0, 129.8, 129.1, 129.0, 128.8, 124.3, 68.2, 49.5; HRMS (ES) calcd for $C_{19}H_{15}Cl_2N_2O_3$ 389.0460, found 389.0475.

A solution of 1-benzyloxycarbonylmethyl-3,5-dichloro-6-phenylpyrazinone (EX-1B) (10.19 g, 26.19 mmol) in 103.0 mL ethyl acetate (0.255M) was added 9.90 mL phenethyl amine in one portion at room temperature. The resulting solution was heated to reflux for 18 hours. The solution was allowed to cool to room temperature which resulted in a thick precipitate forming. The reaction mixture was diluted with ethyl acetate (750.0 mL) and was washed with 0.5 N HCl (1×250 mL), saturated $NaHCO_3$ (1×250 mL) and brine (1×250 mL). The organic solution was dried ($MgSO_4$), filtered and concentrated to give the crude product. Recrystallization from ethyl acetate and hexanes afforded pure 3-(2-phenylethylamino)-5-chloro-6-phenyl-1-benzyloxycarbonylmethylpyrazinone (EX-1C) as light yellow crystals in 96% yield: ^1H NMR (300 MHz, $CDCl_3$) δ7.46–7.28 (m, 15H), 6.39 (br s, 1H), 5.25 (s, 2H), 4.54 (s, 2H), 3.81–3.79 (m, 2H), 3.04–3.00 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ167.2, 151.3, 149.2, 138.9, 135.2, 131.9, 130.7, 129.9, 129.3, 129.0, 128.95, 128.86, 128.83, 128.7, 126.9, 123.3, 67.7, 47.9, 42.5, 35.4; HRMS (EI) calcd for $C_{27}H_{25}ClN_3O_3$ 474.1584, found 474.1591.

A suspension of 3-(2-phenylethylamino)-5-chloro-6-phenyl-1-benzyloxycarbonylmethylpyrazinone (EX-1C) (1.26 g, 2.66 mmol) in 27.0 mL tetrahydrofuran and ethanol (1:1, 0.12 M) was added potassium hydroxide (463.1 mg, 8.25 mmol) in 4.0 mL water. The resulting solution was degassed (via high vacuum) three times. The solution was then added 421.1 mg 5% Pd/C in one portion. The resulting mixture was then stirred under an atmosphere of hydrogen overnight. The reaction mixture was filtered through a pad of Celite 545 then concentrated under reduced pressure to half of the original volume. The solution was then diluted with brine and acidified with 20% (w/w) $KHSO_4$ to a pH of 1. The resulting turbid solution was extracted with ethyl acetate (4×25 mL). The combined organic solutions were washed with brine (1×25 mL), dried ($MgSO_4$), filtered, concentrated to give pure 3-(2-phenethylamino)-6-phenyl-1-methylenecarboxypyrazinone (EX-1D) in 97 % yield as a white solid: ^1H NMR (300 MHz, DMSO) δ7.49–7.48 (m, 3H), 7.40–7.23 (m, 7H), 6.77 (s, 1H), 4.52 (s, 1H), 4.40 (s, 2H), 3.64–3.57 (m, 2H), 2.93 (t, J=7.4Hz, 2H); ^{13}C NMR (75 MHz, DMSO) δ169.6, 151.8, 150.6, 150.5, 143.2, 140.3, 133.2, 130.2, 129.6, 129.4, 129.3, 129.1, 128.8, 128;7, 127.3, 127.1, 126.8, 122.3, 63.6, 47.5, 42.5, 35.2; HRMS (EI) calcd for $C_{20}H_{20}N_3O_3$ 350.1505, found 350.1502.

p-Cyanobenzaldehyde (38.13 mmoles, 5 g) was stirred in 50 mL of tetrahydrofuran at 0° C. under nitrogen while lithium bis(trimethylsilyl)amide (83.89 mmoles, 84 mL of a 1.0M solution in tetrahydrofuran) was added dropwise over 10 min. After addition the mixture was allowed to warm to room temperature and stirred for 3 hr. Water (50 mL) was then added and stirring continued for 30 min. Then 2.5N sodium hydroxide (763 mmoles, 305 mL) and di-tert-butyl dicarbonate (83.89 mmoles, 18.309 g) were added along with tetrahydrofuran (100 mL) and the mixture was allowed to stir for 3 hr. The layers were then separated. The tetrahydrofuran layer was diluted with ethyl acetate and washed with brine. The water layer was extracted twice with ethyl acetate. The combined organic layers were dried over magnesium sulfate, filtered, the solvent removed in vacuo. The residue was chromatographed medium pressure liquid chromatography with 30% ethyl acetate/hexanes to give 4.03 g of desired 4-(t-butoxycarbonylamidino)benzaldehyde in 43% yield. ^1H NMR (300 MHz, $CDCl_3$) δ10.03 (s, 1H), 7.97 (d, 2H) 7.89 (d, 2H), 1.53 (s, 9H).

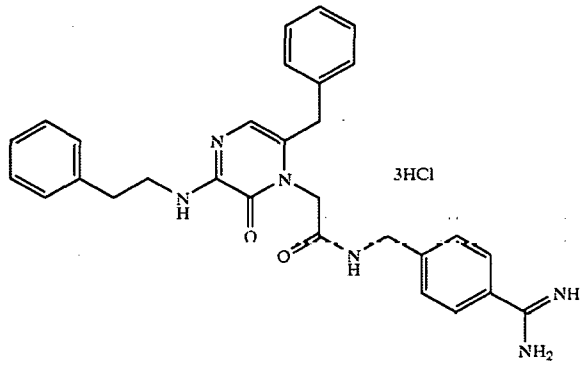
The 4-(t-butoxycarbonylamidino)benzaldehyde (4.03 mmoles, 1.0 g) was stirred in tetrahydrofuran (20 mL) at room temperature under nitrogen while allylamine (6.05 mmoles, 453 uL) was added dropwise. After addition the mixture was allowed to stir for 6 hr. The mixture was diluted with methanol (20 mL) and cooled to 0° C. Then sodium borohydride (6.04 mmoles, 22.8 mg) added in small amounts and allowed to warm to room temperature. After 2 hr the reaction was quenched with water and extracted with dichloromethane. The organic layer was dried over magnesium sulfate, filtered, and the solvent removed in vacuo. The oily residue solidified on standing. The N-allyl-4-(t-butoxycarbonylamidino)benzylamine product was used without further purification. ^1H NMR (300 MHz, $CDCl_3$) δ7.79 (d, 2H), 7.37 (d, 2H), 5.90–6.10 (m, 1H), 5.19 (dd, 2H), 3.81 (s, 2H), 3.24 (d, 2H), 1.53 (s, 9H)

The N-allyl-4-(t-butoxycarbonylamidino)benzylamine (3.97 mmoles, 1.15 g) and chlorotris(triphenylphosphine)-rhodium(I) (0.21 mmoles, 195 mg) was stirred in acetonitrile/water (84:16, 92 mL) under nitroen. The mixture was refluxed for 3 hr and allowed to cool to room temperature. Then the mixture was filtered through a pad of celite and the solvent removed in vacuo. The residue was dried on a high vacuum pump to yield an orange glassy product. 4-(t-Butoxycarbonylamidino)benzylamine product was verified by HPLC/MS and used without further purification.

A solution of 3-(2-phenethylamino)-6-phenyl-1-methylenecarboxypyrazinone (EX-1D) (521.1 mg, 1.491 mmol) in 15.0 mL tetrahydrofuran and dimethylformamide (1:1, 0.1 M) was added N,N-diisopropylethylamine (1.30 mL, 7.463 mmol), N-hydroxybenzotriazole (610.5 mg, 4.518 mmol), and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (855.3 mg, 4.461 mmol). The resulting mixture was allowed to stir for 30 minutes. The reaction mixture was then added 4-(t-butoxycarbonyl-amidino)benzylamine (763.1 mg, 3.061 mmol) prepared above in one portion. The resulting mixture was allowed to stir over night. The reaction mixture was diluted with ethyl acetate (50 mL) and washed with 5% citric acid (1×25 mL), saturated $NaHCO_3$ (1×25 mL), and brine (1×25 mL). The organic solution was dried ($MgSO_4$), filtered and concentrated. The crude reaction was purified by MPLC (75% ethyl acetate/hexanes) to give the product (EX-1E): ^1H NMR (300 MHz, DMSO) δ9.06 (br s, 1H), 8.65 (t, J=5.6 Hz, 1H), 7.94 (d, J=8.1 Hz, 2H), 7.47–7.40 (m, 6H), 7.35–7.21 (m, 8H), 6.75 (s, 1H), 4.41 (s, 2H), 4.36–4.34 (m, 2H), 3.63–3.57 (m, 2H), 2.93 (t, J =7.3 Hz, 2H), 1.48 (s, 9H); ^{13}C NMR (75 MHz, DMSO) δ167.3, 151.9, 150.7, 143.7, 140.4, 133.8, 133.4, 130.3, 129.4, 129.34, 129.29, 129.15, 129.10, 128.3, 127.6, 126.8. 122.2, 78.5, 48.7, 42.6,35.2, 28.7; HRMS (EI) calcd for $C_{33}H_{37}N_6O_4$ 581.2876, found 581.2871.

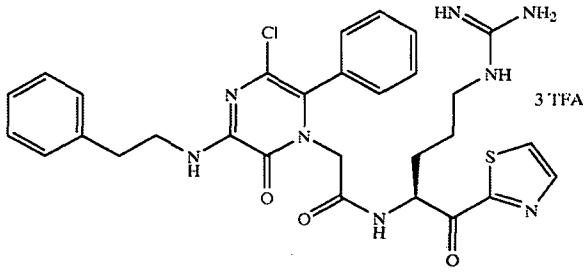
A flask of protected pyrazinone (260.7 mg, 0.449 mmol) was added 5.0 mL of 4 M HCl in dioxane. The resulting solution was allowed to stir overnight (approximately 18 hours). The solution was concentrated and the crude product was triturated from ethyl ether. The resulting white solid was collected by filtration, washed with ethyl ether and dried to give pure product. ^1H NMR (300 MHz, DMSO) δ9.57 (br s, 2H), 9.38 (br s, 2H), 9.06 (br s, 1H), 7.88 (d, J=7.9 Hz, 2H), 7.55–7.52 (m, 3H), 7.42–7.24 (m, 9H), 6.66 (s, 1H), 4.43 (s, 2H), 4.38–4.37 (m, 2H), 3.83 (br s, 2H), 3.03–2.98 (m, 2H); HRMS (EI) calcd for $C_{28}H_{29}N_6O_2$ 481.2352, found 481.2348.

Example 2



By following the method of Example 1 and substituting phenylacetaldehyde for benzaldehyde, the compound was prepared: ^{1}H NMR (400 MHz, DMSO) δ9.43 (s, 2H), 9.25 (s, 2H), 8.84 (br s, 1 H), 7.79 (d, J=8.1 Hz, 2H), 7.40–7.16 (m, 12H), 6.61 (s, 1H), 4.47 (s, 2H), 4.27 (s, 2H), 3.86 (s, 2H), 3.75 (br s, 2H), 2.94–2.90 (m, 2H); HRMS (EI) calcd for $C_{29}H_{30}N_6O_2$ 494.2430, found 494.2438.

Example 3

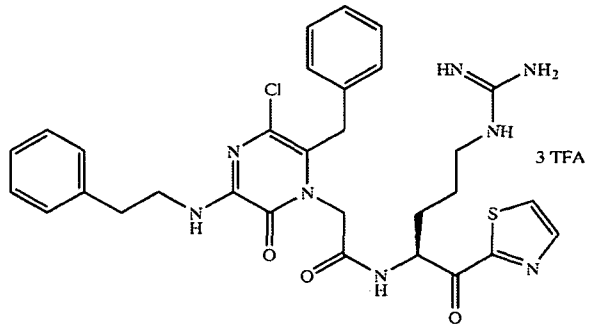


A suspension of 3-(2-phenylethylamino)-5-chlorophenyl-1-benzyloxycarbonylmethylpyrazinone (1.35 g, 2.85 mmol) in 28.0 mL tetrahydrofuran, methanol and water (3:3:1, 0.10 M) was added potassium hydroxide (0.50 g, 8.93 mmol). The mixture was then stirred 3 hours. The reaction mixture was concentrated under reduced pressure to half of the original volume. The solution was then diluted with brine and acidified with 20% (w/w) $KHSO_4$ to a pH of 1. The resulting turbid solution was extracted with ethyl acetate (4×25 mL). The combined organic solutions were washed with brine (1×25 mL), dried ($MgSO_4$), filtered, concentrated to give pure EX-3A (3-(2-phenethylamino)-5-chloro-6-phenyl-1-methylenecarboxypyrazinone) in 88% yield as a white solid; ^{1}H NMR (300 MHz, DMSO) δ13.15 (br s, 1H), 7.84 (br s, 1H), 7.51–7.50 (br m, 3H), 7.33–7.24 (m, 7H), 4.24 (s, 2H), 3.58 (br s, 2H), 2.94 (br s, 2H); ^{13}C NMR (75 MHz, DMSO) δ169.2, 151.0, 149.6, 140.1, 132.4, 131.1, 130.2, 129.6, 129.3, 129.1, 126.9, 125.4, 123.4, 48.1, 42.8, 34.8; HRMS (EI) calcd for $C_{20}H_{19}ClN_3O_3$ 384.1115, found 384.1118.

A solution of (S)-N-[[[4-amino-5-oxo-5-(thiazolyl) pentyl]amino]iminomethyl]-4-methoxy-2,3,6-trimethylbenzenesulfonamide dihydrochloride (1.664 g, 3.161 mmol) in 29.0 mL tetrahydrofuran and dimethylformamide (1:1, 0.10 M) was added N,N-diisopropylethylamine (5.00 mL, 28.70 mmol). The resulting mixture was allowed to stir for 10 minutes at room temperature. The solution was then added 3-(2-Phenylethylamino)-5-chloro-6-phenyl-1-methylenecarboxypyrazinone (1.104 g, 2.877 mmol), N-hydroxybenzotriazole (466.8 mg, 3.454 mmol), and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (673.1 mg, 3.511 mmol). After the addition was complete the solution was allowed to stir over night. The reaction mixture was diluted with ethyl acetate (50 mL). The organic solution was washed with 5% citric acid (1×25 mL), saturated $NaHCO_3$ (1×25 mL), and brine (1×25 mL). The organic solution was dried ($MgSO_4$), filtered and concentrated. The crude reaction mixture was purified by MPLC (75% ethyl acetate/hexanes) to give pure product EX-3B: ^{1}H NMR (300 MHz, $CDCl_3$) δ8.04 (d, J=3.0 Hz, 1H), 7.75 (d, J=2.8 Hz, 1H), 7.57 (br s, 1H), 7.42–7.21 (m, 11H), 6.54 (s, 2H), 6.31 (s, 2H), 5.63 (br s, 1H), 4.60 (d, J=16.2 Hz, 1H), 4.21 (d, J=16.5 Hz, 1H), 3.84 (s, 3H), 3.77–3.66 (m, 2H), 3.17 (br s, 1H), 2.96 (d, J=7.2 Hz, 2H), 2.68 (s, 3H), 2.60 (s, 3H), 2.14 (s, 3H), 1.79–1.66 (m, 3H); HRMS (EI) calcd for $C_{39}H_{44}ClN_8O_6S_2$ 819.2514, found 819.2512.

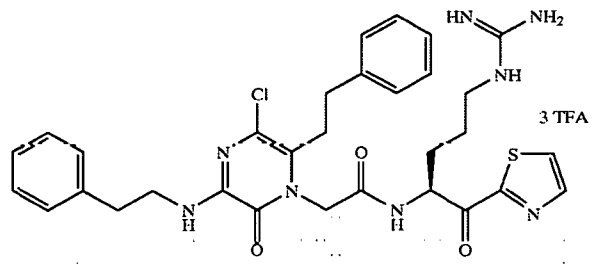
A solution of material EX-3B (928.1 mg, 1.133 mmol) in 11.3 mL trifluoroacetic acid (0.1 M) was added to thioanisole (0.400 mL, 3.407 mmol) at room temperature with stirring. The resulting mixture was allowed to stir 6 hours. The reaction mixture was concentrated under reduced pressure. The crude product was purified by trituration from ethyl ether. A yellow powder was collected by filtration, washed with ethyl ether to give the pure product: ^{1}H NMR (300 MHz, DMF) δ8.76 (d, J=7.2 Hz, 1H), 8.51–8.50 (m, 1H), 8.42–8.41 (m, 1H), 8.17 (br s, 1H), 7.92–7.45 (m, 10 H), 5.74 (br s, 1H), 4.67–4.65 (m, 2H), 3.89–3.87 (m, 2H), 3.52 (br s, 2H), 3.23–3.20 (m, 2H), 2.73 (s, 2H), 2.19 (br s, 1H), 1.88 (br s, 3H); HRMS (EI) calcd for $C_{29}H_{32}ClN_8O_3S$ 607.2007, found 607.2000.

Example 4



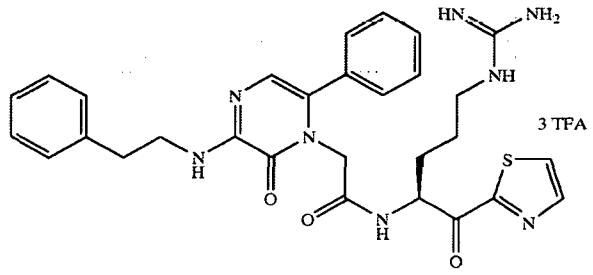
By following the method of Example 3 and substituting 3-(2-phenethylamino)-5-chloro-6-benzyl-1-methylenecarboxypyrazinone for 3-(2-phenethylamino)-5-chloro-6-phenyl-1-methylenecarboxypyrazinone, the title compound was prepared: HRMS (EI) calcd for $C_{30}H_{34}ClN_8O_3S$ 621.2163, found 621.2171.

Example 5



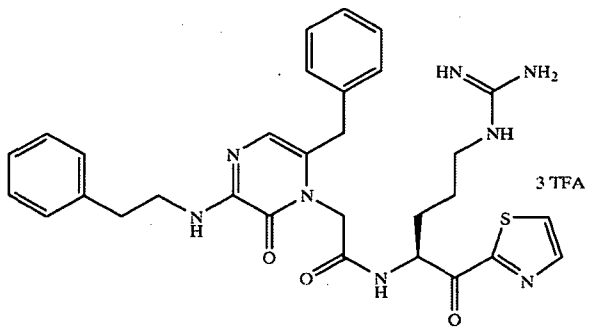
By following the method of Example 3 and substituting 3-(2-phenethylamino)-5-chloro-6-(2-phenylethyl)-1-methylenecarboxypyrazinone for 3-(2-phenethylamino)-5-chloro-6-phenyl-1-methylenecarboxypyrazinone, the title compound was prepared: HRMS (EI) calcd for $C_{31}H_{36}ClN_8O_3S$ 635.2320, found 635.2330.

Example 6



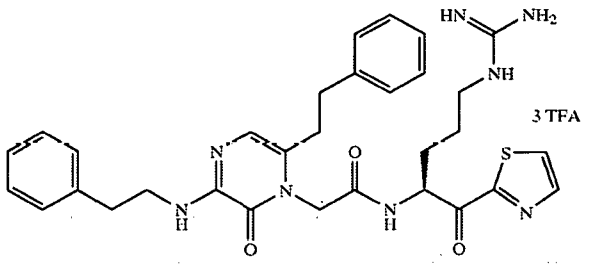
By following the method of Example 3 and substituting 3-(2-phenethylamino)-6-phenyl-1-methylenecarboxypyrazinone for 3-(2-phenethylamino)-5-chloro-6-phenyl-1-methylenecarboxypyrazinone, the title compound was prepared: HRMS (EI) calcd for $C_{29}H_{33}N_6O_3S$ 573.2396, found 573.2399.

Example 7



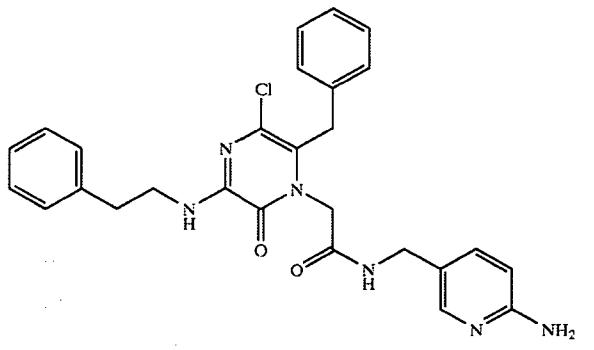
By following the method of Example 3 and substituting 3-(2-phenethylamino)-6-benzyl-1-methylenecarboxypyrazinone for 3-(2-phenethylamino)-5-chlorophenyl-1-methylenecarboxypyrazinone, the title compound was prepared: HRMS (EI) calcd for $C_{30}H_{35}N_8O_3S$ 587.2553, found 587.2564.

Example 8



By following the method of Example 3 and substituting 3-(2-phenethylamino)-6-(2-phenylethyl)-1-methylenecarboxypyrazinone for 3-(2-phenethylamino)-5-chloro-6-phenyl-1-methylenecarboxypyrazinone, the title compound was prepared: HRMS (EI) calcd for $C_{31}H_{37}N_8O_3S$ 601.2709, found 601.2714.

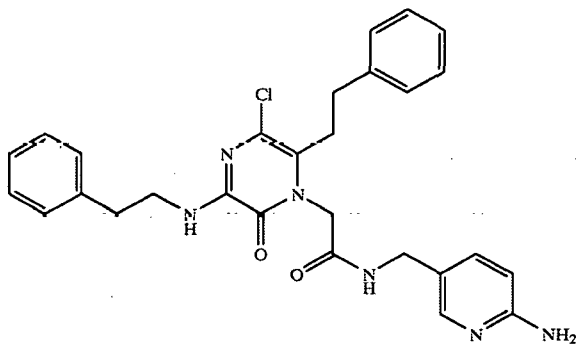
Example 9



A solution of 2-amino-5-aminomethylpyridine in 1.60 mL tetrahydrofuran (0.13 M) was added to N,N-diisopropylethylamine (0.145 mL, 0.832 mmol). The resulting mixture was allowed to stir for 10 minutes at room temperature. The solution was then added to 3-(2-Phenylethylamino)-6-benzyl-5-chloro-1-methylenecarboxypyrazinone (81.6 mg, 0.2051 mmol), N-hydroxybenzotriazole (38.1 mg, 0.2819 mmol), and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (49.6 mg, 3.511 mmol). The reaction mixture was then allowed to stir over night. The reaction mixture was diluted with ethyl acetate (50 mL). The organic solution was washed with 5% citric acid (1×25 mL), saturated $NaHCO_3$ (1×25 mL), and brine (1×25 mL). The organic solution was dried ($MgSO_4$), filtered and concentrated. The crude reaction mixture was purified by MPLC (ethyl acetate) to give pure product: ^1H NMR (300 MHz, DMSO) δ8.50 (br s, 1 H), 7.83 (s, 1H), 7.68 (br s, 1H), 7.34–7.19 (m, 13H), 6.46–6.43 (m, 1H), 5.90 (br s, 1H), 4.42 (s, 2H), 4.09 (br s, 2H), 3.98 (br s, 2H), 3.56 (br s, 3H), 2.94 (br s, 3H); HRMS (EI) calcd for $C_{27}H_{28}ClN_6O_2$ 503.1962, found 503.1968.

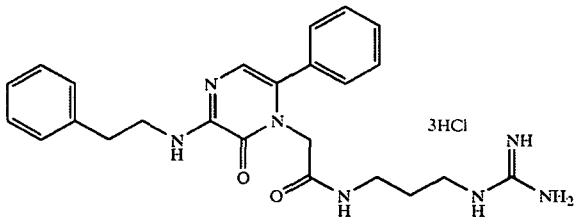
Example 10

3-(2-Phenylethylamino)-5-chloro-6-phenethyl-1-(2-amino-5-methylcarboxamidomethylpyridinyl) pyrazinone



By following the method of Example 9 and substituting 3-(2-phenethylamino)-5-chloro-6-(2-phenylethyl)-1-methylenecarboxypyrazinone for 3-(2-phenethylamino)-5-chlorobenzyl-1-methylenecarboxypyrazinone, the title compound was prepared: HRMS (EI) calcd for $C_{28}H_{30}N_6O_2$ 517.2119, found 517.2127.

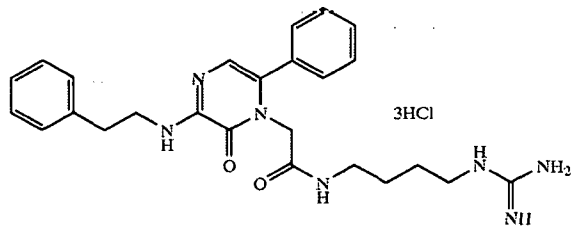
Example 11



A solution of 3-(2-phenethylamino)-6-phenyl-1-methylenecarboxypyrazinone (217.6 mg, 0.6228 mmol) in 6.3 mL tetrahydrofuran and dimethylformamide (1:1, 0.1 M) was added N,N-diisopropylethylamine (1.00 mL, 5.741 mmol), N-hydroxybenzotriazole (171.1 mg, 1.266 mmol), and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (240.0 mg, 1.252 mmol). The resulting mixture was allowed to stir for 30 minutes. The reaction mixture was then added to the 3-(di-Boc-guanidino)propanamine (1.30 mg, 3.684 mmol) in one portion. The resulting mixture was allowed to stir over night. The reaction mixture was diluted with ethyl acetate (50 mL) and washed with 5% citric acid (1×25 mL), saturated $NaHCO_3$ (1×25 mL), and brine (1×25 mL). The organic solution was dried ($MgSO_4$), filtered and concentrated. The crude reaction was purified by MPLC (75% ethyl acetate/hexanes) to give the product EX-11A: ^{1}H NMR (300 MHz, DMSO) δ11.42 (s, 1H), 8.46 (t, J=6.3 Hz, 1H), 7.92 (t, J=6.0 Hz, 1H), 7.46–7.41 (m, 5H), 7.37–7.23 (m, 5H), 6.86 (s, 1H), 6.24 (br s, 1H), 4.49 (s, 2H), 3.79–3.72 (m, 2H), 3.48–3.42 (m, 2H), 3.31–3.25 (m, 2H), 3.00 (t, J=7.1 Hz, 2 H), 1.53 (s, 9H), 1.40 (s, 9H); HRMS (EI) calcd for $C_{34}H_{457}O_6$ 648.3510, found 648.3498.

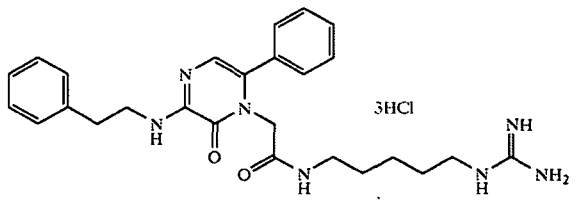
A flask of protected guanidine EX-11A (260.7 mg, 0.449 mmol) was added to 5.0 mL of 4 M HCl in dioxane. The resulting solution was allowed to stir for 4 hours. The solution was concentrated and the crude product was triturated from ethyl ether. The resulting white solid was collected by filtration, washed with ethyl ether and dried to give pure product: ^{1}H NMR (300 MHz, DMSO) δ9.65 (br s, 1H), 8.48 (t, J=5.1 Hz, 1H), 7.96 (t, J=5.4 Hz, 1H), 7.60–7.22 (m, 13H), 6.66 (s, 1H), 4.32 (s, 2H), 3.82 (br s, 2H), 3.13–3.09 (m, 2H), 3.03–2.98 (m, 2H), 1.59–1.54 (m, 2H); HRMS (EI) calcd for $C_{24}H_{29}N_7O_2$ 448.2461, found 448.2425.

Example 12



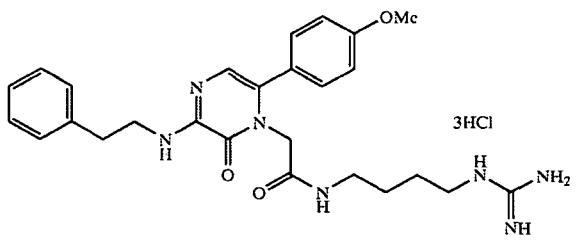
By following the method of Example 11 and using the appropriate butanamine, the title compound was prepared: HRMS (EI) calcd for $C_{25}H_{31}N_7O_2$ 462.2617, found 462.2575.

Example 13



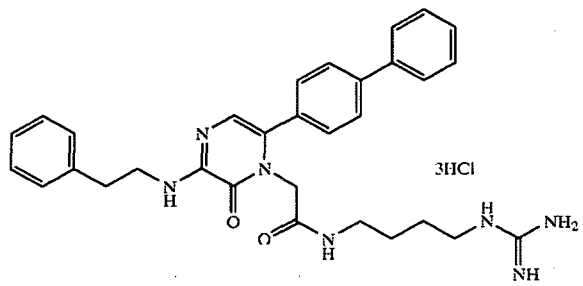
By following the method of Example 11 and using the appropriate pentanamine, the title compound was prepared: FRMS (EI) calcd for $C_{26}H_{33}N_7O_2$ 476.2774, found 476.2783.

Example 14



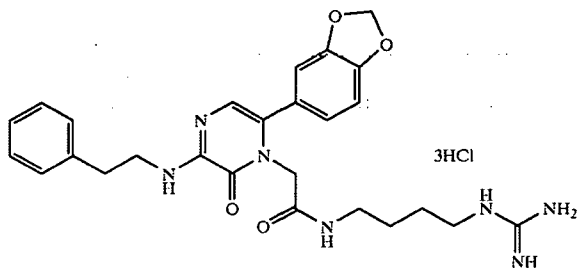
By following the method of Example 11 and using the appropriate butanamine with 3-(2-phenethylamino)-6-(4-methoxyphenyl)-1-methylenecarboxypyrazinone, title compound was prepared: HRMS (EI) calcd for $C_{26}H_{34}N_7O_3$ 492.2723, found 492.2693.

Example 15



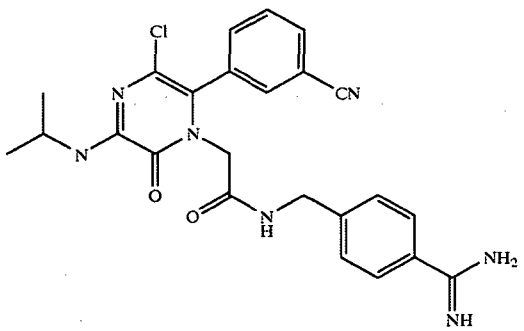
By following the method of Example 11 and using the appropriate butanamine with 3-(2-phenethylamino)-6-(4-biphenyl)-1-methylenecarboxypyrazinone, the title compound was prepared: HRMS (EI) calcd for $C_{31}H_{36}N_7O_2$ 538.2930, found 538.2918.

Example 16



By following the method of Example 11 and using the appropriate butanamine with 3-(2-phenethylamino)-6-(3,4-methylenedioxyphenyl)-1-methylenecarboxypyrazinone, the title compound was prepared: HRMS (EI) calcd for $C_{26}H_{32}N_7O_4$ 506.2516, found 506.2506.

Example 17

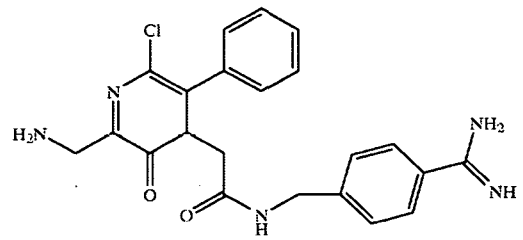


Using the procedures of Schemes 1 and 2 and Example 1, 2-{5-chloro-6-(3-bromophenyl)-3-[(methylethyl)amino]-2-oxohydropyrazinyl}acetic acid was prepared.

A solution of 2-{5-chloro-6-(3-bromophenyl)-3-[(methylethyl)amino]-2-oxohydropyrazinyl}acetic acid (7.4 g, 18.47 mmol) and copper (1) cyanide (1.75 g, 19.55 mmol) in 75.0 mL dimethylsulfoxide was heated at 150° C. for 20 hours. The flask was then cooled and the contents were poured into a solution of 500 mL water and 100 mL 1M HCl. The mixture was then extracted with ethyl acetate (2×1 L). The ethyl acetate layers were separated, combined, dried over magnesium sulfate, filtered, and stripped of solvent under reduced pressure. Purification by HPLC (25% ethyl acetate in hexanes) provided 2-{5-chloro-6-(3-cyanophenyl)-3-[(methylethyl)amino]-2-oxohydropyrazinyl}acetic acid (EX-17A) of adequate purity: ^{1}H NMR (400 MHz, $CDCl_3$) δ7.8–7.4 (br, 4H), 4.4 (br, 2H), 2.2 (br, 1H), 1.3 (br d, 6H); MS (ES) calcd for $C_{15}H_{15}ClN_4O_3$ 346, found 347 (M+H).

2-{5-chloro-6-(3-cyanophenyl)-3-[(methylethyl)amino]-2-oxohydropyrazinyl}acetic acid (EX-17A) was converted to the product as described in Example 1. Mass spectral analysis gave an m/z+1 of 478.

Example 18



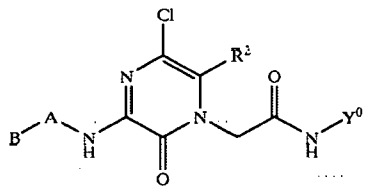
A solution of 3.90 g (10 mmol) of EX-1B in 50 mL of CH_3NO_2 was treated with 4.5 mL of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). After 30 minutes, the reaction was poured into 300 mL of ethyl acetate and washed with 2×25 mL 1 N HCl (aq). The excess organic solvent was removed under reduced pressure. The resulting oil was treated with 25 mL H_2O and 25 mL CH_3OH. The solution was treated with 2.8 g of KOH. After 60 minutes, the reaction was diluted with 300 mL of acetonitrile. The resulting solid was washed with 100 mL of acetonitrile. The solid was dissolved in 50 mL 1N HCl (aq) and extracted with 2×100 mL CH_2Cl_2. The organic layer was dried with $MgSO_4$, and the excess solvent removed under reduced pressure. The resulting solid was washed with diethyl ether and dried in ambient conditions to give 2.1 g (6.4 mmol; 64% yield) of desired product (EX-18A). LC/MS showed a single peak at 254 nm and a M+Na at 346. ^{1}H-NMR (dmso-d_6): 4.4 ppm (2H, s); 5.6 ppm (2H, s); 7.3–7.5 ppm (5H, m).

The product was obtained using standard coupling conditions and deprotection methods under reducing conditions of Example 1 to give the desired product after purification by HPLC. LC/MS showed a single peak at 254 nm and a M+H at 425. ^{1}H-NMR (dmso-d_6): 4.2 ppm (2H, s); 4.4 ppm (2H, m); 4.6 ppm (2H, m); 7.4 ppm (5H, m) 7.6–7.8 ppm (4H, m); 8.4 ppm (2H, bs); 8.7 (1H,m); 9.1 ppm (2H, bs); 9.3 ppm (2H,bs).

Using the procedures of Scheme 1, Scheme 2, and Example 1 through Example 18 with suitable reagents, starting materials, intermediates, and additional pyrazinones of the present invention were prepared by one skilled in the art using similar methods and these pryazinones summarized in Table 1.

TABLE 1

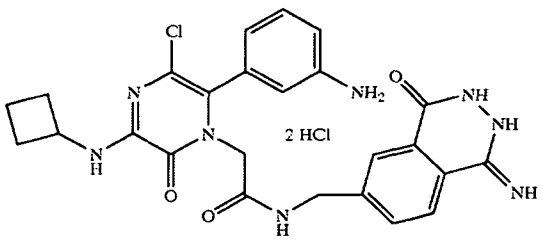
Additional Substituted Pyrazinones Prepared by Procedures of Scheme 1, Scheme 2, and Examples 1 through 18



General Structure

Ex. No.	R^2	B-A	Y^0	MW (m/z + 1)
19	phenyl	2-(4-pyridyl)ethyl	4-amidinobenzyl	516.3
20	benzyl	2-phenylethyl	4-amidinobenzyl	528.9
21	biphenyl	2-(3-pyridyl)ethyl	4-amidinobenzyl	591.9
22	biphenyl	2-(4-chlorophenyl)-ethyl	4-amidinobenzyl	625.5
23	3-chlorophenyl	benzyl	4-amidinobenzyl	535.3
24	biphenyl	2-phenylethyl	4-amidinobenzyl	591.5

Example 25



To a solution of 2-iodo-5-methyl benzoic acid (10.0 g, 0.038 mol) in toluene (200 mL) was added trimethylorthoacetate (25 mL) at room temperature. The reaction mixture was refluxed for 12 hours. The reaction mixture was cooled to room temperature and diluted with saturated sodium bicarbonate and ethyl acetate. The layers were separated and the organic layer washed with brine. The organic layer was dried ($MgSO_4$) and solvent removed to give 10.35 g of methyl 2-iodo-5-methylbenzoate (EX-25A) as a yellow oil with an m/z+1=277.

A degasssed mixture of ester EX-25A (10.35 g, 0.037 mol)), $Pd(dba)_3$ (0.017 g, 0.018 mmol)), dppf (0.025 g, 0.045 mmol)) and $Zn(CN)_2$ (2.6 g, 0.02 mol) in DMF (100 mL) was heated to 120° C. for 2 hours. The reaction mixture was poured into water and ethyl acetate. The organic layer was washed with water (2×) and brine (1×). The organic layer was collected, dried ($MgSO_4$) and the solvent removed in vacuo to give 5.28 g methyl 2-cyano-5-methylbenzoate (EX-25B) as a brownish oil with m/z+1=176.

To a solution of EX-25B (5.28 g, 0.03 mol) in CCl_4 (100 mL) was added NBS (5.37 g, 0.03 mol) and benzoyl peroxide (0.36 g, 0.0015 mol) at room temperature. The reaction mixture was heated to reflux for 15 hours. The reaction was cooled and the precipitate filtered away. The organic filtrate was diluted with ether and washed with saturated sodium bicarbonate. The organic layer was dried ($MgSO_4$) and the solvent removed in vacuo to give an oil, which after chromatography (silica, hexanes to 30% ether/hexanes) gave 1.57 g methyl 2-cyano-5-bromomethylbenzoate (EX-25C) as a tan solid with m/z+1=255.

To a solution of di-tert-butyl iminodicarboxylate (1.48 g, 7.5 mmol) in THF at 0° C. was added NaH (0.31 g, 7.8 mmol). After stirring at room temperature for 30 minutes, EX-25C (1.57 g, 6.0 mmol) was added as a solution in THF via canula. The reaction was complete after 2.5 hours at room temperature. The reaction was quenched by addition of water and ether. The layers were separated and the organic layer washed with brine (2×), dried ($MgSO_4$) and the solvent removed in vacuo to give 2.36 g methyl 2-cyano-5-(N,N-bis-Bocaminomethylbenzoate (EX-25D) as a yellowish solid with m/z+1=391.

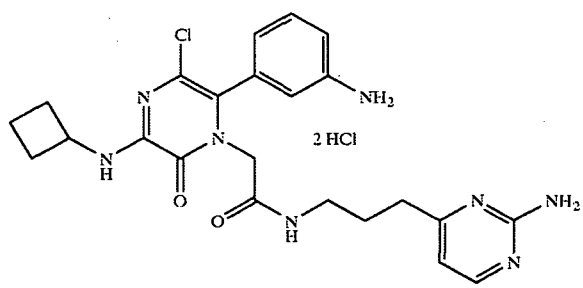
To a solution of EX-25D (0.20 g, 0.5 mmol) in anhydrous methanol (10 mL) was added anhydrous hydrazine (1 mL, 32 mmol)) at room temperature. The reaction was heated to 70° C. overnight. The solvent was removed in vacuo to give a solid, which was suspended in ether and filtered to give 0.11 g of the product EX-25E as a white solid with an m/z+1=291.

To a solution of EX-25E (0.22 g, 0.78 mmol) in dichloromethane (5 mL) at room temperature was added trifluoroacetic acid (5 mL). After 30 min, the solvent was removed in vacuo to give a clear residue, which upon drying on high vacuum became a white solid EX-25F (0.39 g) with m/z+1=191.

To a solution of 2-{5-chloro-6-(3-aminophenyl)-3-cyclobutylamino-2-oxohydropyrazinyl}acetic acid (0.93 g, 2.6 mmol) in DMF (20 mL) was added EDC (0.64 g, 3.3 mmol) and HOBt (0.44 g, 3.2 mmol) at room temperature. After 30 min, the amine EX-25F in a solution of DMF and triethylamine (1.76 mL, 0.01 mol) was added to the acid. The reaction mixture was stirred for 1 hour and then poured into $NaHCO_{3\ (aq)}$ and ethyl acetate. The layers were separated and the aqueous layer extracted with ethyl acetate (2×) The organic layer was washed with brine (1×), dried ($MgSO_4$), and the solvent removed in vacuo to give a brown oil, which after chromatography (silica, dicholoromethane to 10% methanol/dichloromethane) gave the product EX-25G (0.29 g) with m/z+1=521.

To a suspension of EX-25G (0.29 g, 5.6 mmol) in ether (5 mL) was added 25 mL of 2.0 M HCl in ether. The reaction was stirred for 30 min to give a fine precipitate which was filtered and dried to give the product (0.37 g) with m/z+1=521. Analysis $C_{25}H_{25}Cl_2N_8O_3$+1.8 HCl+2.15 H_2O gave C, 47.78%; H, 5.22%; N, 16.29%; O, 12.59%; Cl, 15.43%.

Example 26



To a solution of 2-Amino-4-methylpyrimidine (1.0 g, 9.0 mmol) in THF (100 mL) at 0° C. was added TMEDA (4.15 mL, 27.0 mmol) and n-butyl lithium (17.2 mL, 27.0 mmol).

After stirring at 0° C. for 30 min, (2-bromoethoxy)-tert-butyldimethylsilane (2.16 mL, 10 mmol) was added in a solution of THF (20 mL) dropwise via canula. The reaction was allowed to warm to room temperature overnight. The reaction was diluted with water and ether. The aqueous layer was extracted (2×) with ether. The organic layer was washed with brine, dried ($MgSO_4$), and solvent removed in vacuo to give a brown oil, which after chromatography (silica, dichloromethane to 10% methanol/dicholoromethane) gave EX-26A (1.26 g) with m/z+1=268.

To a solution of EX-26A (4.36 g, 16.0 mmol) in dichloromethane (100 mL) was added triethylamine (3.4 mL, 24 mmol), di-tert-butyl dicarbonate (4.53 g, 24 mmol) and DMAP (0.2 g, 0.16 mmol). After stirring at room temperature for 24 hours the reaction was poured into aqueous sodium bicarbonate and ether. The layers were separated and the aqueous layer extracted (2×) with ether. The organic layer was washed with brine, and the solvent removed in vacuo to give a red oil (4.4 g). The oil was purified by chromatography (silica, 60% ethyl acetate/hexanes) to give a yellow oil EX-26B (2.77 g) with m/z+1=468.

To a solution of EX-26B (2.77 g, 6.0 mmol) in THF (100 mL) was added TBAF (7.1 mL, 1 M in THF) dropwise. After 4 hours at room temperature the reaction was complete. The reaction mixture was poured into ethyl acetate and brine. The aqueous layer was extracted 2× with ethyl acetate. The organic layer was dried ($MgSO_4$) and the solvent removed to give a yellow oil, which after chromatography (silica, 70% ethyl acetate/hexanes to 100% ethyl acetate) gave 1.51 g of the alcohol 2-(bis-Boc-amino)-4-(3-hydroxypropyl) pyrimidine (EX-26C) as a yellow oil with an m/z+1=354.

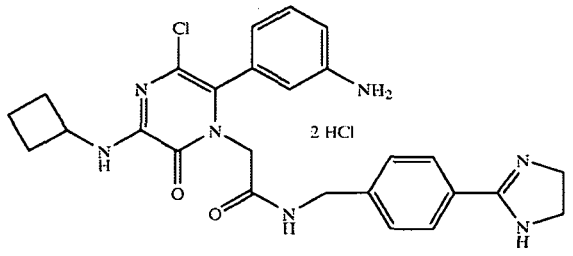
To a solution of EX-26C (1.38 g, 4.0 mmol) in toluene (20 mL) was added triethylamine (0.54 mL, 4.0 mmol) and methanesulfonyl chloride (0.30 mL, 4.0 mmol). After 10 min, no starting material was observed by TLC. The reaction mixture was poured into dichloromethane and water. The layers were separated and the organic layer was washed with brine and dried (Na_2SO_4). The solvent was removed to give a yellow oil EX-26D which was used without further purification. To the crude mesylate EX-26D (1.73 g, 4.0 mmol) in DMF (10 mL) was added NaN_3 (2.6 g, 40 mmol) and water (1 mL). The reaction mixture was stirred at room temperature for 18 hours. The reaction was diluted with ether and water. The layers were separated and the organic layer washed with brine and dried (Na_2SO_4). The solvent was removed to give an oil, which after chromatography (silica, 60% ethyl acetate/hexanes) gave the azide EX-26E (0.91 g) with a m/z+1=379.

To a solution of 2-(bis-Boc-amino)-4-(3-azidopropyl) pyrimidine (EX-26E) (0.39 g, 1.0 mmol) in ethanol at room temperature was added 10% Pd/C and a hydrogen balloon. After stirring at room temperature for 3 hours the reaction was complete by TLC. The reaction mixture was filtered through a pad of celite and washed with ethanol. The solvent was removed in vacuo to give an oil (0.35 g) which was a mixture of Boc derivatives EX-26F. To a solution of EX-26F (0.32 g) in dichloromethane (7 mL) was added trifluoroacetic acid (3 mL) dropwise. After 30 min, the solvent was removed in vacuo to give 0.34 g of the free amine 2-amino-4-(3-aminopropyl)pyrimidine (EX-26G) as an oil with an m/z+1=353.

To a solution of anilino-acid 2-{5-chloro-6-(3-aminophenyl)-3-cyclobutylamino-2-oxohydropyrazinyl}acetic acid (1.46 g, 4.2 mmol) in DMF (30 mL) was added HOBt (0.91 g, 6.7 mmol) and EDAC (1.29 g, 6.7 mmol) at room temperature. After stirring for 30 min, EX-26G (1.59 g, 4.2 mmol) in DMF (8 mL) and triethylamine (3.5 mL, 25.2 mmol) was added. After 30 min, the reaction was diluted with aqueous sodium bicarbonate and ethyl acetate. The layers were separated and aqueous layer extracted (2×) with ethyl acetate. The organic layer was washed with brine and dried ($MgSO_4$). The solvent was removed in vacuo to give an oil, which after chromatography (dichloromethane to 15% methanol dichloromethane) gave the product EX-26H (1.20 g) as a yellow foam with an m/z+1=483.

To a solution of EX-26H (0.32 g, 0.67 mmol) in 5 mL of ether was added 20 mL of 3.0 M HCl in ether at room temperature. The reaction mixture was stirred at room temperature for 20 minutes to give a precipitate which was filtered to give a yellow solid (0.34 g) of the di-hydrochloride salt. The solid was purified by RP-HPLC to give (0.22 g) with an m/z+1=483.

Example 27



To a solution of the mixture N-Boc and N,N-bis-Boc 4-(N'-Z-amidino)benzylamines (3.0 g, 6.2 mmol) in 50 mL of EtOH and 20 mL THF was added 300 mg of 5% Pd(C). The solution was hydrogenated at 40 psi H_2 in a Parr shaker for 18 hrs. The catalyst was filtered off, and the filtrate concentrated in-vacuo to afford the mixture EX-27A (2.1 g, 6.0 mmol) of N-Boc and N,N-bis-Boc 4-amidinobenzylamines as a brownish oil with M+H of 250 (monoBoc) and M+H of 350 (diBoc).

A solution of EX-27A (2.1 g, 6.0 mmol) in MeOH was treated with ethylenediamine (1.13 g, 18.9 mmol). The mixture was heated to reflux for 18 hrs, cooled to room temperature and concentrated in vacuo. 50 mL of H_2O was added and extracted 3× with CH_2Cl_2. The organic extracts were dried over $MgSO_4$, filtered and condensed in vacuo to afford the mixture EX-27B (2.2 g, 5.9 mmol) as a tan solid with M+H of 276 (monoBoc) and M+H of 376 (diBoc).

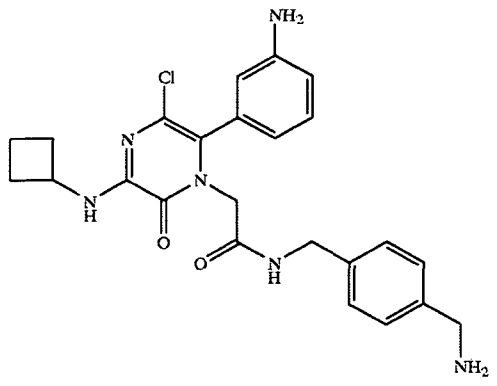
A solution of the mixture EX-27B (2.2 g, 5.9 mmol) in 20 mL methylene chloride and 5 mL pyridine was treated with benzyl chloroformate (1.3 g, 7.7 mmol). The mixture was stirred for 1.5 hrs and then was added 100 mL methylene chloride and 100 mL 0.5 N HCl. The layers were seperated, and the aqueous extracted 2× with methylene chloride The organics were combined, washed 1× with brine, dried over $MgSO_4$, filtered and condensed in vacuo. Purification by column chromatography (silica gel 200–400 mesh) using 50% ethyl acetate as elutant afforded the mixture EX-27C (1.1 g, 2.2 mmol) as a tan oil with M+H 410 (monoBoc) and M+H 510 (diBoc).

A solution of the mixture EX-27C (800 mg, 1.6 mmol) in 10 mL of methylene chloride was treated with 5 mL of 4N HCl in dioxane. The mixture was stirred for 1.5 hrs. and then diethyl ether was added to precipitate the product. The precipitate was filtered off and washed extensively with diethyl ether to afford the HCl salt EX-27D (520 mg, 1.7 mmol) as a tan solid with an M+H of 310.

A solution of 2-{5-chloro-6-(3-nitrophenyl)-3-cyclobutylamino-2-oxohydropyrazinyl}acetic acid (329 mg, 0.86 mmol) in 10 mL of methylene chloride was treated with HOBt (127 mg, 0.94 mmol) for 20 min. Then was added EDC (180 mg, 0.94 mmol), DIEA (335 mg, 2.6 mmol), and EX-27D (300 mg, 0.86 mmol), and the reaction was allowed to stir for 1 hr. Water was then added, and the reaction mixture extracted 3× with methylene chloride. The organics were then washed 1× with brine, dried over $MgSO_4$, filtered and condensed in vacuo. Purification by column chromatography (silica gel 200–400 mesh) eluting with 90% ethyl acetate/hexane and then 100% ethyl acetate afforded EX-27E (325 mg, 0.48 mmol) as a yellow solid which gave an M+H of 670.

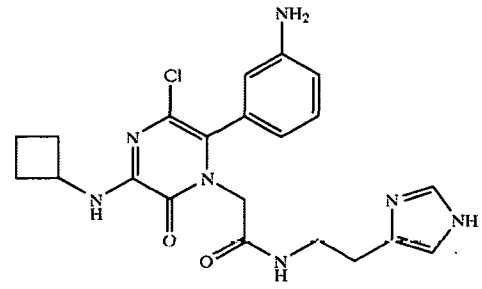
A solution of EX-27E (325 mg, 0.48 mmol) in 10 mL of MeOH was treated with 0.7 mL of 3N HCl in MeOH and 5% Pd(C) (50 mg). The mixture was hydrogenated at 45 psi on a Parr shaker apparatus for 2 hrs. The catalyst was then filtered off and washed extensively with MeOH. The filtrate was concentrated in vacuo. The residue was dissolved in EtOH and triturated with diethyl ether. The solid formed was filtered and extensively washed with diethyl ether to afford the HCl salt product (220 mg, 0.43 mmol) as an off-white solid which gave M+H's of 506 (100%) and 508 (60%).

Example 28



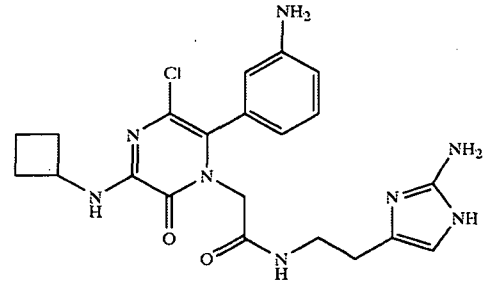
Using the procedures of Scheme 1, Scheme 2, and Example 1 through Example 18 with suitable reagents, starting materials, 2-{5-chloro-6-(3-nitrophenyl)-3-cyclobutylamino-2-oxohydropyrazinyl}acetic acid and 4-(N-Boc-aminomethyl)benzylamine prepared according to the literature reference (Callahan, J. F., Ashton-Shue, D., et al., *J. Med. Chem.* 1989, 32, 391–396), the product was obtained and gave an m/z(M+H)$^+$ of 467.

Example 29



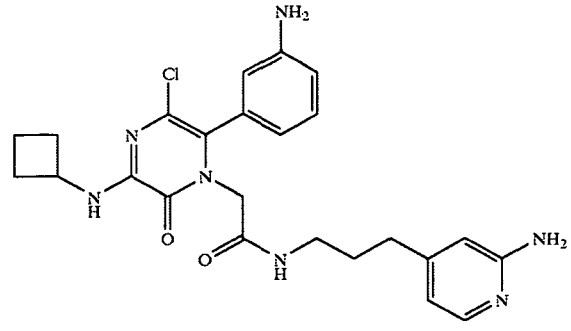
Using the procedures of Scheme 1, Scheme 2, and Example 1 through Example 18 with suitable reagents, starting materials, 2-{5-chloro-6-(3-nitrophenyl)-3-cyclobutylamino-2-oxohydropyrazinyl}acetic acid, and 2-(4-imidazoyl)ethanamine commercially available form Fluka, the product was obtained and gave an m/z(M+H)$^+$ of 442.

Example 30



Using the procedures of Scheme 1, Scheme 2, and Example 1 through Example 18 with suitable reagents, starting materials, 2-{5-chloro-6-(3-nitrophenyl)-3-cyclobutylamino-2-oxohydropyrazinyl}acetic acid and 2-(4-(2-aminoimidazoyl))ethanamine prepared according to the literature reference (Nagai, W. Kirk, K. L., Cohen, L. A., *J. Org. Chem.* 1973, 33, 1971–1974), the product was obtained and gave an m/z(M+H)$^+$ of 457.

Example 31



2-Amino-4-picoline (5.00 g, 46.2 mmol) and 11.20 g of di-tert-butyl dicarbonate (50.8 mmol) were stirred in 100 mL of tert-butanol at 30° C. overnight. The reaction mixture was concentrated in vacuo and chromatographed on silica gel

with 25% EtOAc/Hexane to give 8.20 g (85% yield) of the product EX-31A.

To a solution of 3.00 g of N-Boc-2-amino-4-picoline (EX-31A, 14.4 mmol) in 150 mL of THF at −78° C. was added 14.4 mL of 2.5 M n-BuLi/Hexanes solution. The reaction mixture was allowed to warm up to room temperature and stirred for 40 min. The reaction mixture was cooled down to −78° C. and 1-bromo-2-chloroethane was added. The mixture was stirred at −78° C. for overnight. The reaction mixture was quenched with HOAc at −78° C. and concentrated in vacuo. The crude was dissolved in EtOAc and washed with brine. The EtOAc layer was dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by silica gel chromatography with 20% EtOAc/Hexane to give 2.00 g (50%) of the product EX-31B.

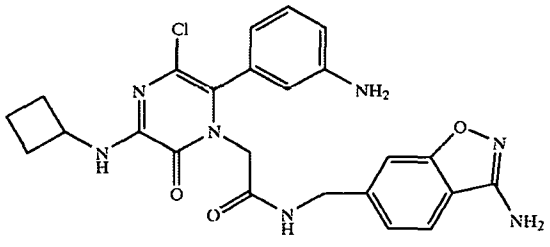
To a solution of 2.00 g of the chloride EX-31B (6.91 mmol) and 0.50 g of sodium azide (7.69 mmol) in 80 mL of DMF was added 10 mL of water and 0.52 g of sodium iodide. The reaction mixture was stirred at 55° C. overnight. The mixture was washed with brine and extracted with EtOAc. The EtOAc layer was dried over $MgSO_4$ and concentrated in vacuo. The crude product was chromatographed on silica gel with 20% EtOAc/Hexane to give 1.80 g (94%) of the product EX-31C.

To a solution of 1.74 g of the azide EX-31C (6.27 mmol) in 30 mL of THF was added 1.64 g of triphenylphosphine (6.27 mmol) and 1 mL of water. The reaction mixture was stirred at room temperature overnight. The reaction mixture was concentrated in vacuo and chromatographed on silica gel with 10% CH_3OH/CH_2Cl_2 to give 1.26 g (80%) of the amine product EX-31D.

To a solution of 0.77 g of 2-{5-chloro-6-(3-aminophenyl)-3-cyclobutylamino-2-oxohydropyrazinyl}acetic acid (2.21 mmol) in 50 mL of DMF was added 0.47 g of EDC.HCl and 0.33 g of HOBt. The mixture was stirred at room temperature for 30 min. After the addition of 0.61 g of the amine EX-31D (2.43 mmol) and 0.50 g of triethylamine the reaction mixture was stirred at room temperature overnight. The mixture was washed with water and extracted with EtOAc. The EtOAc layer was washed with brine and concentrated in vacuo. The crude product was chromatographed on silica gel with 3% CH_3OH/CH_2Cl_2 to afford 1.10 g (86%) of the Boc protected product EX-31E.

The Boc protected product EX-31E (0.50 g) was treated with 2.0 M of HCl/ether solution for overnight. The mixture was concentrated in vacuo and chromatographed by DeltaPrep with 10% CH_3CN/H_2O to give 0.32 g of the product (78%) as a TFA salt. The TFA salt was converted to the HCl salt by ion exchange chromatography with BioRad AG 2-X8 resin and 10% CH_3CN/H_2O and analyzed by mass sprectrometry to give an (M+H) of 482.16.

Example 32



A mixture of 26.5 mmol of 4-bromo-3-fluorotoluene, 29 mmol of copper cyanide and 25 ml of dry DMF is refluxed for 12 hr, then 150 ml water was added and the reaction mixture filtered. The precipitate was triturated with 100 ml of concentrated ammonium hydroxide, extracted twice with 50 ml of dichloromethane. The organic layer was washed with ammonium hydroxide (100 ml) and water (100) and then concentrated and recrystallized (hexane) to yield 2 g solid 4-cyano-3-fluorotoluene (EX-32A). NMR and MS confirmed the structure of EX-32A.

A mixture of 2-fluoro-4-methylbenzonitrile (EX-32A) (2 g, 14.8 mmol), NBS (2.6 g, 14.8 mmol) and benzoyl peroxide (178 mg, 0.74 mmol) in CCl_4 (30 ml) was refluxed for 16 hr, then cooled and filtered. The mixture was then concentrated and purified with silica-gel column to yield 1.5 g oil EX-32B. NMR and MS confirmed the structure of EX-32B.

$N,N\text{-}(Boc)_2NH$ (1.1 g, 5.17 mmol) in THF (20 ml) was cooled to 0° C. and NaH (60%, 0.25 g, 6.11 mmol) was added. The mixture was kept stirring for 30 min., then benzylbromide EX-32B (1 g, 4.7 mmol) in THF (2 ml) was added. The mixture was stirred for 3 hr. Then water was added and extracted with EtOAc (3×15 ml). The combined EtOAc was then concentrated and recrystalized in hexane to yield 0.6 g white solid EX-32C. NMR and MS all confirmed the structure of EX-32C.

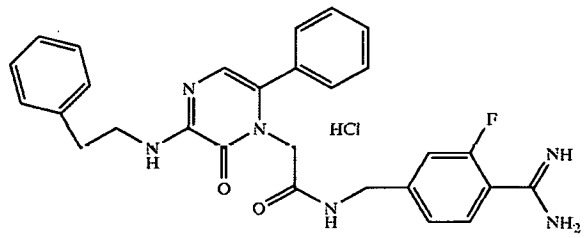
To the compound EX-32C (200 mg) in CH_2Cl_2 (3 ml) was added TFA (1.5 ml). The reaction mixture was stirred at RT for 3 h and concentrated to afford oil EX-32D which was directly used for next amide coupling reaction.

To 2-{5-chloro-6-(3-nitrophenyl)-3-cyclobutylamino-2-oxohydropyrazinyl}acetic acid (227 mg, 0.6 mmol) was added HOBt (106.1 mg, 0.7 mmol) and EDC (126.7 mg, 0.7 mmol) in DMF (3mnl). The mixture was stirred at RT for 30 min. Then the amine TFA salt EX-32D in DMF (1 ml) and triethyl amine (0.2 ml) was added to the mixture which was stirred overnight. The mixture was concentrated, purified to yield 200 mg solid EX-32E, confirmed by NMR and MS.

EX-32E(0.2 g) in THF (5 ml) was added with Pd/C (10%, 20 mg). The mixture was stirred at RT under N_2, and then H_2 gas balloon was connected to the flask. The reaction was stirred for 24 hr to complete reaction. The mixture was filtered, washed with ethanol, and then dried to yield 0.16 g white solid EX-32F which was directly used for next cyclization reaction.

To acetohydroxamic acid (37 mg, 0.5 mmol) in DMF (2 ml) was added potassium t-butoxide (1M, 0.5 ml, 0.5 mmol) at room temperature. After stirring for 30 min, benzonitrile EX-32F (160 mg, 0.33 mmol) in DMF (2 ml) was added. The reaction mixture was stirred overnight, and then poured into a mixture of brine and ethyl acetate. The aqueous layer was extracted with EtOAc (3×2 ml), and the combined EtOAc was washed with brine, dried, concentrated and purified on reverse-phase HPLC to yield 60 mg of the HCl salt. NMR and MS both confirmed the structure of product.

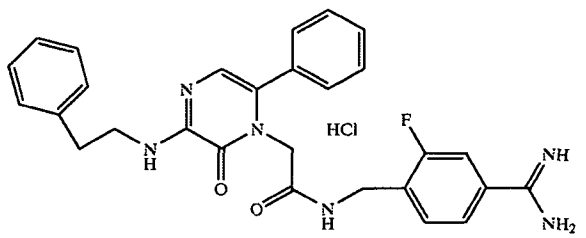
Example 33



By substituting 2-fluoro-4-methylbenzonitrile for 4-methylbenzonitrile, 2-fluoro-4-methylbenzonitrile (EX-32A) was converted to the protected amidine, 4-(N-benzyloxycarbonylamidino)-3-fluorobenzylamine hydrogen chloride salt (EX-33A), using the procedure outlined in Synthetic Communications, 28(23), 4419–4429 (1998) for preparing 4-(N-benzyloxycarbonylamidino)benzylamine hydrogen chloride salt. EX-33A was characterized by: MS (LR-ESI) m/z 302 $(M+H)^+$; ^{1}HNMR (DMSO, 300 MHz) δ8.75 (bs, 3H, CH_2NH_3), δ7.79–7.02 (m, 8H, aromatic CH), δ5.31–5.07 (m, 2H, $C_6H_5CH_2$), δ4.10 (s, 2H, CH_2NH_3).

Using the procedure of Example 44 by substituting 2-[3-(N-{2-phenylethyl}amino)-2-oxo-6-phenylhydropyrazinyl] acetic acid (EX-1D) for 2-[3-({2-[(tert-butoxy) carbonylamino]ethyl}amino)-5-chloro-2-oxo-6-phenylhydropyrazinyl]acetic acid, EX-33A was converted to the product which gave an m/z+1 of 499.

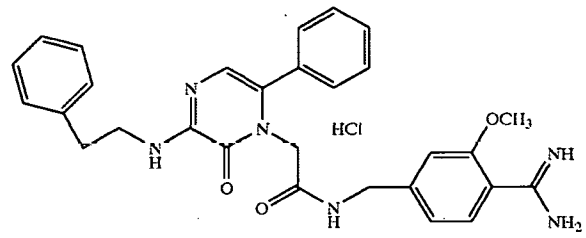
Example 34



By substituting 3-fluoro-4-methylbenzonitrile for 4-methylbenzonitrile, 3-fluoro-4-methylbenzonitrile was converted to the protected amidine, 4-(N-benzyloxycarbonylamidino)-2-fluorobenzylamine hydrogen chloride salt (EX-34A), using the procedure outlined in Synthetic Communications, 28(23), 4419–4429 (1998) for preparing 4-(N-benzyloxycarbonylamidino)benzylamine hydrogen chloride salt. EX-34A was characterized by: MS (LR-ESI) m/z 302 $(M+H)^+$; ^{1}HNMR (DMSO, 300 MHz) δ8.82 (bs, 3H, CH_2NH_3), δ7.92–7.26 (m, 8H, aromatic CH), δ5.32 (s, 2H, $C_6H_5CH_2$), δ4.10 (s, 2H, CH_2NH_3).

Using the procedure of Example 44 by substituting 2-[3-(N-{2-phenylethyl}amino)-2-oxo-6-phenylhydropyrazinyl] acetic acid (EX-1D) for 2-[3-({2-[(tert-butoxy) carbonylamino]ethyl}amino)-5-chloro-2-oxo-6-phenylhydropyrazinyl]acetic acid, EX-34A was converted to the product which gave an m/z+1 of 499.

Example 35



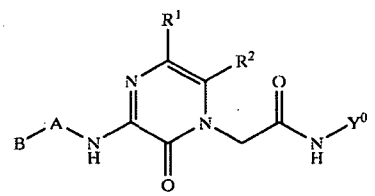
By substituting 2-methoxy-4-methylbenzonitrile for 4-methylbenzonitrile, 2-methoxy-4-methylbenzonitrile was converted to the protected amidine, 4-(N-benzyloxycarbonylamidino)-3-methoxybenzylamine hydrogen chloride salt (EX-35A), using the procedure outlined in Synthetic Communications, 28(23), 4419–4429 (1998) for preparing 4-(N-benzyloxycarbonylamidino)benzylamine hydrogen chloride salt. EX-35A was characterized by: MS (LR-ESI) m/z 314 $(M+H)^+$; ^{1}HNMR (DMSO, 300 MHz) δ7.77–6.95 (m, 8H, aromatic CH), δ4.74 (bs, 2H, $C_6H_5CH_2$), δ4.10–3.95 (m, 2H, CH_2NH_3), δ3.80 (s, 3H, OCH_3).

Using the procedure of Example 44 by substituting 2-[3-(N-{2-phenylethyl}amino)-2-oxophenylhydropyrazinyl] acetic acid (EX-1D) for 2-[3-({2-[(tert-butoxy) carbonylamino]ethyl}amino)-5-chloro-2-oxo-6-phenylhydropyrazinyl]acetic acid, EX-35A was converted to the product which gave an m/z+1 of 511.

Using the procedures of Scheme 1, Scheme 2, and the Examples herein with suitable reagents, starting materials, and intermediates, additional pyrazinones of the present invention were prepared and these pryazinones are summarized in Table 2.

TABLE 2

Additional Substituted Pyrazinones of the Present Invention Prepared based on the Procedures of Scheme 1, Scheme 2, and Examples herein.

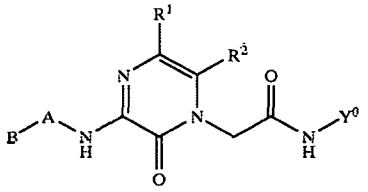


General Structure

Ex. No.	R^2	R^1	B-A-	Y^0	MW (m/z + 1)
36	Phenyl	H	2-phenethyl	1-(4-guanidino)-2-butynyl	458
37	Phenyl	H	2-phenylethyl	1-(4-guanidino)-cis-2-butenyl	460
38	Phenyl	H	2-phenylethyl	(3-aminoindazol-5-yl) methyl	494
39	Phenyl	H	2-phenylethyl	(3-aminoindazol-6-yl) methyl	494
40	3-amino-phenyl	Cl	cyclobutyl	(4-amidino-3-fluoro)-benzyl	498
41	3-amino-phenyl	Cl	cyclobutyl	(4-amidino-2-fluoro)-benzyl	511
42	3-amino-phenyl	Cl	isopropyl	(4-amidino-3-fluoro)-benzyl	486

TABLE 2-continued

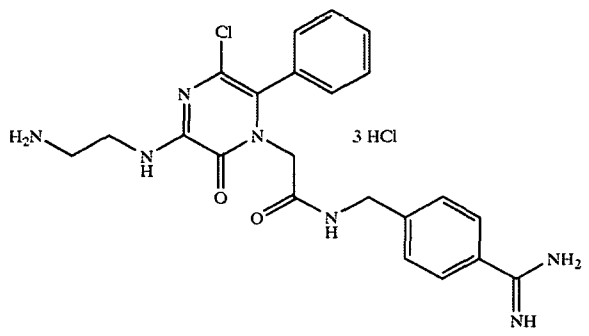
Additional Substituted Pyrazinones of the Present Invention Prepared based on the Procedures of Scheme 1, Scheme 2, and Examples herein.



General Structure

Ex. No.	R^2	R^1	B-A-	Y^0	MW (m/z + 1)
43	3-amino-phenyl	H	isopropyl	(4-amidino-3-fluoro)-benzyl	452

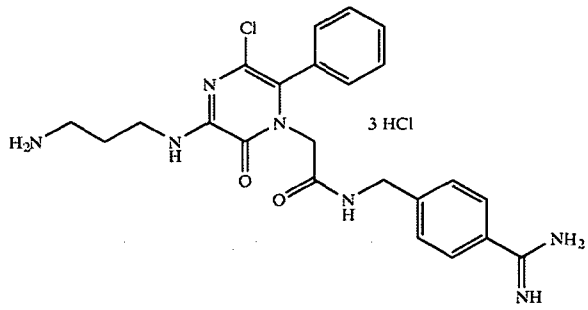
Example 44



To a solution of 2-[3-({2-[(tert-butoxy)carbonylamino] ethyl}amino)-5-chloro-2-oxo-6-phenylhydropyrazinyl] acetic acid (6.50 g, 15.38 mmol) prepared as described in EX-1C using 2-(tert-butoxycarbonylamino)ethylamine in place of 2-phenethylamine in 100.0 mL dimethylformamide was added N,N-diisopropylethylamine (21.0 mL, 120.56 mmol), N-hydroxybenzotriazole (2.73 g, 20.21 mmol), and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (3.84 g, 20.04 mmol). The resulting mixture was stirred for 30 minutes. To the reaction mixture was added in one portion (5.9723 g, 18.68 mmol) of the protected amidine, 4-(N-benzyloxycarbonylamidino)benzylamine hydrogen chloride salt, prepared using the procedure outlined Synthetic Communications, 28(23), 4419–4429 (1998). The resulting mixture was stirred over night. The reaction mixture was diluted with ethyl acetate (250 mL) and washed with 5% citric acid (1×50 mL), saturated $NaHCO_3$ (1×50 mL), and brine (1×50 mL). The organic solution was dried ($MgSO_4$), filtered and concentrated. The crude reaction was purified by MPLC (80% ethyl acetate/hexanes) to give pure product EX-44A: ^1H NMR (300 MHz, DMSO) δ8.59–8.53 (1H), 7.99–7.96 (m, 2H), 7.81–7.75 (m, 1H), 7.51–7.25 (m, 12H), 6.99 (br m, 1H), 5.14 (s, 2H), 4.32–4.27 (m, 4H), 3.42–3.35 (m, 4H), 3.24–3.20 (m, 2H), 1.41 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ166.6, 163.0, 156.5, 151.3, 149.9, 143.9, 137.8, 133.5, 132.6, 131.3, 130.1, 129.5, 129.2, 129.1, 128.9, 128.7, 128.4, 127.7, 124.0, 78.5, 66.8, 49.3, 42.6, 36.5, 31.5, 29.0; HRMS (EI) calcd for $C_{35}H_{38}ClN_7O_6$ 688.2650, found 688.2614.

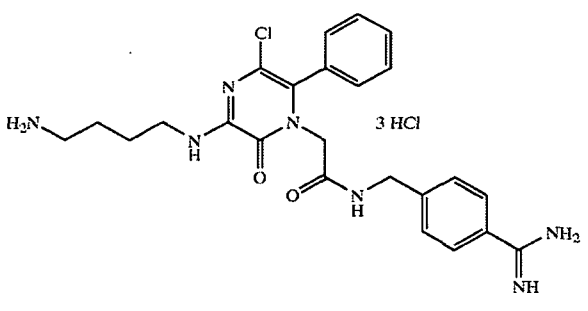
A solution of pyrazinone EX-44A (334.4 mg, 0.4593 mmol) in 5.0 mL ethanol/4 M HCl in dioxane (3:1, 0.1 M) was flushed with hydrogen gas. To the solution was then added 113.1 mg 10% Pd/C (wet), and the resulting suspension was stirred at room temperature under an atmosphere of hydrogen (balloon pressure) for approximately 18 hours. The reaction mixture was filtered through a pad of Celite 545 and rinsed with ethanol. The solvent was removed under reduced pressure. The resulting oil was triturated with ethyl ether to provide pure product as a white solid: ^1H NMR (400 MHz, DMSO) d 9.50 (s, 2H), 9.29 (s, 2H), 8.8/0 (s, 1H), 8.22 (s, 3H), 7.85–7.80 (m, 3H), 7.44 (br s, 3H), 7.27–7.24 (m, 4H), 4.23 (s, 4H), 3.58–3.54 (m, 4H); HRMS (ES) calcd for $C_{22}H_{25}ClN_7O_2$ 454.1758, found 454.1741.

Example 45



By following the method of Example 45 and substituting 2-[3-({3-[(tert-butoxy)carbonylamino]propyl}amino)-5-chloro-2-oxo-6-phenylhydropyrazinyl]acetic acid for 2-[3-({2-[(tert-butoxy)carbonylamino]ethyl}amino)-5-chloro-2-oxo-6-phenylhydropyrazinyl]acetic acid, the product was prepared: ^1H NMR (400 MHz, DMSO) d 9.51 (br s, 2H), 8.28 (br s, 2H), 8.77 (s, 1H), 8.15 (3, 3H), 7.86–7.79 (m, 3H), 7.42 (s, 3H), 7.26–7.24 (m, 4H), 5.37 (br s, 2H), 4.21 (s 4H), 3.39–3.29 (m, 2H), 2.81–2.76 (br s, 2H), 1.86 (br s, 2H); ^{13}C NMR (100 MHz, DMSO) d 166.7, 166.0, 151.2, 149.7, 146.0, 132.5, 131.1, 129.5, 128.8, 127.9, 126.8, 125.1, 123.9, 65.6, 56.6, 49.2, 42.4, 38.1, 37.3, 34.6, 26.7, 19.2, 15.8; HRMS (EI) calcd for $C_{23}H_{26}ClN_3O_6$ 469.1755, found 469.1725.

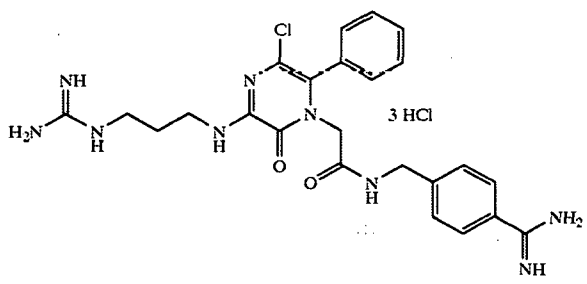
Example 46



By following the method of Example 44 and substituting 2-[3-({4[(tert-butoxy)carbonylamino]butyl}amino)-5-chloro-2-oxo-6-phenylhydropyrazinyl]acetic acid for 2-[3-({2-[(tert-butoxy)carbonylamino]ethyl}amino)-5-chloro-2-oxo-6-phenylhydropyrazinyl]acetic acid, the product was prepared: ^1H NMR (400 MHz, DMSO) d 9.49 (br s, 2H),

9.28 (s, 2H), 8.75 (s, 1H), 8.08 (s, 3H), 7.89–7.76 (m, 3H), 7.42 (s, 3H), 7.26–7.24 (m, 4H), 4.70 (br s, 4H), 4.23–4.21 (m, 3H), 2.73 (br s, 2H), 1.57 (br s, 3H), 1.03–0.96 (m, 2H); HRMS (EI) calcd for $C_{24}H_{29}ClN_7O_2$ 482.2071, found 482.2040.

Example 47

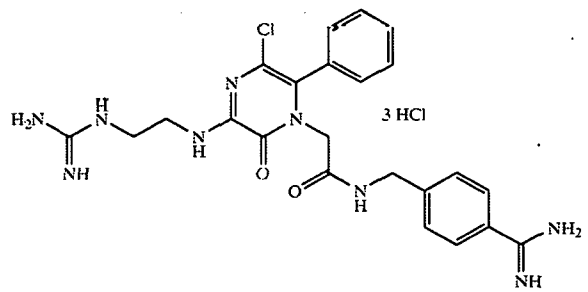


A solution of 1-(N-{4-[N-benzyloxycarbonylamidino] benzylamido}carbonylmethyl)-3-({3-[(tert-butoxy) carbonylamino]propyl}amino)-5-chloro-6-phenylpyrazinone hydrochloride (2.0075 g, 2.859 mmol), prepared as an intermediate in Example 45, in 28.0 mL ethanol/4 M HCl in dioxane (1:1, 0.1 M) was allowed to stir at room temperature for approximately 4 hours. The solvent was removed under reduced pressure. Purification by trituration with ethyl ether gave pure product EX-47A as a yellow solid: ^{1}H NMR (400 MHz, DMSO) d 11.67 (br s, 1H), 10.53 (br s, 1H), 8.90–8.87 (m, 1H), 8.30–8.25 (m, 31H), 7.89–7.83 (m, 1H), 7.75–7.73 (m, 2H), 7.46–7.23 (m, 13H), 5.532 (s, 2H), 4.26–4.23 (m, 3H), 3.50 (s, 2H), 3.36–3.35 (m, 2H), 2.75 (br m, 2H); HRMS (EI) calcd for $C_{31}H_{32}ClN_7O_4$ 602.2283, found 602.2253.

To a solution of amino pyrazinone EX-47A (1.9093 g, 2.684 mmol) in 10.0 mL dimethyl formamide (0.25 M) was added triethylamine (1.90 mL, 13.63 mmol) To the resulting mixture was then added N,N'-di-BOC-N'-triflylguanidine (1.4021 g, 3.583 mmol, prepared according to Feichtinger, K., Zapf, C., Sings, H. L., and Goodman, M., *J. Org. Chem.*, 63, 3804–3805 (1998)) in one portion at room temperature. The resulting suspension was allowed to stir over night. The reaction mixture was diluted ethyl acetate (250 mL) and washed with saturated $NaHCO_3$ (2x100 mL) and brine (2x100 mL). The organic solution was dried ($MgSO_4$), filtered and concentrated. Purification by MPLC (75% ethyl acetate/hexanes) afforded EX-47B: ^{1}H NMR (400 MHz, $CDCl_3$) d 11.53 (s, 1H), 8.55–8.48 (m, 2H), 7.97–7.93 (m, 4H), 7.49–7.24 (m, 13H), 5.13 (s, 2H), 4.30–4.25 (m, 4H), 3.90–3.33 (m, 4H), 1.84–1.79 (m, 2H), 1.49 (s, 9H), 1.41 (s, 9H); HRMS (EI) calcd for $C_{42}H_{51}ClN_9O_8$ 844.3549, found 844.3521.

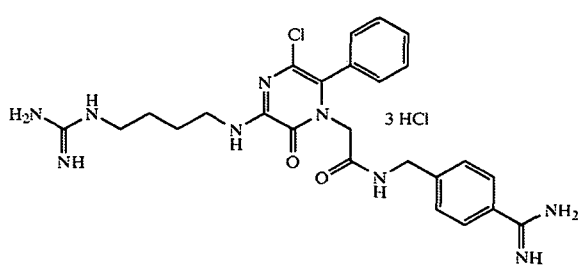
A solution of pyrazinone EX-47B (1.5450 g, 1.8298 mmol) in 18.0 mL ethanol/4 M HCl in dioxane (3:1, 0.1 M) was flushed with hydrogen gas. To the solution was then added 157.2 mg 10% Pd/C (wet), and the resulting suspension was stirred at room temperature under an atmosphere of hydrogen (balloon pressure) for approximately 18 hours. The reaction mixture was filtered through a pad of Celite 545 and rinsed with ethanol. The solvent was removed under reduced pressure. The resulting oil was triturated with ethyl ether to provide the pure product in 63% yield: ^{1}H NMR (400 MHz, DMSO) d 9.50 (s, 2H), 9.28 (s, 2H), 8.77 (s, 1H), 7.91 (s, 1H), 7.81–7.79 (m, 3H), 7.42 (br s, 4H), 7.26–7.24 (m, 5H), 6.28 (br s, 2H), 4.23–4.21 (m, 4H), 3.36–3.27 (m, 2H), 3.14–3.13 (br m, 2H), 1.77–1.74 (m, 2H); HRMS (ES) calcd for $C_{24}H_{29}ClN_9O_2$ 510.2133, found 510.2080.

Example 48



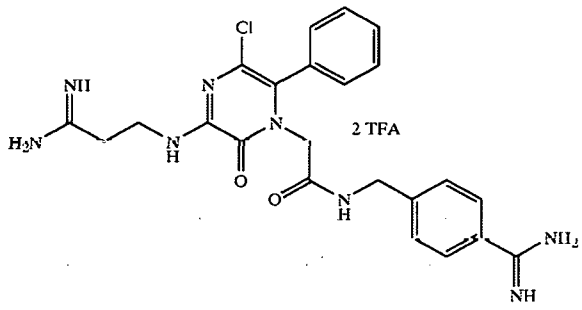
Using the method of Example 47 and substituting 1-(N-{4-[N-benzyloxycarbonylamidino] benzylamido}carbonylmethyl)-3-({2-[(tert-butoxy) carbonylamino]ethyl}amino)-5-chloro-6-phenylpyrazinone hydrochloride, prepared as an intermediate in Example 44, for the propyl analog used in Example 47, the product was prepared: ^{1}H NMR (400 MHz, DMSO) d 9.51 (s, 2H), 9.29 (s, 2H), 8.80 (s, 1H), 7.90–7.78 (m, 5H), 7.43–7.37 (m, 5H), 7.35–7.23 (m, 5H), 4.23 (s, 4H), 4.03 (s, 2H), 3.40–3.34 (m, 4H); HRMS (EI) calcd for $C_{23}H_{27}ClN_9O_2$ 496.1976, found 496.1952.

Example 49



By following the method of Example 47 and substituting 1-(N-{4-[N-benzyloxycarbonylamidino] benzylamido}carbonylmethyl)-3-({4-[(tert-butoxy) carbonylamino]butyl}amino)-5-chloro-6-phenylpyrazinone hydrochloride (2.0075 g, 2.859 mmol), prepared as an intermediate in Example 46, for the propyl analog used in Example 47, the product was prepared: ^{1}H NMR (400 MHz, DMSO) d 9.47 (s, 2H), 9.28 (s, 2H), 8.74–8.72 (m, 1H), 7.88 (br s, 1H), 7.80–7.73 (m, 3H), 7.43–7.31 (m, 4H), 7.27–7.20 (m, 5H), 5.36–5.32 (m, 3H), 4.25–4.21 (m, 4H), 3.28–3.27 (m, 2H), 3.10–3.08 (m, 2H), 1.58–1.53 (m, 2H), 1.48–1.43 (m, 2H); HRMS (EI) calcd for $C_{25}H_{31}ClN_9O_2$ 524.2289. found 524.2292.

Example 50

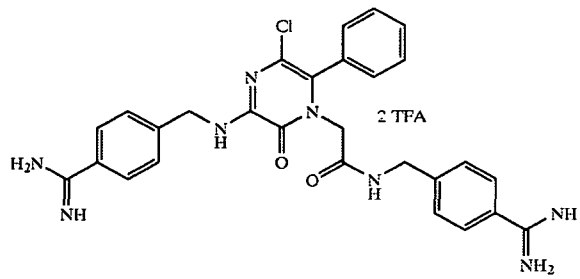


To a solution of 2-{5-chloro-3-[(2-cyanoethyl)amino]-2-oxo-6-phenylhydropyrazinyl}acetic acid (2.09 g, 6.28 mmol) in 31.0 mL dimethylformamide/tetrahydrofuran (1:1) was added N,N-diisopropylethylamine (5.50 mL, 31.57 mmol), N-hydroxybenzotriazole (1.02 g, 7.6 mmol), and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (1.45 g, 7.51 mmol). The resulting mixture was stirred for 30 minutes. To the reaction mixture was then added 4-cyanobenzylamine (1.28 g, 7.57 mmol) in one portion. The resulting mixture was allowed to stir over night. The reaction mixture was diluted with ethyl acetate (250 mL) and washed with 5% citric acid (1×50 mL), saturated $NaHCO_3$ (1×50 mL), and brine (1×50 mL). The organic solution was dried ($MgSO_4$), filtered and concentrated. The crude reaction was purified trituration with ethyl ether to give EX-50A: ^1H NMR (300 MHz, DMSO) δ8.59 (t, J=5.6 Hz, 1H), 8.10 (t, J=5.6 Hz, 1H), 7.82 (d, J=8.1 Hz, 2H), 7.53–7.46 (m, 3H), 7.35–7.32 (m, 4H) 4.33–4.29 (m, 4H), 3.63–3.57 (m, 2H), 2.89 (t, J=6.3 Hz, 2H); ^{13}C NMR (75 MHz, DMSO) δ166.7, 151.1, 149.6, 145.6, 132.93, 132.45, 131.16, 130.21, 129.55, 128.63, 124.97, 124.72, 120.0, 119.6, 110.4, 49.3, 42.6, 37.3, 17.3; HRMS (EI) calcd for $C_{23}H_{20}ClN_6O_2$ 447.1336, found 447.1330.

To a suspension of bis-nitrile pyrazinone EX-50A (2.26, 58.07 mmol) in 50 mL ethanol/H_2O (2.6:1, 0.1 M) was added hydroxyl amine hydrochloride (2.61 g, 37.6 mmol) followed by potassium carbonate (3.08 g, 22.3 mmol). The resulting white suspension was stirred and heated to 60° C. over night. The reaction mixture was cooled to room temperature and diluted with water (75.0 mL). The mixture was placed in an ice bath, and the pH was adjusted to approximately 7 using dilute acid. The precipitate that formed was collected by filtration, washed with cold water and dried under vacuum to afford pure EX-50B: ^1H NMR (300 MHz, DMSO) δ9.63 (s, 1H), 8.95 (s, 1H), 8.47 (br s, 1H), 7.66–7.61 (m, 2H), 7.53–7.47 (m, 4H), 7.32 (d, J=5.2 Hz), 7.16–7.13 (m, 2H), 5.83 (s, 2H), 5.47 (s, 2H), 4.25 (s, 4H), 3.61–3.53 (m, 2H), 2.39–2.35 (m, 2H); 13C NMR (75 MHz, DMSO) δ166.5, 151.68, 151.35, 151.23, 149.6. 140.3. 132.70, 132.63, 131.3, 130.1, 129.5, 127.6, 126.0, 125.3, 49.2, 42.6, 38.4, 30.6; HRMS (EI) calcd for $C_{23}H_{26}ClN_8O_4$ 513.1766, found 513.1735.

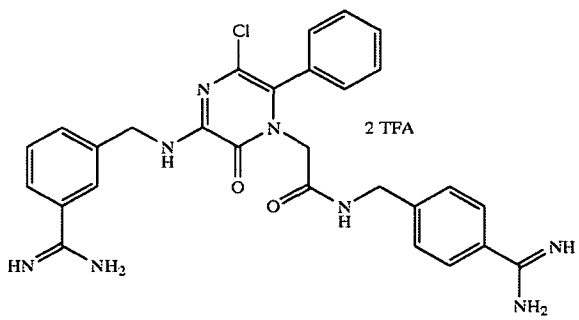
To a solution of Bis-hydroxyamidine EX-50B (2.40 g, 4.67 mmol) in 19.0 mL acetic acid (0.25 M) was added acetic anhydride (1.80 mL, 19.1 mmol). The resulting mixture was stirred for 10 minutes and flushed with hydrogen gas. To the solution was then added Pd/C (wet) and the resulting mixture was allowed to stir under an atmosphere of hydrogen (balloon pressure) at room temperature, over night. The reaction mixture was filtered through a pad of Celite 545 and concentrated under vacuum. Purification by HPLC (1% acetonitrile to 60% acetonitrile/H_2O/0.1% trifluoroacetic acid) afford pure product: ^1H NMR (400 MHz, DMSO) δ9.51 (s, 2H), 9.30 (s, 2H), 9.03 (s, 2H), 8.93 (s, 2H), 8.62–8.59 (m, 1H), 7.89–7.86 (m, 2H), 7.74 (d, J=8.3 Hz, 2H), 7.47–7.40 (m, 3H), 7.28–7.23 (m, 4H), 4.27–4.24 (m, 4H), 3.63–3.59 (m, 2H), 2.70–2.68 (m, 2H); HRMS (EI) calcd for $C_{22}H_{26}ClN_8O_2$ 481.1867, found 481.1836.

Example 51



By following the method of Example 50 and substituting 2-{5-chloro-3-[(4-cyanobenzyl)amino]-2-oxo-6-phenylhydropyrazinyl}acetic acid for the 2-cyanoethylamino analog, the product was prepared: ^1H NMR (400 MHz, DMSO) d 9.44 (d, J=16.9 Hz, 3H), 9.26 (d, J=17.2 Hz, 8.61 (br s, 1H), 8.47–8.44 (m, 1H), 7.74 (d, J=7.0 Hz, 4H), 7.52 (d, J=Hz, 2H), 7.43–7.42 (m, 3H), 7.28–7.22 (m, 4H), 4.56–4.55 (m, 2H), 4.25 (s, 4H); HRMS (EI) calcd for $C_{28}H_{28}ClN_8O_2$ 543.2024, found 543.1986.

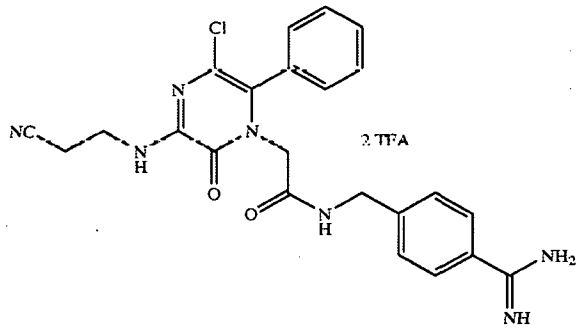
Example 52



By following the method of Example 50 and substituting 2-{5-chloro-3-[(3-cyanobenzyl)amino]-2-oxo-6-phenylhydropyrazinyl}acetic acid for the 2-cyanoethylamino analog, the product was prepared: ^1H NMR (400 MHz, DMSO) d 9.41 (s, 4H), 9.28 (d, J=11.0 Hz, 4H), 8.61–8.58 (m, 1H), 8.35–8.32 (m, 1H), 7.77–7.72 (m, 3H), 7.66–7.64 (m, 2H), 7.55–7.52 (m, 1H), 7.45–7.39 (m, 3H), 7.29–7.23 (m, 4H), 4.57–4.55 (m, 2H), 4.26–4.21 (m, 4H); ^{13}C NMR (100 MHz, DMSO) δ166.7, 166.1, 159.8,

159.4, 151.2, 149.6, 145.9, 140.6, 133.3, 132.4, 131.1, 130.1, 129.6, 129.5, 129.1, 128.7, 127.93, 127.86, 127.3, 124.9, 124.5, 49.1, 44.0, 42.4; HRMS (EI) calcd for $C_{28}H_{28}ClN_8O_2$ 543.2024, found 543.2032.

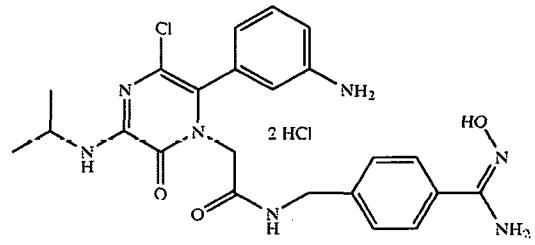
Example 53



To a solution of 2-{5-chloro-3-[(2-cyanoethyl)amino]-2-oxo-6-phenylhydropyrazinyl}acetic acid (1.45 g, 3.25 mmol) in 17.0 mL dimethylformamide was added N,N-diisopropylethylamine (3.00 mL, 17.2 mmol), N-hydroxybenzotriazole (0.536 mg, 3.96 mmol), and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.752 mg, 3.923 mmol). The resulting mixture was allowed to stir for 30 minutes. The reaction mixture was then added the Cbz protected amidine (1.2631 g, 3.950 mmol) prepared and used in Example 44 in one portion. The resulting mixture was allowed to stir over night. The reaction mixture was diluted with ethyl acetate (250 mL) and washed with 5% citric acid (1×50 mL), saturated $NaHCO_3$ (1×50 mL), and brine (1×50 mL). The organic solution was dried ($MgSO_4$), filtered and concentrated. The crude reaction was purified by MPLC (100% ethyl acetate) to give pure EX-53A in 82% yield: ^1H NMR (400 MHz, DMSO) δ9.06 (br s, 1H), 8.50–8.47 (m, 1H), 8.05–8.02 (m, 1H), 7.89 (d, J=8.2 Hz, 2H) 7.46–7.26 (m, 11H), 7.18 (d, J=8.2 Hz, 2H), 5.07 (s, 2H), 4.24–4.21 (m, 4H), 3.55–3.51 (m, 2H), 2.83–2.80 (m, 2H); HRMS (EI) calcd for $C_{31}H_{28}ClN_7O_4$ 598.1970, found 598.1970.

To a solution of pyrazinone EX-53A (1.497 g, 2.50 mmol) in 25.0 mL ethanol/4 M HCl in dioxane (3:1, 0.1 M) was flushed with hydrogen gas. To the solution was then added 10% Pd/C (wet) and the resulting suspension was allowed to stir at room temperature under an atmosphere of hydrogen (balloon pressure) for approximately 18 hours. The reaction mixture was filtered through a pad of Celite 545 and rinsed with ethanol. The solvent was removed under reduced pressure. Purification by HPLC (5% acetonitrile to 95% acetonitrile/H_2O/0.1% trifluoroacetic acid) provided pure product: ^1H NMR (400 MHz, DMSO) d 9.51 (s, 2H), 9.29 (s, 2H), 8.63–8.60 (m, 1H), 8.03–8.00 (m, 1H), 7.74 (d, J=8.3 Hz, 2H), 7.44–7.40 (m, 3H), 7.29–7.27 (m, 4H), 4.27–4.24 (m, 4H), 3.55–3.51 (m, 3H), 2.83–2.80 (m, 3H); HRMS (ES) calcd for $C_{23}H_{23}ClN_7O_2$ 464.1602, found 464.1624.

Example 54



A solution of p-bromophenethylamine (40 g, 199.92 mmol) and phthalic anhydride (29.6 g, 199.84 mmol) in 250 mL of dioxane and 25 mL of dimethylformamide was heated at 120° C. for 24 hours. The flask was then cooled, and the resulting white precipitate was filtered and washed with methanol (200 mL) to give EX-54A in exceptional yield and purity: ^1H NMR (400 MHz, $CDCl_3$) d 7.8 (m, 2H), 7.7 (m, 2H), 7.4 (d, 2H), 7.1 (d, 2H), 3.8 (t, 2H), 2.95 (t, 2H); MS (ES) calcd for $C_{16}H_{12}BrNO_2$ 330, found 331 (M+H).

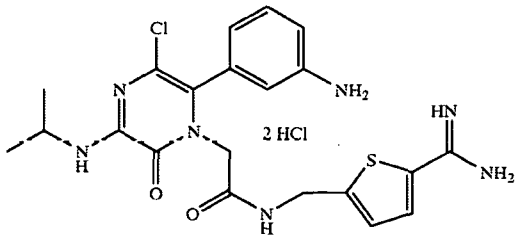
A nitrogen purged solution of EX-54A (40 g, 121.15 mmol) and copper (I) cyanide (16.28 g, 181.72 mmol) in 500 mL of dimethylformamide was heated at 170° C. for 24 hours. The solvent was removed under vacuum, and the resulting material was taken up in ethyl acetate. The ethyl acetate suspension was flashed through celite and concentrated under vacuum. The resulting white precipitate EX-54B was of exceptional yield and purity: ^1H NMR (300 MHz, $CDCl_3$) d 7.82 (m, 2H), 7.75 (m, 2H), 7.6 (d, 2H), 7.35 (d, 2H), 3.95 (t, 2H), 3.05 (t, 2H); MS (ES) calcd for $C_{17}H_{12}N_2O_2$ 276, found 277 (M+H).

A solution of p-cyanophenethylamine EX-54B (25 g, 90.48 mmol) and hydroxylamine hydrochloride (8 g, 115.12 mmol) in 1 L of ethanol and 20 mL (114.82 mmol) of diisopropylethylamine was heated at reflux for 16 hours. The flask was then cooled, and the resulting white precipitate was filtered and air dried to give EX-54C in an adequate yield and purity: ^1H NMR (300 MHz, DMSO) d 7.75 (d, 2H), 7.55 (d, 2H), 7.25 (d, 2H), 7.2 (d, 2H), 3.8 (m, 2H), 2.95 (m, 2H); MS (ES) calcd for $C_{17}H_{15}N_3O_3$ 309, found 310 (M+H).

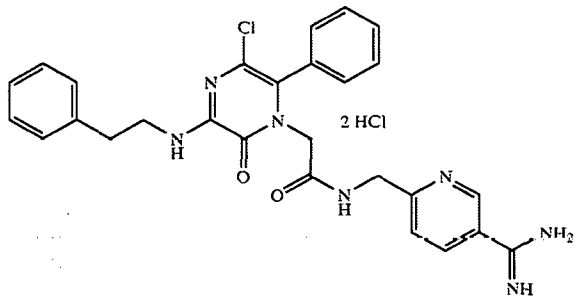
A solution of p-(N-hydroxy)amidinophenethyl phthalimide (EX-54C) (4.53 g, 14.64 mmol) in 200 mL of chloroform was treated with hydrazine monohydrate (1 mL, 20.62 mmol). The reaction was stirred vigorously at 50° C. for 24 hours. The flask was then cooled and the resulting white precipitate was filtered and washed with chloroform (200 mL). A 50:50 mixture of product EX-54D and phthalhydrazide was obtained and used as is: ^1H NMR (300 MHz, DMSO) d 7.6 (d, 2H), 7.2 (d, 2H), 2.8 (t, 2H), 2.7 (m, 2H); MS (ES) calcd for $C_{17}H_{15}N_3O_3$ 179, found 180 (M+H).

Reacting EX-54D containing phthalhydrazide with 2-{5-chloro-6-(3-nitrophenyl)-3-[N-(1-methylethyl)amino]-2-oxohydropyrazinyl}acetic acid in place of 2-{5-chloro-6-(3-nitrophenyl)-3-cyclobutylamino-2-oxohydropyrazinyl}acetic acid and EX-27D and then hydrogenating the resulting intermediate according to the final two procedures described in Example 27 gave the product with an m/z+1 of 484.

Example 55



Example 56



A solution of diisopropylamine (35.3 ml, 0.251 moles) in tetrahydrofuran (500 ml) was cooled to −78° C. under a nitrogen blanket. To this was added 1.6M n-butyllithium in hexanes (157 ml, 0.251 moles) and allowed to stir for 5 min. Then slowly added thiopene-2-carbonitrile (21.33 ml, 0.229 moles) in tetrahydrofuran (115 ml) and allowed to stir. After 45 min. was added NN-dimethylformamide (88.66 ml, 1.145 moles) at −78° C. Citric acid (40 g) was added after 2 h. followed by water (240 ml) and stirred for 18 h. The reaction was concentrated in vacuo, transferred to a separatory funnel, diluted with brine, and extracted twice with ether. The combined ether layers were washed with brine, dried over magnesium sulfate, filtered, and the solvent removed in vacuo. Chromatography yielded 15.8 g (50%) of 2-cyano-5-formylthiophene (EX-55A) as a brown solid: ^{1}H NMR (300 MHZ, $CDCl_3$) d 10.02 (s, 1H), 7.79 (m, 1H), 7.30 (m, 1H).

2-Cyano-5-formylthiophene (EX-55A) (15.8 g, 0.229 moles) was stirred in ethanol (375 ml), and sodium borohydride (4.36 g, 0.115 moles) added in small portions. After 15 min., the solvent was removed in vacuo, and residue taken up in ethyl acetate. After the ethyl acetate was washed with 1 N potassium hydrogen sulfate and brine, the organic layer was dried over magnesium sulfate, filtered, and solvent removed in vacuo. The residue was dried on vacuum pump to yield 9.57 g (59%) of the alcohol EX-55B as a brown-orange oil: ^{1}H NMR (300 MHz, $CDCl_3$) d 7.53 (m, 1H), 7.00 (m, 1H), 4.88 (s, 2H), 2.84 (br s, 1H).

To a stirring solution of EX-55B (9.57 g, 0.069 moles) in tetrahydrofuran (80 ml) was added triphenylphosphine (19.86 g, 0.075 moles) and carbon tetrabromide (25.11 g, 0.075 moles). After 18 h. the reaction was concentrated in vacuo, and the crude material chromatographed to yield EX-55C as a brown oil: ^{1}H NMR (300 MHz, $CDCl_3$) d 7.52 (m, 1H), 7.14 (m, 1H), 4.69 (s,2H).

2-Aminomethyl-5-carbobenzyloxyamidinothiophene dihydrogen chloride salt (EX-55D) was prepared by the method outlined in Synthetic Communications, 28(23), 4419–4429 (1998) by substituting 5-bromomethyl-2-cyanothiophene (EX-55C) for 4-cyanobenzyl bromide to give after trituration with acetonitrile EX-55D: ^{1}H NMR (300 MHz, DMSO) d 9.98 (br s, 1H), 8.83 (br s, 2H), 8.10 (s, 1H), 7.40–7.48 (m, 7H), 5.26 (s, 2H), 4.31 (s, 2H); HRMS calcd for $C_{14}H_{16}N_3O_2S$ 290.0963, found 290.0949.

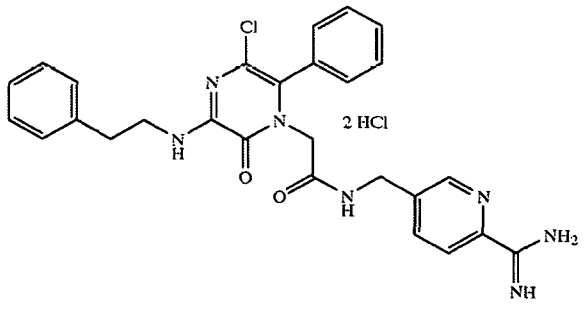
Reacting EX-55D with 2-{5-chloro-6-(3-nitrophenyl)-3-[N-(1-methylethyl)amino]-2-oxohydropyrazinyl}acetic acid in place of 2-{5-chloro-6-(3-nitrophenyl)-3-cyclobutylamino-2-oxohydropyrazinyl}acetic acid and EX-27D and then hydrogenating the resulting intermediate according to the final two procedures described in Example 27 gave the product with an m/z+1 of 474.

To a stirring solution of 3-cyano-6-methylpyridine (20 g, 0.169 moles) in carbon tetrachloride (850 ml) was added N-bromosuccinimde (30 g, 0.169 moles) and benzoyl peroxide (4.1 g, 0.0169 moles), and the solution was heated to reflux. After 18 h, the heat was discontinued, diluted with carbon tetrachloride (1 L) and washed twice with water (1 L). The solvent was removed in vacou and the crude material chromatographed to yield 12.05 g (36%) of dark brown solid EX-56A: ^{1}H NMR (300 MHz, $CDCl_3$) d 8.86 (d, 1H), 7.00 (m, 1H), 7.62 (m, 1H), 4.60 (s, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) d 156.38, 147.70, 135.82, 118.98, 111.75, 104.66, 27.82; HRMS (EI) calcd for $C_7H_6BrN_2$ 196.9714, found 196.9661.

2-Aminomethyl-5-carbobenzyloxyamidinopyridine dihydrogen chloride salt (EX-56B) was prepared by the method outlined in Synthetic Communications, 28(23), 4419–4429 (1998) by substituting 5-bromomethyl-2-cyanopyridine (EX-55A) for 4-cyanobenzyl bromide to give EX-56B: HPLC/LRMS; 98%, $(M+H)^+$ 285.

Reacting EX-56B with 2-{5-chloro-6-phenyl-3-[N-(2-phenylethyl)amino]-2-oxohydropyrazinyl}acetic acid in place of 2-{5-chloro-6-(3-nitrophenyl)-3-cyclobutylamino-2-oxohydropyrazinyl}acetic acid and EX-27D and then hydrogenating the resulting intermediate according to the final two procedures described in Example 27 gave the product with an m/z+1 of 482.

Example 57



2-Cyano-5-methylpyridine (EX-57A) was prepared following the procedure outlined in Synthetic Communications, 19(13&14), 2371–2374(1989): HRMS (EI) calcd for $C_7H_7N_2$ 119.0609, found 119.0587.

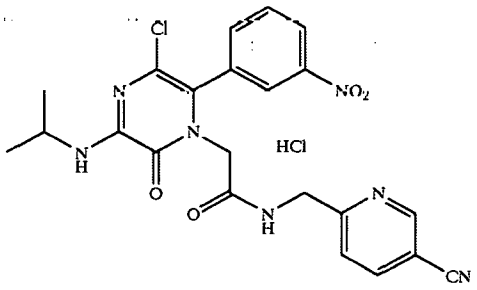
By following the procedure of Example 56 and substituting 2-cyano-5-methylpyridine for 3-cyano-6-methylpyridine, the intermediate 5-bromomethyl-2-cyanopyridine (EX-57B) was prepared.

2-Aminomethyl-5carbobenzyloxyamidinopyridne dihydrogen chloride salt (EX-57C) was prepared by the method

outlined in Example 56 substituting 5-bromomethyl-2-cyanopyridine for 6-bromomethyl-3-cyanopyridine: HPLC/LRMS; 95%, $(M+H)^+$ 285.

Reacting 2-Aminomethyl-5carbohenzyloxyamidinopyridne dihydrogen chloride salt (EX-57C) with 2-{5-chlorophenyl-3-[N-(2-phenylethyl) amino]-2-oxohydropyrazinyl}acetic acid as described in Example 56 gave the product with an m/z+1 of 482.

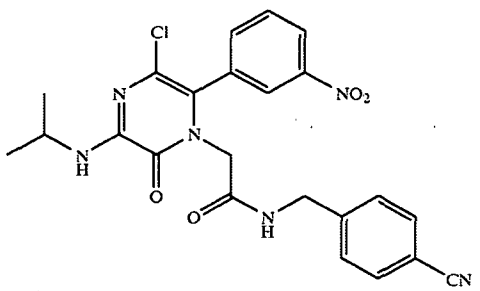
Example 58



2-Aminomethyl-5-cyanopyridine hydrochloride (EX-58A) was prepared by the deprotection with 4N HCl Dioxane of the intermediate 2-{N,N-bis-(tert-butoxycarbonyl) aminomethyl}-5-cyanopyridine used to prepare 2-aminomethyl-5-carbobenzyloxyamidinopyridine dihydrogen chloride salt in Example 56: ^1H NMR (400 MHz, DMSO) d 9.04 (s, 1H), 8.64 (br s, 2H), 8.34 (m, 1H), 7.69 (m, 1H), 4.25 (s, 2H); HRMS (EI) calcd for $C_7H_8N_3$ 134.0718, found 134.0699.

Using the procedure of Example 44 by substituting 2-[5-chloro-3-(N-{1-methylethyl}amino)-2-oxo-6-phenylhydropyrazinyl]acetic acid (EX-1D) for 2-[3-({2-[(tert-butoxy)carbonylamino]ethyl}amino)-5-chloro-2-oxo-6-phenylhydropyrazinyl]acetic acid, EX-58A was converted to the product which gave an m/z+1 of 482.

Example 59



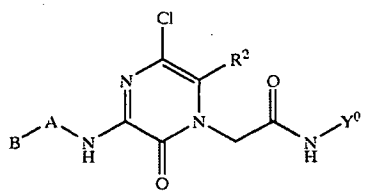
4-cyanobenzylamine hydrochloride (EX-59A) was prepared from 10 g (0.030 moles) of 4-{N,N-bis-(tert-butoxycarbonyl)aminomethyl}benzonitrile, prepared following Synthetic Communication, 28(23), 4419–4429 (1998), by stirring it in 4N HCl Dioxane (75 ml). After 3 h, the solution was concentraed in vacuo and triturated with ether. The solid was collected by filtration and vacuum dried to yield 5 g (98%) of EX-59A as a white solid: ^1H NMR (DMSO) d 8.68 (br s, 2H) 7.84 (m, 2H), 7.67 (m, 2H), 4.06 (s, 2H); HRMS (EI) calcd for $C_8H_8N_2$ 133.0766, found 133.0807.

Using the procedure of Example 58, EX-59A was converted to the product which gave an m/z+1 of 481.

Using the procedures of Scheme 1, Scheme 2, and the Examples herein with suitable reagents, starting materials, and intermediates, additional pyrazinones of the present invention were prepared and these pryazinones are summarized in Table 3.

TABLE 3

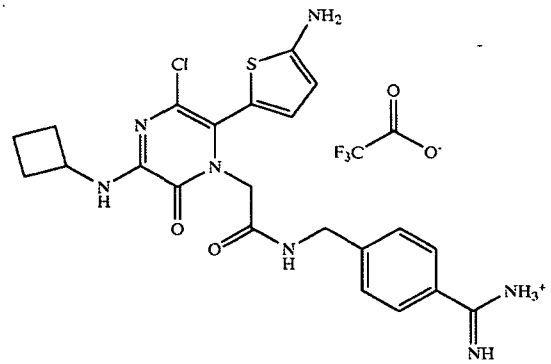
Additional Substituted Pyrazinones of the Present Invention Prepared based on the Procedures of Scheme 1, Scheme 2, and Examples herein.



General Structure

Ex. No.	R^2	B-A-	Y^0	MW (m/z + 1)
60	Phenyl	2-phenylethyl	4-amidinobenzyl	487
61	3-Nitrophenyl	isopropyl	4-(N-hydroxyamidino) benzyl	514
62	3-Aminophenyl	isopropyl	2-(4-amidinophenyl) ethyl	482
63	Phenyl	2-phenylethyl	2-(4-amidinophenyl) ethyl	495
64	3-Carbomethoxy phenyl	isopropyl	4-amidinobenzyl	511
65	3-Carboxyphenyl	isopropyl	4-amidinobenzyl	497
66	2-hydroxyphenyl	cyclobutyl	4-amidinobenzyl	481
67	3-hydroxyphenyl	cyclobutyl	4-amidinobenzyl	481
68	3-acetamido phenyl	isopropyl	2-(4-amidinophenyl) ethyl	524

Example 69



1-Benzyloxycarbonylmethyl-6-(5-bromothiophen-2yl)-3,5-dichloro pyrazinone (EX-69A) was synthesized as described in the general schemes of the patent and as described, for example, specifically for EX-1B substituting 5bromothiophenecarbaldehyde for benzaldehyde. EX-69A is a yellow crystalline solid: HPLC-MS (5 to 95% AcCN/6 min @ 1.0 mL/Min @ 254 nm @ 50° C.): retention time 4.38 min. $M+Na^+=494.9$ for formula $C_{17}H_{11}BrCl_2N_2O_3SNa$; ^1H NMR (400 MHz, $CDCl_3$): d 4.62 (s, 2H), 5.19 (s, 2H), 6.79 (d, J=4.0 Hz, 1H), 7.00 (d, J=4.0 Hz, 1H) 7.32 (m, 2H), 7.37 (m, 3H); ^{13}C NMR (101 MHz,

$CDCl_3$): d 49.0, 68.1, 117.8, 126.5, 128.6, 128.7, 128.8, 130.1, 130.7, 132.0, 134.5, 147.8, 151.9, 166.2.

EX-69A (12.15 g, 25.75 mmol) was treated with cyclobutylamine (3.80 g, 53.52 mmol) in 250 ml toluene at room temperature for 4 hours. The toluene solution was washed with saturated ammonium chloride solution and dried over anhydrous $MgSO_4$. After removing the toluene, the pure product EX-69B was obtained as a yellow solid (13.05 g, 99%): HPLC-MS (5 to 95% AcCN/6 min @ 1.0 mL/Min @ 254 nm @ 50° C.): retention time 4.90 min, $M+H^+$=508.0 for formula $C_{21}H_{20}BrClN_3O_3S$.

Potassium phthalimide (4.56 g, 24.6 mmol) and CuI (18.0 g, 94.7 mmol) were mixed in 200 ml dimethylacetamide. The mixture was stirred at room temperature for 10 minutes. To this mixture was added compound EX-69B (12.0 g, 23.7 mol). The resulting mixture was heated to 160° C. and stirred for 5 hours at an open air atmosphere. The reaction solution was filtered to remove all the insoluble solid and was concentrated via high vacuum distillation at a rotavapor. Aqueous work-up and silica gel flush chromatography yielded the pure product EX-69C as light yellow solid (6.8 g, 50%) with the des-bromo side product formation the reason for the low yield: HPLC-MS (5 to 95% AcCN/6 min @ 1.0 mL/Min @ 254 nm @ 50° C.): retention time 3.82 min, $M+H^+$=575.5 for formula $C_{29}H_{24}ClN_4O_5S$; ^1H NMR (400 MHz, $CDCl_3$): d 1.69 (m, 2H), 1.92 (m, 2H), 2.36 (m, 2H), 4.45 (m, 1H), 4.49 (s, 2H), 5.07 (s, 2H), 6.54 (d, J=8.0 Hz, 1H), 6.75 (d, J=3.6 Hz, 1H), 7.17–7.25 (m, 7H), 7.50 (d, J=4.0 Hz, 1H), 7.71 (dd, J=2.8, 5.2 Hz, 2H), 7.85 (dd, J=2.8, 5.2 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): d 15.2, 30.9, 45.8, 47.4, 67.4, 114.7, 118.2, 123.9, 126.5, 128.28, 128.33, 128.36, 128.39, 128.42, 128.45, 129.5, 129.9, 131.1, 134.8, 134.9, 135.7, 148.5, 150.8, 165.2, 166.9.

EX-69C (0.55 g, 0.96 mmol) was treated with 1 ml hydrazine in 10 ml methanol and 5 ml dichloromethane for 4 hours. The reaction solution was acidified with 1N HCl and filtered to remove the solid by-product. Aqueous work-up yield the crude (90% pure) product EX-69D (0.49 g): HPLC-MS (5 to 95% AcCN/6 min @ 1.0 mL/Min @ 254 nm @ 50° C.): retention time 3.29 min, $M+H^+$=445.3 for formula $C_{21}H_{22}ClN_4O_3S$.

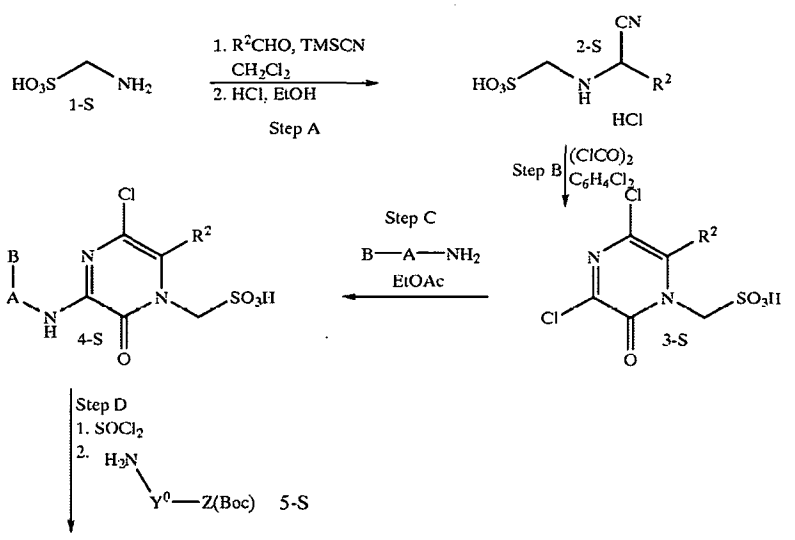
EX-69D (0.48 g, 1.08 mmol) was mixed with Boc anhydride (0.28 g, 1.30 mmol), triethylamine (0.22 g, 2.16 mmol) and DMAP (12 mg, 0.1 mmol). The reaction mixture was stirred for 4 hours at room temperature. After an aqueous work-up, the crude product in 2 ml CH_3CN and 2 ml THF was treated with 2 ml 1M LiOH for 3 hours. Aqueous work-up yield the crude carboxylic acid EX-69E: HPLC-MS (5 to 95% AcCN/6 min @ 1.0 mL/Min @ 254 nm @ 50° C.): retention time 3.18 min, $M+H^+$=455.4 for formula $C_{19}H_{24}ClN_4O_5S$.

EX-69E was coupled with the protected amidine, 4-(N-benzyloxycarbonylamidino)benzylamine hydrogen chloride salt, prepared using the procedure outlined Synthetic Communications, 28(23), 4419–4429 (1998) in the same way as described before using EDC, HOBt and DIEA in DMF to give the protected product EX-69F. EX-69F was purified by reverse phase HPLC using C18 column to give an off-white amorphous solid: HPLC-MS (5 to 95% AcCN/6 min @ 1.0 mL/Min @ 254 nm @ 50° C.): retention time 3.28 min, $M+H^+$=720.9 for formula $C_{35}H_{38}ClN_7O_6S$; ^1H NMR (400 MHz, $CDCl_3$): d 1.49 (s, 9H), 1.80 (m, 2H), 2.03 (m, 2H), 2.45 (m, 2H), 4.3 (b, 2H), 4.49 (b, 3H), 5.07 (s, 2H), 6.66–6.78 (m, 2H), 7.0–7.18 (m, 2H), 7.33–7.47 (m, 5H).

EX-69F was converted to the product by hydrogenation as described before. After the hydrogenation, it was treated with HCl saturated methanol solution to remove the Boc group. The product was purified by reverse phase HPLC with a C18 column with amobile phase was 0.1% TFA in water and acetonitrile to give the product as a TFA salt and an off-white amorphous solid: HPLC-MS (5 to 95% AcCN/6 min @ 1.0 mL/Min @ 254 nm @ 50° C.): retention time 1.94 min, $M+H^+$=486.4 for formula $C_{22}H_{25}ClN_7O_2S$; ^1H NMR (400 MHz, methanol-d_4): d 1.79 (m, 2H), 2.06 (m, 2H), 2.39 (m, 2H), 4.45 (s, 2H), 4.46 (m, 1H), 4.57 (s, 1H), 4.58 (s, 1H), 6.01 (d, J=4 Hz, 1H), 6.52 (m, 1H), 7.49 (d, J=8.4 Hz, 2H), 7.75 (m, 2H).

Sulfonyl analogs of pyrazinones wherein a sulfonyl is present as a replacement for the carbonyl of the acetamide at the N-1 position of the pyrazinone can be prepared using Scheme 3: Sulfonyl Pyrazinone detailed below along with the specific Example 70.

Scheme 3:
Sulfonyl Pyrazinones



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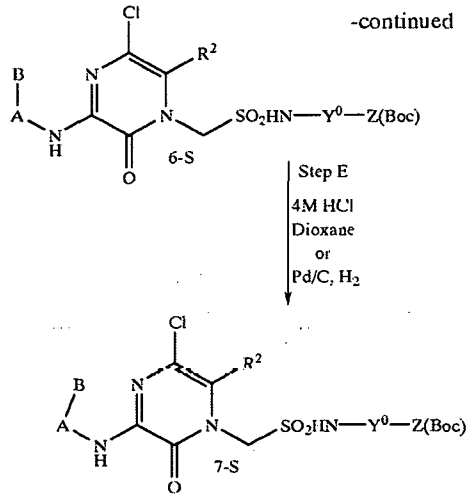
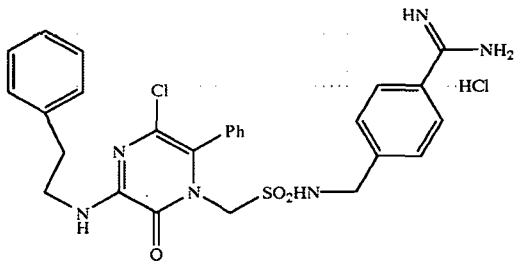


Example 70



Benzaldehyde (1 eq.) is added slowly by syringe to a solution of aminomethanesulfonic acid (1 eq.) in dichloromethane at room temperature. Trimethylsilyl cyanide (1 eq.) is added dropwise via syringe over a 10 minute period. The reaction is stirred for 4 hours at room temperature and then concentrated under reduced pressure. The residue is diluted with ethyl acetate, washed with brine, dried ($MgSO_4$), and concentrated. The residue is diluted with ethyl acetate (80 mL) and 9.9 M HCl (1.05 eq.) in ethanol is added (prepared by addition of 28.90 mL acetyl chloride to 41.0 mL cold ethanol), resulting in precipitation of the intermediate product EX-70A. The precipitate is collected by filtration, washed with ethyl ether, and dried to give pure product EX-70A.

To a suspension of 1 eq. of EX-70A in dry 1,2-dichlorobenzene (1.0 M) is added oxalyl chloride (4 eq.) with stirring at room temperature. The resulting suspension is heated at 100° C. for approximately 18 hours. The reaction is allowed to cool to room temperature and the volatiles are removed under reduced pressure. The remaining solution is passed through a silica gel column (hexane flush, followed by 50% ethyl acetate/hexanes). Concentration of the solution gives crude product EX-70B, which is purified by column chromatography.

Phenethylamine (3 eq.) is added to a solution of EX-70B (1 eq.) in ethyl acetate at room temperature. The resulting solution is heated at reflux for 18 hours. The solution is allowed to cool to room temperature, resulting in formation of a thick precipitate. The reaction mixture is diluted with ethyl acetate, washed with 0.5 N HCl, saturated $NaHCO_3$ and brine. The organic solution is dried ($MgSO_4$), filtered and concentrated to give the crude product. Recrystallization from ethyl acetate and hexanes affords pure product EX-70C.

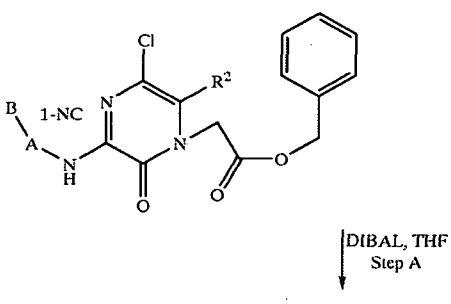
A solution of 1 eq. of EX-70C in dichloromethane with several drops of dimethylformamide added is cooled to 0° C. Thionyl chloride (1.1 eq.) is added dropwise and the solution is slowly warmed to room temperature. After completion of the reaction, the volatile components are removed under reduced pressure and the product EX-70D is immediately used in the next step.

To the sulfonyl chloride EX-70D (1 eq.) in dichloromethane is added the amine, 4-(N-tert-butoxycarbonylamidino)benzylamine hydrochloride, in DMF with 5 eq. of N-methylmorpholine. After completion of the reaciton, polyaldehyde and/or polyamine resin (10 eq.) are added to remove any unreacted starting materials. The resins are filtered, rinsed with DMF/DCM (1:1) and the solvents are removed under reduced pressure to give pure product EX-70E.

To 1 eq. of EX-70E is added 40 eq. of 4 M HCl/dioxane. The resulting solution is stirred at room temperature overnight. The solution is concentrated and the crude product is triturated from solvent to afford pure product.

Methylene analogs of pyrazinones wherein a methylene is present as a replacement for the carbonyl of the acetamide at the N-1 position of the pyrazinone can be prepared using Scheme 4: Methylene Pyrazinone detailed below along with the specific Example 71.

Scheme 4
Methylene Pyrazinone



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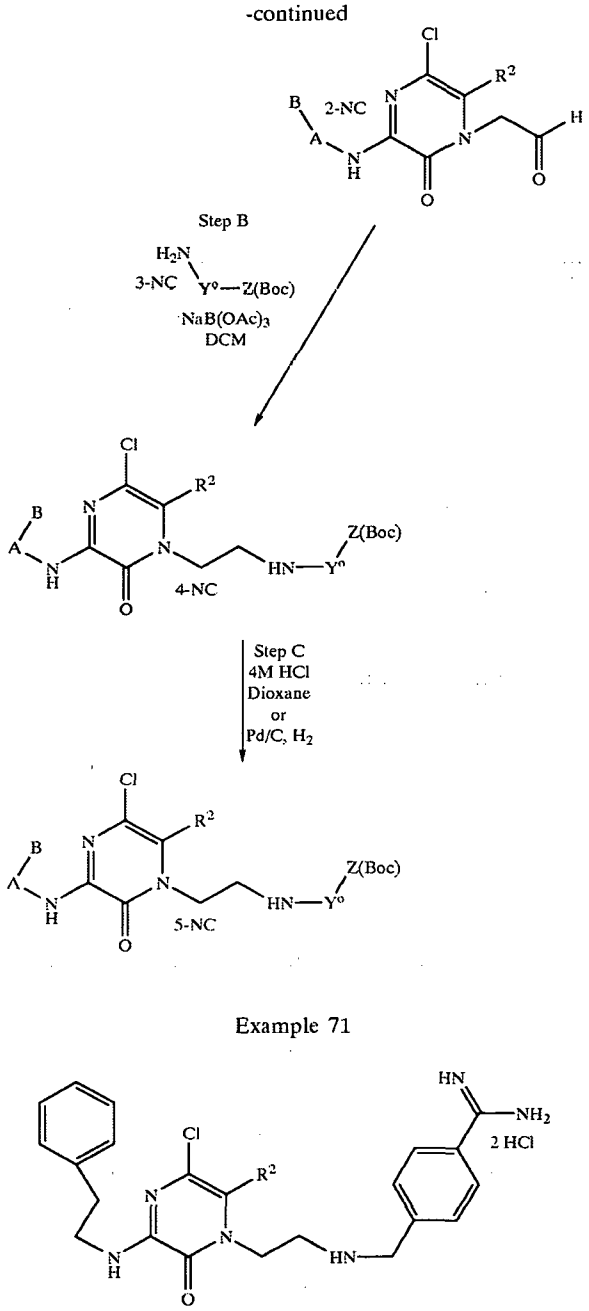


Example 71

Diisobutylaluminum hydride (1.05 equiv.) is added over a period of 15 min to a cooled solution (−78° C.) of 1 eq. of 1-benzyloxycarbonylmethyl-chloro-6-phenyl-3-(2-phenylethylamino)pyrazinone in tetrahydrofuran. After stirring for 1 h at −78° C. the reaction is slowly quenched at −78° C. with cold methanol. The mixture is slowly poured into ice-cold 1N HCl and the aqueous mixture is extracted with ethyl acetate. The combined organic layers are washed with brine, dried with $MgSO_4$, filtered, and the solvents are removed under reduced pressure. The crude product is purified by column chromatography to afford purified product EX-71A.

Sodium triacetoxyborohydride (1.2 eq.) and a catalytic amount of acetic acid are added to a suspension of 1.0 eq. of EX-71A and 1.0 eq. of the amine, 4-(N-tert-butoxycarbonylamidino)benzylamine hydrochloride, in dichloromethane. The suspension quickly clears and becomes homogeneous. The reaction is stirred for several hours. The solution is cooled in an ice bath and basified with 1.0 N NaOH. The reaction mixture is diluted with dichloromethane and washed with brine. The organic solution is dried ($MgSO_4$), filtered and concentrated to give the crude product. The crude product is purified by silica gel chromatography to afford purified product EX-71B.

To 1 eq. of EX-71B is added 40 eq. of 4 M HCl/dioxane. The resulting solution is stirred at room temperature overnight. The solution is concentrated and the crude product is triturated from ethyl ether to afford pure product.

General Robotics and Experimental Procedure for the Robotic Parallel Synthesis of a Series of Amides E-i and Z-i from A-i

Scheme 5 specifically illustrates the derivatization of the scaffold A-i to afford the desired product D-i in a parallel array synthesis format. In a parallel array synthesis reaction block, individual reaction products were prepared in each of multiple reaction block vessels in a spatially addressed format. A solution of the desired scaffold A-i (limiting amount) in acetonitrile (ACN) was added to the reaction vessels followed by a three-fold stoichiometric excess solution of the primary amine B-i in acetonitrile. Excess primary amine was used as a base and to effect complete conversion of scaffold A-i to product C-i. The reaction mixtures were incubated at 70° C. for 16–20 h. After cooling to ambient temperature, each reaction vessel was charged with one mL of methanol and an excess (3–4 fold stoichiometric excess) of aqueous potassium hydroxide. The reaction block was shaken vertically for 14–20 h on an orbital shaker at ambient temperature. The contents of each reaction vessel were then acidified with aqueous HCl. Each reaction vessel was then opened, and the solutions were evaporated to dryness under N_2 and/or a Savant apparatus. Polyamine resin R-1 (10–15 fold stoichiometric excess) was added to the solid carboxylic acid followed by dichloromethane and water (10:1). The mixture was shaken laterally for 14–20 h on an orbital shaker at ambient temperature (rotating the vials at least once so each side of the vial was agitated for a minimum of 2 h). The desired product D-i was sequestered away from the reaction by-products and excess reactants as the insoluble adduct D-x. Simple filtration of the insoluble resin-adduct D-x and rinsing of the resin cake with DMF, DCM, MeOH, and DCM afforded the desired resin-bound product. After drying the resin under vacuum for 2 h, an excess of HCl/dioxane (7–8 fold stoichiometric excess based on the loading of amine functionality) along with dichloromethane was added to each reaction vessel to cleave the desired product D-i from the resin. The reaction block was shaken laterally for 2–20 h on an orbital shaker at ambient temperature. Simple filtration of the solution, rinsing of the resin cake with dimethylformamide/dichloromethane, and evaporation of the solvents afforded the desired product D-i in purified form.

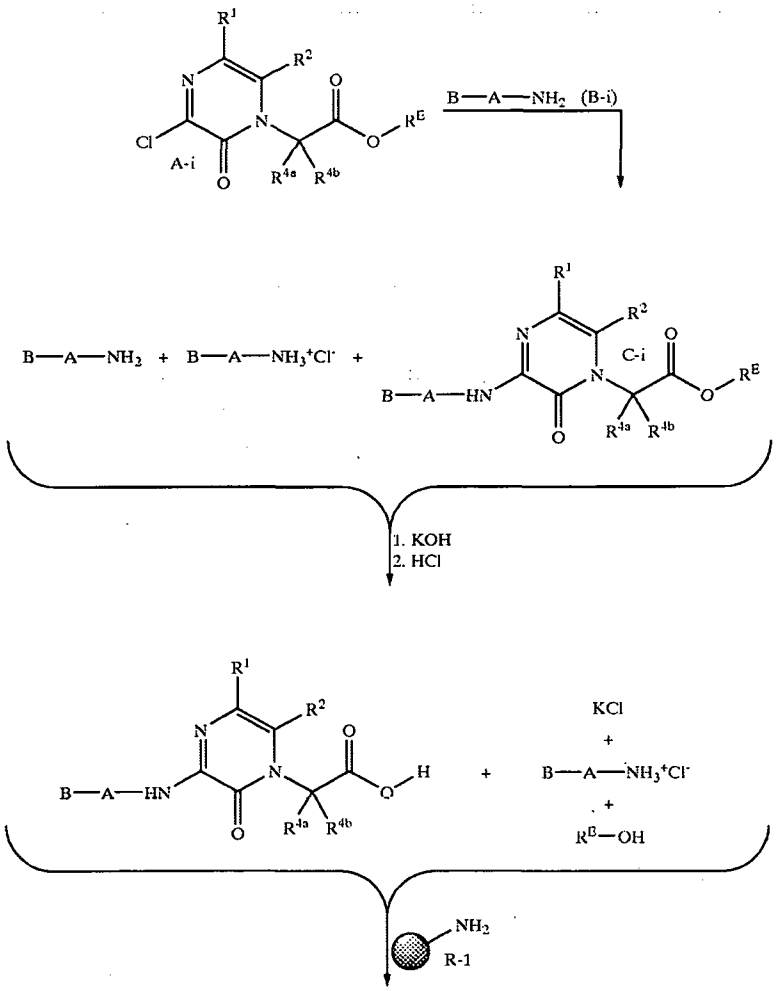
Scheme 6 and Scheme 7 illustrate the conversion of the carboxylic acid-containing scaffold D-i to the desired amide product E-i in a parallel synthesis format. A unique scaffold D-i was added as a solution in dichloromethane/dimethylformamide to each reaction vessel. A solution of hydroxybenzotriazole B-2 in dichloromethane/dimethylformamide was added to each reaction vessel, followed by the polymer-bound carbodiimide reagent R-2 (1.5 fold stoichiometric excess). The parallel reaction block was agitated vertically on an orbital shaker for 30 min to 1 h. A

limiting amount of the same amine B-3 (0.8 equivalents) in DMF, along with a 3 fold stoichiometric excess of NMM if the amine B-3 was a salt, was added to the unique contents of each vessel. The parallel reaction block was then agitated vertically on an orbital shaker for 2–3 h at ambient temperature. An excess of the amine-functionalized resin R-1 and aldehyde resin R-3, along with dichloromethane solvent were added to each reaction vessel. The resin-charged reaction block was shaken vertically for 2 h on an orbital shaker at ambient temperature. The amine-containing resin R-1 sequestered B-2 and any remaining D-i as their resin-bound adducts, B-4 and D-2, respectively. The aldehyde-containing resin R-3 sequestered any unreacted B-3 as its resin-bound adduct R-5. Filtration of the insoluble resins and resin adducts R-1, R-2, R-3, R-4, R-5, B-4, and D-2 and subsequent rinsing of the vessel resin-bed with dichloromethane/dimethylformamide afforded filtrates containing the purified products E-i. Concentration of the filtrates afforded the purified products E-i, which were weighed and analyzed by LC/MS.

For those amines B-3 which contain a protecting group, a final deprotection step was required after the coupling reaction (Scheme 8). The residues E-i were dissolved in methanol, Pd/C was added, and the reaction mixtures were stirred under 10 psi of H_2 for 16–20 h. The mixtures were filtered through Celite, rinsed with methanol and concentrated to afford pure products Z-i, which were weighed and analyzed by LC/MS. If necessary, the products were purified by reverse-phase HPLC. Conversely, the deprotection step was done, as needed, in the presence of ammonium formate (5 fold stoichiometric excess) in place of the 10 psi of H_2.

A third method of deprotection uses TMSI generated in situ. The residues E-i were dissolved in acetonitrile. Sodium iodide and TMSCl (5 fold stoichiometric excess of each) were added, and the reaction mixtures were agitated vertically at 55° C. for 14–20 h. Methanol and (N,N-dimethyl) aminomethylpolystyrene resin were added to each vessel, and the mixtures were agitated for another 3 h. The mixtures were filtered through Celite, rinsed with acetonitrile and concentrated to afford products Z-i, which were weighed and analyzed by LC/MS. If necessary, the products were purified by reverse-phase HPLC.

Scheme 5
General Robotic Synthesis



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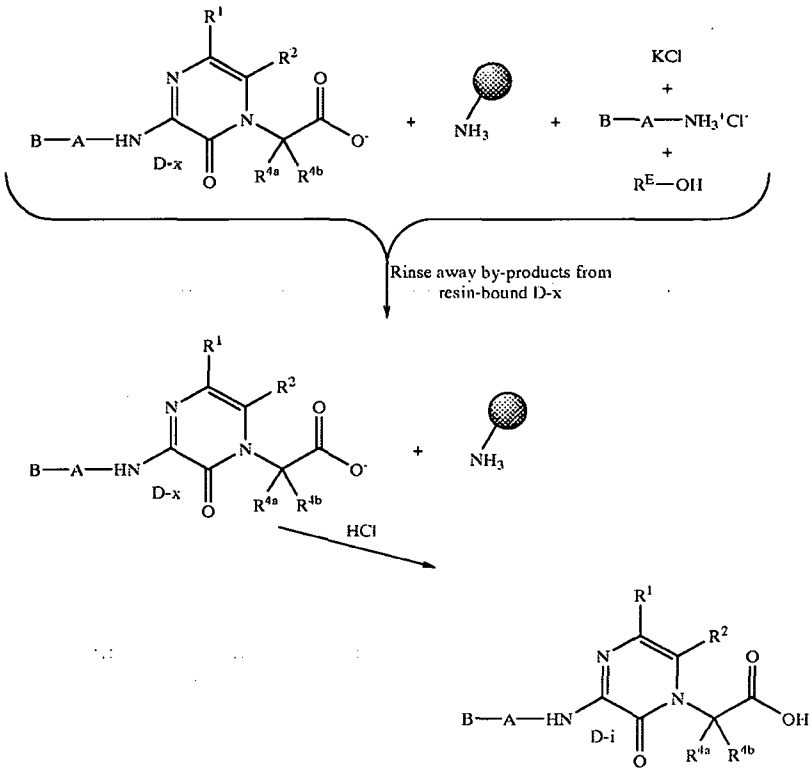
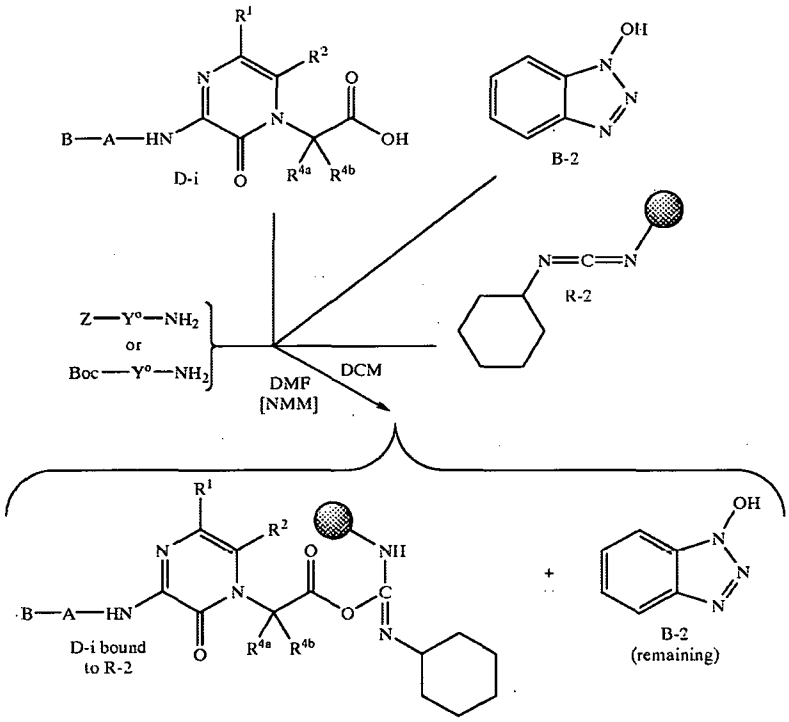


Scheme 6
General Robotic Synthesis (Continued)



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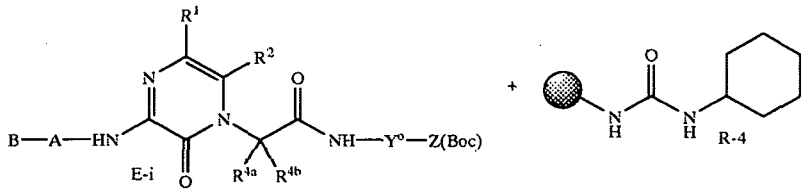
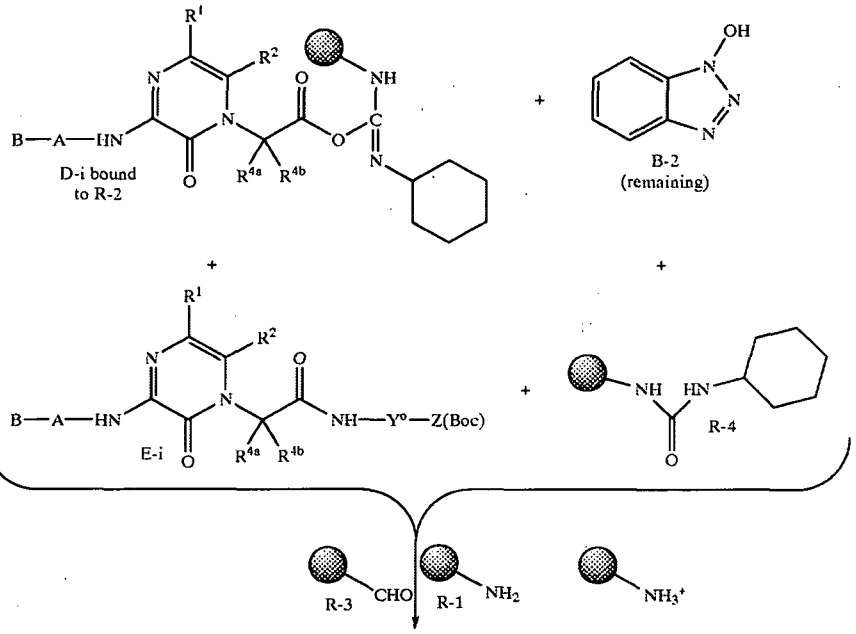
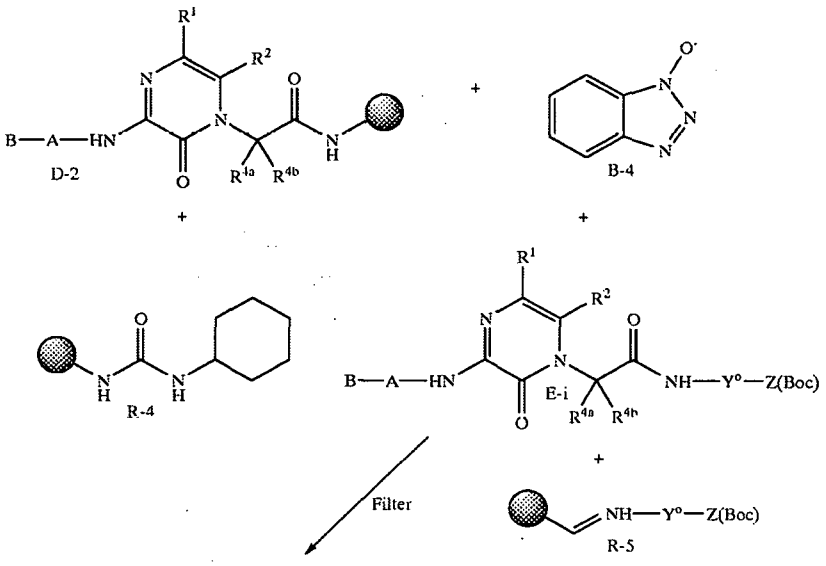


Scheme 7
General Robotic Synthesis (Continued)





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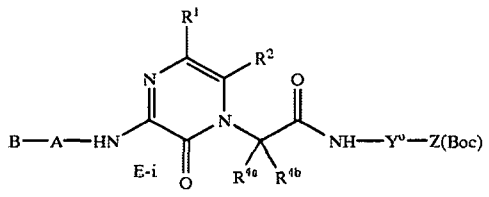
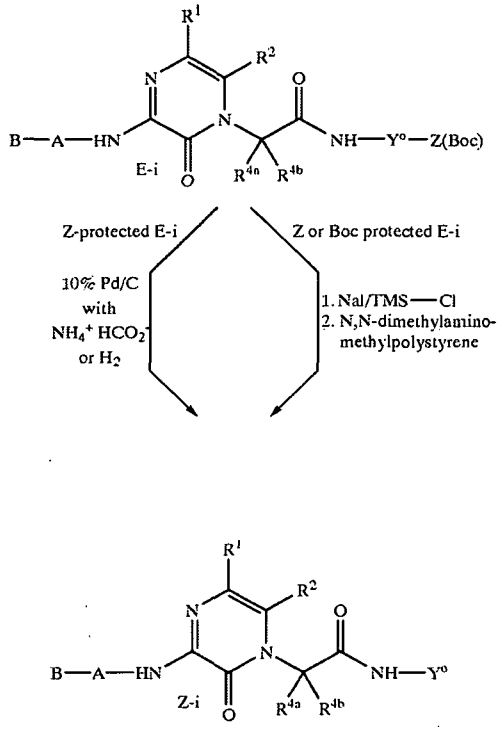


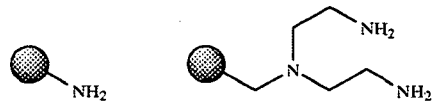
Scheme 8
General Robotic Synthesis (Concluded)



Although Schemes 5, 6, 7, and 8 describe the use of parallel array chemical library technology to prepare compounds of general formulae D-i, E-i and Z-i, it is noted that one with ordinary skill in the art of classical synthetic organic chemistry would be able to prepare D-i, E-i, and Z-i by conventional means (one compound prepared at a time in conventional glassware and purified by conventional means such as chromatography and/or crystallization).

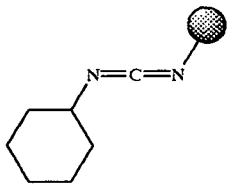
The various functionalized resins utilized to prepare and purify parallel reaction mixtures, their source commercially or in the scientific literature, and the three representations (ie, the R number, an abbreviated functional structure, and the actual structural unit bound to the resin for each) are summarized below as follows:

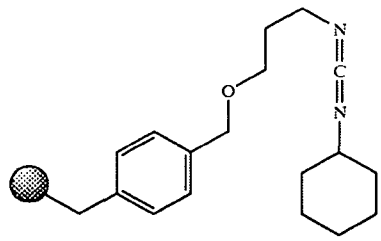
R-1



R-1 Reference: Prepared as reported in T. J. Parlow, D. A. Mischke, and S. S. Woodard, *J. Organic Chemistry*, 62, 5908–5919 (1997)

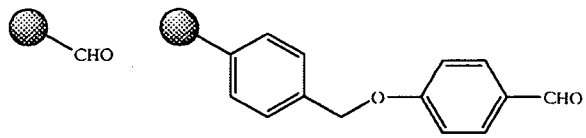
R-2





R-2 Reference: Polystyrene bound N-cyclohexylcarbodiimide (Argonaut Catalog Number 800371

R-3



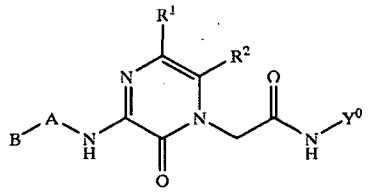
R-3 Reference: Polystyrene bound benzaldehyde Novabiochem Catalog Number 01-640182

The specific compounds prepared, by using the General Robotics and Experimental Procedure, Schemes 5 through 8, and general synthetic methods and processes disclosed

herein, are listed below in Tables 4 through Table 7. Tables 4 through Table 7 further summarize the mass spectral characterization data that confirmed the indicated structure for each compound of the present invention disclosed in these tables.

TABLE 4

Structures of Pyrazinones Prepared by General Robotic and Experimental Procedures

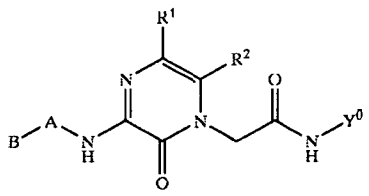


General Structure

Ex. No.	R^2	B-A-	Y^0	R^1	MW (m/z + 1)
73	5-amino-2-fluorophenyl	isopropyl	4-amidino-2-fluorobenzyl	Cl	504
74	2-chloro-5-pyridyl	isopropyl	4-amidino-2-fluorobenzyl	Cl	506
75	3-pyridyl	isopropyl	4-amidinobenzyl	Cl	454
76	5-amino-2-methyl-thiophenyl	isopropyl	4-amidinobenzyl	Cl	515
77	3-nitrophenyl	2-phenylethyl	4-amidinobenzyl	Cl	560.2
78	2-methylphenyl	2-phenylethyl	4-amidinobenzyl	Cl	529.4
79	4-methylphenyl	2-phenylethyl	4-amidinobenzyl	Cl	529.3
80	1-naphthyl	2-phenylethyl	4-amidinobenzyl	Cl	565.3
81	3-methylphenyl	2-phenylethyl	4-amidinobenzyl	Cl	529.5
82	2-naphthyl	2-phenylethyl	4-amidinobenzyl	Cl	564.9
83	3-methylphenyl	2-phenylethyl	4-amidinobenzyl	H	495.8
84	3-methylphenyl	2-phenylethyl	4-amidinobenzyl	H	495.5
85	3-methylphenyl	2-phenylethyl	4-amidinobenzyl	H	495.4
86	3-aminophenyl	2-phenylethyl	4-amidinobenzyl	Cl	530.3
87	3-aminophenyl	2-(3-chloro phenyl)ethyl	4-amidinobenzyl	Cl	563.9
88	3-aminophenyl	benzyl	4-amidinobenzyl	Cl	516.2
89	3-aminophenyl	cyclobutyl	2-phenylethyl	Cl	452.3
90	3-aminophenyl	cyclobutyl	4-amidinobenzyl	Cl	480.5
91	3-aminophenyl	benzyl	5-guanidino-1-oxo-1-(2-thiazolyl)-2-pentyl	Cl	608.4

TABLE 4-continued

Structures of Pyrazinones Prepared by General Robotic and Experimental Procedures

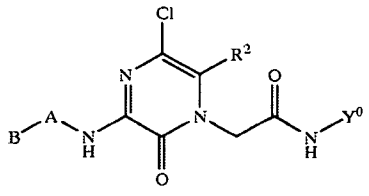


General Structure

Ex. No.	R^2	B-A-	Y^0	R^1	MW (m/z + 1)
92	3-aminophenyl	cyclobutyl	4-amidinobenzyl	H	446.2
93	3-aminophenyl	t-butyl	4-amidinobenzyl	Cl	482
94	3-aminophenyl	N,N-dimethyl amino	4-amidinobenzyl	Cl	469.2
95	3-(N-methylamino)-phenyl	2-phenylethyl	4-amidinobenzyl	Cl	543.9
96	3-(N-methylamino)-phenyl	isopropyl	4-amidinobenzyl	Cl	481.6
97	2-methyl-3-aminophenyl	isopropyl	4-amidinobenzyl	Cl	482.2
98	2-methyl-3-aminophenyl	isopropyl	4-amidinobenzyl	H	448.8
99	3-aminophenyl	cyclobutyl	benzyl	Cl	438.4

TABLE 5

Structures of Pyrazinones Prepared by General Robotic and Experimental Procedures

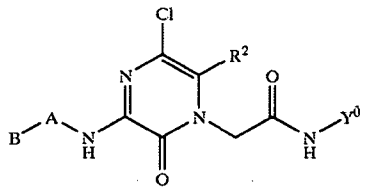


General Structure

Ex. No.	R^2	B—A—	Y^0	MW (m/z + 1)
E-0001	methyl	benzyl	2-(4-pyridyl)ethyl	412
E-0002	methyl	2-phenylethyl	2-(4-pyridyl)ethyl	426
E-0003	methyl	2-(3-chlorophenyl)ethyl	2-(4-pyridyl)ethyl	460
E-0004	methyl	2-(4-chlorophenyl)ethyl	2-(4-pyridyl)ethyl	460
E-0005	methyl	2-(3-pyridyl)ethyl	2-(4-pyridyl)ethyl	427
E-0006	methyl	2-(4-pyridyl)ethyl	2-(4-pyridyl)ethyl	427
E-0007	methyl	2-(4-morpholinyl)ethyl	2-(4-pyridyl)ethyl	435

TABLE 5-continued

Structures of Pyrazinones Prepared by General Robotic and Experimental Procedures

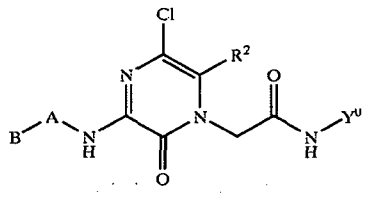


General Structure

Ex. No.	R^2	B—A—	Y^0	MW (m/z + 1)
E-0008	methyl	4-pyridylmethyl	2-(4-pyridyl)ethyl	413
E-0009	phenyl	benzyl	2-(4-pyridyl)ethyl	474
E-0010	phenyl	2-phenylethyl	2-(4-pyridyl)ethyl	488
E-0011	phenyl	2-(3-chlorophenyl)ethyl	2-(4-pyridyl)ethyl	522
E-0012	phenyl	2-(4-chlorophenyl)ethyl	2-(4-pyridyl)ethyl	522
E-0013	phenyl	2-(3-pyridyl)ethyl	2-(4-pyridyl)ethyl	489
E-0014	phenyl	2-(4-pyridyl)ethyl	2-(4-pyridyl)ethyl	489
E-0015	phenyl	2-(4-morpholinyl)ethyl	2-(4-pyridyl)ethyl	497
E-0016	phenyl	4-pyridylmethyl	2-(4-pyridyl)ethyl	475
E-0017	4-chlorophenyl	benzyl	2-(4-pyridyl)ethyl	508
E-0018	4-chlorophenyl	2-phenylethyl	2-(4-pyridyl)ethyl	522
E-0019	4-chlorophenyl	2-(3-chlorophenyl)ethyl	2-(4-pyridyl)ethyl	557
E-0020	4-chlorophenyl	2-(4-chlorophenyl)ethyl	2-(4-pyridyl)ethyl	557
E-0021	4-chlorophenyl	2-(3-pyridyl)ethyl	2-(4-pyridyl)ethyl	523
E-0022	4-chlorophenyl	2-(4-pyridyl)ethyl	2-(4-pyridyl)ethyl	523
E-0023	4-chlorophenyl	2-(4-morpholinyl)ethyl	2-(4-pyridyl)ethyl	531
E-0024	4-chlorophenyl	4-pyridylmethyl	2-(4-pyridyl)ethyl	509
E-0025	4-chlorophenyl	benzyl	2-(4-pyridyl)ethyl	508
E-0026	4-chlorophenyl	2-phenylethyl	2-(4-pyridyl)ethyl	522
E-0027	4-chlorophenyl	2-(3-chlorophenyl)ethyl	2-(4-pyridyl)ethyl	557
E-0028	4-chlorophenyl	2-(4-chlorophenyl)ethyl	2-(4-pyridyl)ethyl	557
E-0029	4-chlorophenyl	2-(3-pyridyl)ethyl	2-(4-pyridyl)ethyl	523
E-0030	4-chlorophenyl	2-(4-pyridyl)ethyl	2-(4-pyridyl)ethyl	523
E-0031	4-chlorophenyl	2-(4-morpholinyl)ethyl	2-(4-pyridyl)ethyl	531
E-0032	4-chlorophenyl	4-pyridylmethyl	2-(4-pyridyl)ethyl	509
E-0033	4-methoxyphenyl	benzyl	2-(4-pyridyl)ethyl	504
E-0034	4-methoxyphenyl	2-phenylethyl	2-(4-pyridyl)ethyl	518
E-0035	4-methoxyphenyl	2-(3-chlorophenyl)ethyl	2-(4-pyridyl)ethyl	552
E-0036	4-methoxyphenyl	2-(4-chlorophenyl)ethyl	2-(4-pyridyl)ethyl	552
E-0037	4-methoxyphenyl	2-(3-pyridyl)ethyl	2-(4-pyridyl)ethyl	519
E-0038	4-methoxyphenyl	2-(4-pyridyl)ethyl	2-(4-pyridyl)ethyl	519
E-0039	4-methoxyphenyl	2-(4-morpholinyl)ethyl	2-(4-pyridyl)ethyl	527
E-0040	4-methoxyphenyl	4-pyridylmethyl	2-(4-pyridyl)ethyl	505
E-0041	3,4-methylene-dioxyphenyl	benzyl	2-(4-pyridyl)ethyl	518
E-0042	3,4-methylene-dioxyphenyl	2-phenylethyl	2-(4-pyridyl)ethyl	532
E-0043	3,4-methylene-dioxyphenyl	2-(3-chlorophenyl)ethyl	2-(4-pyridyl)ethyl	566
E-0044	3,4-methylene-dioxyphenyl	2-(4-chlorophenyl)ethyl	2-(4-pyridyl)ethyl	566
E-0045	3,4-methylene-dioxyphenyl	2-(3-pyridyl)ethyl	2-(4-pyridyl)ethyl	533
E-0046	3,4-methylene-dioxyphenyl	2-(4-pyridyl)ethyl	2-(4-pyridyl)ethyl	533
E-0047	3,4-methylene-dioxyphenyl	2-(4-morpholinyl)ethyl	2-(4-pyridyl)ethyl	541
E-0048	3,4-methylene-dioxyphenyl	4-pyridylmethyl	2-(4-pyridyl)ethyl	519
E-0049	4-biphenyl	benzyl	2-(4-pyridyl)ethyl	550
E-0050	4-biphenyl	2-phenylethyl	2-(4-pyridyl)ethyl	564
E-0051	4-biphenyl	2-(3-chlorophenyl)ethyl	2-(4-pyridyl)ethyl	599
E-0052	4-biphenyl	2-(4-chlorophenyl)ethyl	2-(4-pyridyl)ethyl	599
E-0053	4-biphenyl	2-(3-pyridyl)ethyl	2-(4-pyridyl)ethyl	565
E-0054	4-biphenyl	2-(4-pyridyl)ethyl	2-(4-pyridyl)ethyl	565
E-0055	4-biphenyl	2-(4-morpholinyl)ethyl	2-(4-pyridyl)ethyl	573
E-0056	4-biphenyl	4-pyridylmethyl	2-(4-pyridyl)ethyl	551
E-0057	benzyl	benzyl	2-(4-pyridyl)ethyl	488
E-0058	benzyl	2-phenylethyl	2-(4-pyridyl)ethyl	502
E-0059	benzyl	2-(3-chlorophenyl)ethyl	2-(4-pyridyl)ethyl	536
E-0060	benzyl	2-(4-chlorophenyl)ethyl	2-(4-pyridyl)ethyl	536
E-0061	benzyl	2-(3-pyridyl)ethyl	2-(4-pyridyl)ethyl	503
E-0062	benzyl	2-(4-pyridyl)ethyl	2-(4-pyridyl)ethyl	503

TABLE 5-continued

Structures of Pyrazinones Prepared by General Robotic and Experimental Procedures

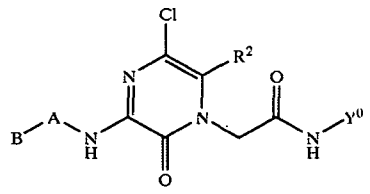


General Structure

Ex. No.	R^2	B—A—	Y^0	MW (m/z + 1)
E-0063	benzyl	2-(4-morpholinyl)ethyl	2-(4-pyridyl)ethyl	511
E-0064	benzyl	4-pyridylmethyl	2-(4-pyridyl)ethyl	489
E-0065	2-phenylethyl	benzyl	2-(4-pyridyl)ethyl	502
E-0066	2-phenylethyl	2-phenylethyl	2-(4-pyridyl)ethyl	516
E-0067	2-phenylethyl	2-(3-chlorophenyl)ethyl	2-(4-pyridyl)ethyl	550
E-0068	2-phenylethyl	2-(4-chlorophenyl)ethyl	2-(4-pyridyl)ethyl	550
E-0069	2-phenylethyl	2-(3-pyridyl)ethyl	2-(4-pyridyl)ethyl	517
E-0070	2-phenylethyl	2-(4-pyridyl)ethyl	2-(4-pyridyl)ethyl	517
E-0071	2-phenylethyl	2-(4-morpholinyl)ethyl	2-(4-pyridyl)ethyl	525
E-0072	2-phenylethyl	4-pyridylmethyl	2-(4-pyridyl)ethyl	503
E-0073	3-chlorophenyl	benzyl	2-(4-pyridyl)ethyl	508
E-0074	3-chlorophenyl	benzyl	2-(3-pyridyl)ethyl	508
E-0075	3-chlorophenyl	benzyl	4-piperidinylmethyl	573
E-0076	3-chlorophenyl	2-phenylethyl	2-(4-pyridyl)ethyl	522
E-0077	3-chlorophenyl	2-phenylethyl	2-(3-pyridyl)ethyl	522
E-0078	3-chlorophenyl	2-phenylethyl	4-piperidinylmethyl	587
E-0079	3-chlorophenyl	2-(3-chlorophenyl)ethyl	2-(4-pyridyl)ethyl	557
E-0080	3-chlorophenyl	2-(3-chlorophenyl)ethyl	2-(3-pyridyl)ethyl	557
E-0081	3-chlorophenyl	2-(3-chlorophenyl)ethyl	4-piperidinylmethyl	622
E-0082	3-chlorophenyl	2-(4-chlorophenyl)ethyl	2-(4-pyridyl)ethyl	557
E-0083	3-chlorophenyl	2-(4-chlorophenyl)ethyl	2-(3-pyridyl)ethyl	557
E-0084	3-chlorophenyl	2-(4-chlorophenyl)ethyl	4-piperidinylmethyl	622
E-0085	3-chlorophenyl	benzyl	2-(4-pyridyl)ethyl	508
E-0086	3-chlorophenyl	benzyl	2-(3-pyridyl)ethyl	508
E-0087	3-chlorophenyl	benzyl	4-piperidinylmethyl	573
E-0088	3-chlorophenyl	2-phenylethyl	2-(4-pyridyl)ethyl	522
E-0089	3-chlorophenyl	2-phenylethyl	2-(3-pyridyl)ethyl	522
E-0090	3-chlorophenyl	2-phenylethyl	4-piperidinylmethyl	587
E-0091	3-chlorophenyl	2-(3-chlorophenyl)ethyl	2-(4-pyridyl)ethyl	557
E-0092	3-chlorophenyl	2-(3-chlorophenyl)ethyl	2-(3-pyridyl)ethyl	557
E-0093	3-chlorophenyl	2-(3-chlorophenyl)ethyl	4-piperidinylmethyl	622
E-0094	3-chlorophenyl	2-(4-chlorophenyl)ethyl	2-(4-pyridyl)ethyl	557
E-0095	3-chlorophenyl	2-(4-chlorophenyl)ethyl	2-(3-pyridyl)ethyl	557
E-0096	3-chlorophenyl	2-(4-chlorophenyl)ethyl	4-piperidinylmethyl	622
E-0097	4-methoxyphenyl	benzyl	2-(4-pyridyl)ethyl	504
E-0098	4-methoxyphenyl	benzyl	2-(3-pyridyl)ethyl	504
E-0099	4-methoxyphenyl	benzyl	4-piperidinylmethyl	569
E-0100	4-methoxyphenyl	2-phenylethyl	2-(4-pyridyl)ethyl	518
E-0101	4-methoxyphenyl	2-phenylethyl	2-(3-pyridyl)ethyl	518
E-0102	4-methoxyphenyl	2-phenylethyl	4-piperidinylmethyl	583
E-0103	4-methoxyphenyl	2-(3-chlorophenyl)ethyl	2-(4-pyridyl)ethyl	552
E-0104	4-methoxyphenyl	2-(3-chlorophenyl)ethyl	2-(3-pyridyl)ethyl	552
E-0105	4-methoxyphenyl	2-(3-chlorophenyl)ethyl	4-piperidinylmethyl	617
E-0106	4-methoxyphenyl	2-(4-chlorophenyl)ethyl	2-(4-pyridyl)ethyl	552
E-0107	4-methoxyphenyl	2-(4-chlorophenyl)ethyl	2-(3-pyridyl)ethyl	552
E-0108	4-methoxyphenyl	2-(4-chlorophenyl)ethyl	4-piperidinylmethyl	617
E-0109	4-biphenyl	benzyl	2-(4-pyridyl)ethyl	550
E-0110	4-biphenyl	benzyl	2-(3-pyridyl)ethyl	550
E-0111	4-biphenyl	benzyl	4-piperidinylmethyl	615
E-0112	4-biphenyl	2-phenylethyl	2-(4-pyridyl)ethyl	564
E-0113	4-biphenyl	2-phenylethyl	2-(3-pyridyl)ethyl	564
E-0114	4-biphenyl	2-phenylethyl	4-piperidinylmethyl	629
E-0115	4-biphenyl	2-(3-chlorophenyl)ethyl	2-(4-pyridyl)ethyl	599
E-0116	4-biphenyl	2-(3-chlorophenyl)ethyl	2-(3-pyridyl)ethyl	599
E-0117	4-biphenyl	2-(3-chlorophenyl)ethyl	4-piperidinylmethyl	663
E-0118	4-biphenyl	2-(4-chlorophenyl)ethyl	2-(4-pyridyl)ethyl	599
E-0119	4-biphenyl	2-(4-chlorophenyl)ethyl	2-(3-pyridyl)ethyl	599
E-0120	4-biphenyl	2-(4-chlorophenyl)ethyl	4-piperidinylmethyl	663
E-0121	methyl	benzyl	4-piperidinylmethyl	477
E-0122	methyl	2-phenylethyl	4-piperidinylmethyl	491
E-0123	methyl	2-(3-chlorophenyl)ethyl	4-piperidinylmethyl	525
E-0124	methyl	2-(4-chlorophenyl)ethyl	4-piperidinylmethyl	525
E-0125	methyl	2-(3-pyridyl)ethyl	4-piperidinylmethyl	528

TABLE 5-continued

Structures of Pyrazinones Prepared by General Robotic and Experimental Procedures

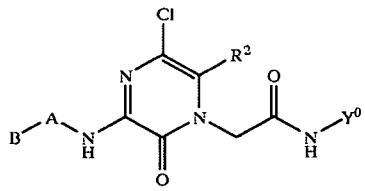


General Structure

Ex. No.	R^2	B—A—	Y^0	MW (m/z + 1)
E-0126	methyl	2-(4-pyridyl)ethyl	4-piperidinylmethyl	528
E-0127	methyl	2-(4-morpholinyl)ethyl	4-piperidinylmethyl	536
E-0128	methyl	2-(1-methylimidazol-4-yl)ethyl	4-piperidinylmethyl	531
E-0129	methyl	2-(1-methylimidazol-5-yl)ethyl	4-piperidinylmethyl	531
E-0130	methyl	4-pyridylmethyl	4-piperidinylmethyl	514
E-0131	phenyl	benzyl	4-piperidinylmethyl	539
E-0132	phenyl	2-phenylethyl	4-piperidinylmethyl	553
E-0133	phenyl	2-(3-chlorophenyl)ethyl	4-piperidinylmethyl	587
E-0134	phenyl	2-(4-chlorophenyl)ethyl	4-piperidinylmethyl	587
E-0135	phenyl	2-(3-pyridyl)ethyl	4-piperidinylmethyl	590
E-0136	phenyl	2-(4-pyridyl)ethyl	4-piperidinylmethyl	590
E-0137	phenyl	2-(4-morpholinyl)ethyl	4-piperidinylmethyl	598
E-0138	phenyl	2-(1-methylimidazol-4-yl)ethyl	4-piperidinylmethyl	593
E-0139	phenyl	2-(1-methylimidazol-5-yl)ethyl	4-piperidinylmethyl	593
E-0140	phenyl	4-pyridylmethyl	4-piperidinylmethyl	576
E-0141	4-chlorophenyl	benzyl	4-piperidinylmethyl	573
E-0142	4-chlorophenyl	2-phenylethyl	4-piperidinylmethyl	587
E-0143	4-chlorophenyl	2-(3-chlorophenyl)ethyl	4-piperidinylmethyl	622
E-0144	4-chlorophenyl	2-(4-chlorophenyl)ethyl	4-piperidinylmethyl	622
E-0145	4-chlorophenyl	2-(3-pyridyl)ethyl	4-piperidinylmethyl	625
E-0146	4-chlorophenyl	2-(4-pyridyl)ethyl	4-piperidinylmethyl	625
E-0147	4-chlorophenyl	2-(4-morpholinyl)ethyl	4-piperidinylmethyl	633
E-0148	4-chlorophenyl	2-(1-methylimidazol-4-yl)ethyl	4-piperidinylmethyl	628
E-0149	4-chlorophenyl	2-(1-methylimidazol-5-yl)ethyl	4-piperidinylmethyl	628
E-0150	4-chlorophenyl	4-pyridylmethyl	4-piperidinylmethyl	611
E-0151	4-chlorophenyl	benzyl	4-piperidinylmethyl	573
E-0152	4-chlorophenyl	2-phenylethyl	4-piperidinylmethyl	587
E-0153	4-chlorophenyl	2-(3-chlorophenyl)ethyl	4-piperidinylmethyl	622
E-0154	4-chlorophenyl	2-(4-chlorophenyl)ethyl	4-piperidinylmethyl	622
E-0155	4-chlorophenyl	2-(3-pyridyl)ethyl	4-piperidinylmethyl	625
E-0156	4-chlorophenyl	2-(4-pyridyl)ethyl	4-piperidinylmethyl	625
E-0157	4-chlorophenyl	2-(4-morpholinyl)ethyl	4-piperidinylmethyl	633
E-0158	4-chlorophenyl	2-(1-methylimidazol-4-yl)ethyl	4-piperidinylmethyl	628
E-0159	4-chlorophenyl	2-(1-methylimidazol-5-yl)ethyl	4-piperidinylmethyl	628
E-0160	4-chlorophenyl	4-pyridylmethyl	4-piperidinylmethyl	611
E-0161	4-methoxyphenyl	benzyl	4-piperidinylmethyl	569
E-0162	4-methoxyphenyl	2-phenylethyl	4-piperidinylmethyl	583
E-0163	4-methoxyphenyl	2-(3-chlorophenyl)ethyl	4-piperidinylmethyl	617
E-0164	4-methoxyphenyl	2-(4-chlorophenyl)ethyl	4-piperidinylmethyl	617
E-0165	4-methoxyphenyl	2-(3-pyridyl)ethyl	4-piperidinylmethyl	620
E-0166	4-methoxyphenyl	2-(4-pyridyl)ethyl	4-piperidinylmethyl	620
E-0167	4-methoxyphenyl	2-(4-morpholinyl)ethyl	4-piperidinylmethyl	628
E-0168	4-methoxyphenyl	2-(1-methylimidazol-4-yl)ethyl	4-piperidinylmethyl	623
E-0169	4-methoxyphenyl	2-(1-methylimidazol-5-yl)ethyl	4-piperidinylmethyl	623
E-0170	4-methoxyphenyl	4-pyridylmethyl	4-piperidinylmethyl	606
E-0171	3,4-methylene-dioxyphenyl	benzyl	4-piperidinylmethyl	583
E-0172	3,4-methylene-dioxyphenyl	2-phenylethyl	4-piperidinylmethyl	597
E-0173	3,4-methylene-dioxyphenyl	2-(3-chlorophenyl)ethyl	4-piperidinylmethyl	631
E-0174	3,4-methylene-dioxyphenyl	2-(4-chlorophenyl)ethyl	4-piperidinylmethyl	631

TABLE 5-continued

Structures of Pyrazinones Prepared by General Robotic and Experimental Procedures

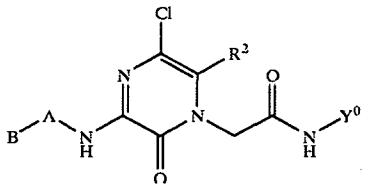


General Structure

Ex. No.	R^2	B—A—	Y^0	MW (m/z + 1)
E-0175	3,4-methylene-dioxyphenyl	2-(3-pyridyl)ethyl	4-piperidinylmethyl	634
E-0176	3,4-methylene dioxyphenyl	2-(4-pyridyl)ethyl	4-piperidinylmethyl	634
E-0177	3,4-methylene-dioxyphenyl	2-(4-morpholinyl)ethyl	4-piperidinylmethyl	642
E-0178	3,4-methylene-dioxyphenyl	2-(1-methylimidazol-4-yl)ethyl	4-piperidinylmethyl	637
E-0179	3,4-methylene-dioxyphenyl	2-(1-methylimidazol-5-yl)ethyl	4-piperidinylmethyl	637
E-0180	3,4-methylene-dioxyphenyl	4-pyridylmethyl	4-piperidinylmethyl	620
E-0181	4-biphenyl	benzyl	4-piperidinylmethyl	615
E-0182	4-biphenyl	2-phenylethyl	4-piperidinylmethyl	629
E-0183	4-biphenyl	2-(3-chlorophenyl)ethyl	4-piperidinylmethyl	663
E-0184	4-biphenyl	2-(4-chlorophenyl)ethyl	4-piperidinylmethyl	663
E-0185	4-biphenyl	2-(3-pyridyl)ethyl	4-piperidinylmethyl	666
E-0186	4-biphenyl	2-(4-pyridyl)ethyl	4-piperidinylmethyl	666
E-0187	4-biphenyl	2-(4-morpholinyl)ethyl	4-piperidinylmethyl	675
E-0188	4-biphenyl	2-(1-methylimidazol-4-yl)ethyl	4-piperidinylmethyl	669
E-0189	4-biphenyl	2-(1-methylimidazol-5-yl)ethyl	4-piperidinylmethyl	669
E-0190	4-biphenyl	4-pyridylmethyl	4-piperidinylmethyl	652
E-0191	benzyl	benzyl	4-piperidinylmethyl	553
E-0192	benzyl	2-phenylethyl	4-piperidinylmethyl	567
E-0193	benzyl	2-(3-chlorophenyl)ethyl	4-piperidinylmethyl	601
E-0194	benzyl	2-(4-chlorophenyl)ethyl	4-piperidinylmethyl	601
E-0195	benzyl	2-(3-pyridyl)ethyl	4-piperidinylmethyl	604
E-0196	benzyl	2-(4-pyridyl)ethyl	4-piperidinylmethyl	604
E-0197	benzyl	2-(4-morpholinyl)ethyl	4-piperidinylmethyl	612
E-0198	benzyl	2-(1-methylimidazol-4-yl)ethyl	4-piperidinylmethyl	607
E-0199	benzyl	2-(1-methylimidazol-5-yl)ethyl	4-piperidinylmethyl	607
E-0200	benzyl	4-pyridylmethyl	4-piperidinylmethyl	590
E-0201	2-phenylethyl	benzyl	4-piperidinylmethyl	567
E-0202	2-phenylethyl	2-phenylethyl	4-piperidinylmethyl	581
E-0203	2-phenylethyl	2-(3-chlorophenyl)ethyl	4-piperidinylmethyl	615
E-0204	2-phenylethyl	2-(4-chlorophenyl)ethyl	4-piperidinylmethyl	615
E-0205	2-phenylethyl	2-(3-pyridyl)ethyl	4-piperidinylmethyl	618
E-0206	2-phenylethyl	2-(4-pyridyl)ethyl	4-piperidinylmethyl	618
E-0207	2-phenylethyl	2-(4-morpholinyl)ethyl	4-piperidinylmethyl	626
E-0208	2-phenylethyl	2-(1-methylimidazol-4-yl)ethyl	4-piperidinylmethyl	621
E-0209	2-phenylethyl	2-(1-methylimidazol-5-yl)ethyl	4-piperidinylmethyl	621
E-0210	2-phenylethyl	4-pyridylmethyl	4-piperidinylmethyl	604

TABLE 6

Structures of Pyrazinones Prepared by General Robotic and Experiental Procedures

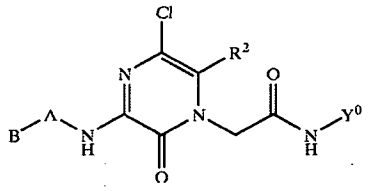


General Structure

Ex. No.	R^2	B—A—	Y^0	MW (m/z + 1)
1471-1	methyl	benzyl	4-amidinobenzyl	439
1471-2	methyl	2-(4-chlorophenyl)ethyl	4-amidinobenzyl	488
1471-3	methyl	4-pyridylmethyl	4-amidinobenzyl	440
1471-4	methyl	2-(4-morpholinyl)ethyl	4-amidinobenzyl	462
1471-5	methyl	2-(4-pyridyl)ethyl	4-amidinobenzyl	454
1471-6	methyl	2-(3-chlorophenyl)ethyl	4-amidinobenzyl	488
1471-7	methyl	2-phenylethyl	4-amidinobenzyl	453
1471-8	methyl	2-(3-pyridyl)ethyl	4-amidinobenzyl	454
1471-9	phenyl	benzyl	4-amidinobenzyl	501
1471-10	phenyl	2-(4-chlorophenyl)ethyl	4-amidinobenzyl	550
1471-11	phenyl	4-pyridylmethyl	4-amidinobenzyl	502
1471-12	phenyl	2-(4-morpholinyl)ethyl	4-amidinobenzyl	525
1471-13	phenyl	2-(4-pyridyl)ethyl	4-amidinobenzyl	517
1471-14	phenyl	2-(3-chlorophenyl)ethyl	4-amidinobenzyl	550
1471-15	phenyl	2-phenylethyl	4-amidinobenzyl	516
1471-16	phenyl	2-(3-pyridyl)ethyl	4-amidinobenzyl	517
1471-17	4-Cl-phenyl	benzyl	4-amidinobenzyl	536
1471-18	4-Cl-phenyl	2-(4-chlorophenyl)ethyl	4-amidinobenzyl	584
1471-19	4-Cl-phenyl	4-pyridylmethyl	4-amidinobenzyl	537
1471-20	4-Cl-phenyl	2-(4-morpholinyl)ethyl	4-amidinobenzyl	559
1471-21	4-Cl-phenyl	2-(4-pyridyl)ethyl	4-amidinobenzyl	551
1471-22	4-Cl-phenyl	2-(3-chlorophenyl)ethyl	4-amidinobenzyl	584
1471-23	4-Cl-phenyl	2-phenylethyl	4-amidinobenzyl	550
1471-24	4-Cl-phenyl	2-(3-pyridyl)ethyl	4-amidinobenzyl	551
1471-25	3-Cl-phenyl	benzyl	4-amidinobenzyl	536
1471-26	3-Cl-phenyl	2-(4-chlorophenyl)ethyl	4-amidinobenzyl	584
1471-27	3-Cl-phenyl	4-pyridylmethyl	4-amidinobenzyl	537
1471-28	3-Cl-phenyl	2-(4-morpholinyl)ethyl	4-amidinobenzyl	559
1471-29	3-Cl-phenyl	2-(4-pyridyl)ethyl	4-amidinobenzyl	551
1471-30	3-Cl-phenyl	2-(3-chlorophenyl)ethyl	4-amidinobenzyl	584
1471-31	3-Cl-phenyl	2-phenylethyl	4-amidinobenzyl	550
1471-32	3-Cl-phenyl	2-(3-pyridyl)ethyl	4-amidinobenzyl	551
1471-33	4-methoxyphenyl	benzyl	4-amidinobenzyl	532
1471-34	4-methoxyphenyl	2-(4-chlorophenyl)ethyl	4-amidinobenzyl	580
1471-35	4-methoxyphenyl	4-pyridylmethyl	4-amidinobenzyl	533
1471-36	4-methoxyphenyl	2-(4-morpholinyl)ethyl	4-amidinobenzyl	555
1471-37	4-methoxyphenyl	2-(4-pyridyl)ethyl	4-amidinobenzyl	547
1471-38	4-methoxyphenyl	2-(3-chlorophenyl)ethyl	4-amidinobenzyl	580
1471-39	4-methoxyphenyl	2-phenylethyl	4-amidinobenzyl	546
1471-40	4-methoxyphenyl	2-(3-pyridyl)ethyl	4-amidinobenzyl	547
1471-41	3,4-methylene-dioxyphenyl	benzyl	4-amidinobenzyl	545
1471-42	3,4-methylene-dioxyphenyl	2-(4-chlorophenyl)ethyl	4-amidinobenzyl	594
1471-43	3,4-methylene-dioxyphenyl	4-pyridylmethyl	4-amidinobenzyl	546
1471-44	3,4-methylene-dioxyphenyl	2-(4-morpholinyl)ethyl	4-amidinobenzyl	569
1471-45	3,4-methylene-dioxyphenyl	2-(4-pyridyl)ethyl	4-amidinobenzyl	561
1471-46	3,4-methylene-dioxyphenyl	2-(3-chlorophenyl)ethyl	4-amidinobenzyl	594
1471-47	3,4-methylene-dioxyphenyl	2-phenylethyl	4-amidinobenzyl	560
1471-48	3,4-methylene-dioxyphenyl	2-(3-pyridyl)ethyl	4-amidinobenzyl	561
1471-57	ethyl	benzyl	4-amidinobenzyl	553
1471-58	ethyl	2-(4-chlorophenyl)ethyl	4-amidinobenzyl	502
1471-59	ethyl	4-pyridylmethyl	4-amidinobenzyl	454
1471-60	ethyl	2-(4-morpholinyl)ethyl	4-amidinobenzyl	476
1471-61	ethyl	2-(4-pyridyl)ethyl	4-amidinobenzyl	468
1471-62	ethyl	2-(3-chlorophenyl)ethyl	4-amidinobenzyl	502

TABLE 6-continued

Structures of Pyrazinones Prepared by General Robotic and Experiental Procedures

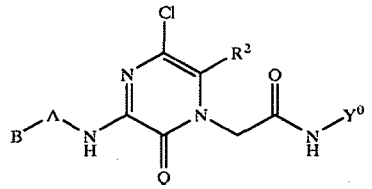


General Structure

Ex. No.	R^2	B—A—	Y^0	MW (m/z + 1)
1471-63	ethyl	2-phenylethyl	4-amidinobenzyl	467
1471-64	ethyl	2-(3-pyridyl)ethyl	4-amidinobenzyl	468
1471-67	4-biphenyl	4-pyridylmethyl	4-amidinobenzyl	579
1471-70	4-biphenyl	2-(3-chlorophenyl)ethyl	4-amidinobenzyl	626
1471-71	4-biphenyl	2-phenylethyl	4-amidinobenzyl	592
1471-72	4-biphenyl	2-(3-pyridyl)ethyl	4-amidinobenzyl	593
1507-01	phenyl	3-trifluoromethylbenzyl	4-amidinobenzyl	569
1507-02	phenyl	1-indanyl	4-amidinobenzyl	528
1507-03	phenyl	2-Cl-benzyl	4-amidinobenzyl	536
1507-04	phenyl	4-trifluoromethoxy benzyl	4-amidinobenzyl	585
1507-05	phenyl	3-(1-imidazolyl)propyl	4-amidinobenzyl	520
1507-06	phenyl	2-(4-bromophenyl)ethyl	4-amidinobenzyl	594
1507-07	phenyl	1,2-(diphenyl)ethyl	4-amidinobenzyl	592
1507-08	phenyl	2-indanyl	4-amidinobenzyl	528
1507-09	phenyl	2,2-(diphenyl)ethyl	4-amidinobenzyl	592
1507-10	phenyl	3,3-(diphenyl)propyl	4-amidinobenzyl	606
1507-11	phenyl	2-(4-methoxyphenyl)ethyl	4-amidinobenzyl	546
1507-12	phenyl	2-(3-methoxyphenyl)ethyl	4-amidinobenzyl	546
1507-13	phenyl	4-methoxybenzyl	4-amidinobenzyl	532
1507-15	phenyl	2-trifluoromethylbenzyl	4-amidinobenzyl	569
1507-16	phenyl	1,2,3,4-tetrahydro-1-naphthyl	4-amidinobenzyl	542
1507-17	phenyl	2-(cyclohex-1-enyl)ethyl	4-amidinobenzyl	520
1507-18	phenyl	2-(2-thienyl)ethyl	4-amidinobenzyl	522
1507-19	phenyl	3-[1-(pyrrolidinyl-2-one)]propyl	4-amidinobenzyl	537
1507-20	phenyl	1-carboethoxy-piperidin-4-yl	4-amidinobenzyl	567
1507-21	phenyl	cyclobutyl	4-amidinobenzyl	465
1507-22	phenyl	2,4-dichlorobenzyl	4-amidinobenzyl	570
1507-23	phenyl	2-(3-chlorophenyl)ethyl	4-amidinobenzyl	516
1507-24	phenyl	2-pyridylmethyl	4-amidinobenzyl	502
1507-25	phenyl	cyclopentyl	4-amidinobenzyl	479
1507-26	phenyl	2,4-difluorobenzyl	4-amidinobenzyl	537
1507-28	phenyl	1-naphthylmethyl	4-amidinobenzyl	552
1507-29	phenyl	cycloheptyl	4-amidinobenzyl	508
1507-30	phenyl	4-bromobenzyl	4-amidinobenzyl	580
1507-31	phenyl	cyclopropyl	4-amidinobenzyl	451
1507-32	phenyl	2-methylpropyl	4-amidinobenzyl	467
1507-33	phenyl	2-methoxyethyl	4-amidinobenzyl	469
1507-34	phenyl	(S)-α-methylbenzyl	4-amidinobenzyl	516
1507-35	phenyl	1,1-diphenylmethyl	4-amidinobenzyl	578
1507-36	phenyl	3-(2,3,4,5-tetrahydro-1,1-dioxothiophenyl)	4-amidinobenzyl	530
1507-38	phenyl	3-chlorobenzyl	4-amidinobenzyl	536
1507-40	phenyl	3,5-bis-trifluoromethylbenzyl	4-amidinobenzyl	637
1507-41	phenyl	2,2,2-trifluoromethyl	4-amidinobenzyl	493
1507-42	phenyl	3-fluorobenzyl	4-amidinobenzyl	519
1507-43	phenyl	4-phenylbutyl	4-amidinobenzyl	544
1507-44	phenyl	2-(3,4-dichloro-phenyl)ethyl	4-amidinobenzyl	584
1507-45	phenyl	2-(4-methylphenyl)ethyl	4-amidinobenzyl	530
1507-46	phenyl	4-chlorobenzyl	4-amidinobenzyl	536
1507-47	phenyl	3-(dimethylamino)propyl	4-amidinobenzyl	497
1507-48	phenyl	3,4-difluorobenzyl	4-amidinobenzyl	537
1512-01	phenyl	2H,3H-benzo[e]1,4-dioxan-2-ylmethyl	4-amidinobenzyl	560
1512-02	phenyl	2,3-dimethoxybenzyl	4-amidinobenzyl	562
1512-04	phenyl	3,4-methylenedioxyphenyl	4-amidinobenzyl	545
1512-05	phenyl	2-(3,4-dimethoxy-phenyl)ethyl	4-amidinobenzyl	576
1512-06	phenyl	3-(phenyl)propyl	4-amidinobenzyl	530

TABLE 6-continued

Structures of Pyrazinones Prepared by General Robotic and Experiental Procedures

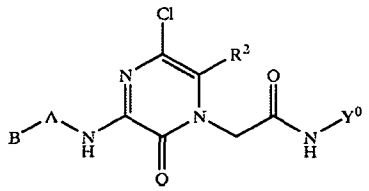


General Structure

Ex. No.	R^2	B—A—	Y^0	MW (m/z + 1)
1512-07	phenyl	2-(3-methoxy)propyl	4-amidinobenzyl	483
1512-11	phenyl	2-ethoxybenzyl	4-amidinobenzyl	546
1512-12	phenyl	3-heptyl	4-amidinobenzyl	510
1512-14	phenyl	butyl	4-amidinobenzyl	467
1512-15	phenyl	2-(dimethylamino)ethyl	4-amidinobenzyl	482
1512-16	phenyl	cycloheptyl	4-amidinobenzyl	508
1512-17	phenyl	4-t-butylcyclohexyl	4-amidinobenzyl	550
1512-19	phenyl	3-(2,3,4,5-tetrahydro-1,1-dioxothiophenyl)	4-amidinobenzyl	530
1512-20	phenyl	phenylamino	4-amidinobenzyl	487
1512-23	phenyl	2,3-dimethylcyclohexyl	4-amidinobenzyl	522
1512-26	phenyl	2-fluoro-4-trifluoro-methylbenzyl	4-amidinobenzyl	587
1512-27	phenyl	2-fluoro-5-trifluoro-methylbenzyl	4-amidinobenzyl	587
1512-29	phenyl	3-fluoro-5-trifluoro-methylbenzyl	4-amidinobenzyl	587
1512-31	phenyl	2-chloro-6-methylbenzyl	4-amidinobenzyl	550
1512-32	phenyl	3,4,5-trifluorobenzyl	4-amidinobenzyl	555
1512-35	phenyl	2,5-dichlorobenzyl	4-amidinobenzyl	570
1512-36	phenyl	2,5-difluorobenzyl	4-amidinobenzyl	537
1512-39	phenyl	3,5-difluorobenzyl	4-amidinobenzyl	537
1512-40	phenyl	3-trifluoromethoxybenzyl	4-amidinobenzyl	585
1512-41	phenyl	2-(3-trifluoromethyl-phenyl)ethyl	4-amidinobenzyl	584
1512-42	phenyl	2-trifluoromethoxybenzyl	4-amidinobenzyl	585
1512-43	phenyl	2,6-difluorobenzyl	4-amidinobenzyl	537
1512-44	phenyl	2-fluoro-6-trifluoro-methylbenzyl	4-amidinobenzyl	587
1512-45	phenyl	2,4-dichloro-6-methylbenzyl	4-amidinobenzyl	584
1512-46	phenyl	2-(1-methyl-pyrrolidin-2-yl)-ethyl	4-amidinobenzyl	523
1512-47	phenyl	2-(pyrid-2-yl)ethyl	4-amidinobenzyl	517
1515-01	3-trifluoromethyl-phenyl	benzyl	4-amidinobenzyl	569
1515-02	2-methoxyphenyl	benzyl	4-amidinobenzyl	532
1515-03	1-(2-bromo-thienyl)	benzyl	4-amidinobenzyl	586
1515-04	2-chlorophenyl	benzyl	4-amidinobenzyl	536
1515-05	3-methoxyphenyl	benzyl	4-amidinobenzyl	532
1515-06	2-thienyl	benzyl	4-amidinobenzyl	508
1515-07	4-fluorophenyl	benzyl	4-amidinobenzyl	519
1515-08	4-trifluoromethyl-phenyl	benzyl	4-amidinobenzyl	569
1515-09	3-fluorophenyl	benzyl	4-amidinobenzyl	519
1515-10	3-bromophenyl	benzyl	4-amidinobenzyl	580
1515-11	2-fluorophenyl	benzyl	4-amidinobenzyl	519
1515-12	2-trifluoromethyl-phenyl	benzyl	4-amidinobenzyl	569
1515-13	3-trifluoromethyl-phenyl	cyclobutyl	4-amidinobenzyl	533
1515-14	2-methoxyphenyl	cyclobutyl	4-amidinobenzyl	495
1515-15	1-(2-bromothienyl)	cyclobutyl	4-amidinobenzyl	550
1515-16	2-chlorophenyl	cyclobutyl	4-amidinobenzyl	500
1515-17	3-methoxyphenyl	cyclobutyl	4-amidinobenzyl	495
1515-18	2-thienyl	cyclobutyl	4-amidinobenzyl	471
1515-19	4-fluorophenyl	cyclobutyl	4-amidinobenzyl	483
1515-20	4-trifluoro-methylphenyl	cyclobutyl	4-amidinobenzyl	533
1515-22	3-bromophenyl	cyclobutyl	4-amidinobenzyl	544
1515-23	2-fluorophenyl	cyclobutyl	4-amidinobenzyl	483
1515-24	2-trifluoro-methylphenyl	cyclobutyl	4-amidinobenzyl	533

TABLE 6-continued

Structures of Pyrazinones Prepared by General Robotic and Experiental Procedures

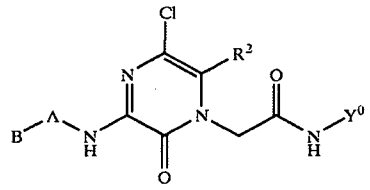


General Structure

Ex. No.	R^2	B—A—	Y^0	MW (m/z + 1)
1515-25	3-trifluoro-methylphenyl	2-phenylethyl	4-amidinobenzyl	584
1515-26	2-methoxyphenyl	2-phenylethyl	4-amidinobenzyl	546
1515-27	3-bromo-2-thienyl)	2-phenylethyl	4-amidinobenzyl	600
1515-28	2-chlorophenyl	2-phenylethyl	4-amidinobenzyl	550
1515-29	3-methoxyphenyl	2-phenylethyl	4-amidinobenzyl	546
1515-30	2-thienyl	2-phenylethyl	4-amidinobenzyl	522
1515-31	4-fluorophenyl	2-phenylethyl	4-amidinobenzyl	534
1515-32	4-trifluoro-methylphenyl	2-phenylethyl	4-amidinobenzyl	584
1515-33	3-fluorophenyl	2-phenylethyl	4-amidinobenzyl	534
1515-34	3-bromophenyl	2-phenylethyl	4-amidinobenzyl	594
1515-35	2-fluorophenyl	2-phenylethyl	4-amidinobenzyl	534
1515-36	2-trifluoro-methylphenyl	2-phenylethyl	4-amidinobenzyl	584
1515-37	3-trifluoro-methylphenyl	2-(3,4-dichloro-phenyl)ethyl	4-amidinobenzyl	618
1515-38	2-methoxyphenyl	2-(3,4-dichloro-phenyl)ethyl	4-amidinobenzyl	580
1515-39	1-(2-bromothienyl)	2-(3,4-dichlorophenyl)ethyl	4-amidinobenzyl	635
1515-40	2-chlorophenyl	2-(3,4-dichlorophenyl)ethyl	4-amidinobenzyl	584
1515-41	3-methoxyphenyl	2-(3,4-dichlorophenyl)ethyl	4-amidinobenzyl	580
1515-42	2-thienyl	2-(3,4-dichlorophenyl)ethyl	4-amidinobenzyl	556
1515-43	4-fluorophenyl	2-(3,4-dichlorophenyl)ethyl	4-amidinobenzyl	568
1515-44	4-trifluoro-methylphenyl	2-(3,4-dichlorophenyl)ethyl	4-amidinobenzyl	618
1515-45	3-fluorophenyl	2-(3,4-dichlorophenyl)ethyl	4-amidinobenzyl	568
1515-46	3-bromophenyl	2-(3,4-dichlorophenyl)ethyl	4-amidinobenzyl	629
1515-47	2-fluorophenyl	2-(3,4-dichlorophenyl)ethyl	4-amidinobenzyl	568
1515-48	2-trifluoromethylphenyl	2-(3,4-dichlorophenyl)ethyl	4-amidinobenzyl	618
1522-02	phenyl	2-hydroxyethyl	4-amidinobenzyl	455
1522-05	phenyl	4-hydroxybutyl	4-amidinobenzyl	484
1522-06	phenyl	(R)-2-butyl	4-amidinobenzyl	468
1522-07	phenyl	6-hydroxyhexyl	4-amidinobenzyl	512
1522-08	phenyl	2-(pyrrolidin-1-yl)-ethyl	4-amidinobenzyl	509
1522-09	phenyl	(S)-2-butyl	4-amidinobenzyl	468
1522-11	phenyl	3-pentyl	4-amidinobenzyl	482
1522-12	phenyl	(S)-2-methylbutyl	4-amidinobenzyl	482
1522-13	phenyl	2-methylbutyl	4-amidinobenzyl	482
1522-14	phenyl	3-methylbutyl	4-amidinobenzyl	482
1522-15	phenyl	2-(3-methyl)butyl	4-amidinobenzyl	482
1522-17	phenyl	2-(4-methyl)pentyl	4-amidinobenzyl	496
1522-18	phenyl	3,3-dimethylbutyl	4-amidinobenzyl	496
1522-19	phenyl	tricyclo[5.3.1.1<3,9>]dodec-3-yl	4-amidinobenzyl	546
1522-20	phenyl	tricyclo[5.3.1.1<3,9>]dodec-3-ylmethyl	4-amidinobenzyl	560
1522-21	phenyl	2-propynyl	4-amidinobenzyl	449
1522-23	phenyl	2-(dimethylamino)-propyl	4-amidinobenzyl	497
1522-27	phenyl	N,N-butano	4-amidinobenzyl	465
1522-28	phenyl	N,N-propano	4-amidinobenzyl	451
1522-31	phenyl	benzylthio	4-amidinobenzyl	519
1522-33	phenyl	2-methoxyethyl	4-amidinobenzyl	469
1522-34	phenyl	2-methylpropyl	4-amidinobenzyl	468
1522-35	phenyl	1,2-diethyl-pyrazolidin-4-yl	4-amidinobenzyl	538
1522-36	phenyl	cycloheptyl	4-amidinobenzyl	508
1522-37	phenyl	N-(3-chloro-5-trifluoromethyl-pyrid-2-yl)-2-aminoethyl	4-amidinobenzyl	634
1522-38	phenyl	N-(3-trifluoromethyl-pyrid-2-yl)-2-aminoethyl	4-amidinobenzyl	600

TABLE 6-continued

Structures of Pyrazinones Prepared by General Robotic and Experiental Procedures

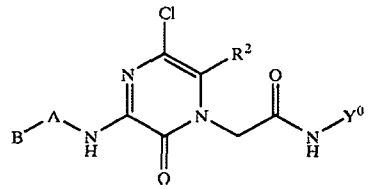


General Structure

Ex. No.	R^2	B—A—	Y^0	MW (m/z + 1)
1522-40	phenyl	6-cyanohexyl	4-amidinobenzyl	507
1522-41	phenyl	3-hydroxypropyl	4-amidinobenzyl	469
1522-42	phenyl	4-(pyrrolidin-1-yl)-butyl	4-amidinobenzyl	537
1522-43	phenyl	(S)-1-cyclohexylethyl	4-amidinobenzyl	522
1522-44	phenyl	2-(2R)-bicyclo-[2.2.1]heptyl	4-amidinobenzyl	506
1522-46	phenyl	3-(2,3,4,5-tetrahydro-1,1-dioxothiophenyl)	4-amidinobenzyl	530
1522-47	phenyl	4-t-butylcyclohexyl	4-amidinobenzyl	550
1526-01	3-aminophenyl	cyclopropyl	4-amidinobenzyl	466
1526-03	3-aminophenyl	cyclopentyl	4-amidinobenzyl	495
1526-04	3-aminophenyl	2,2,2-trifluoroethyl	4-amidinobenzyl	508
1526-05	3-aminophenyl	2-(3-methoxypropyl)	4-amidinobenzyl	499
1526-06	3-aminophenyl	2-(2-methylbutyl)	4-amidinobenzyl	497
1526-07	3-aminophenyl	t-butyl	4-amidinobenzyl	483
1526-09	3-aminophenyl	(S)-2-butyl	4-amidinobenzyl	483
1526-11	3-aminophenyl	3-pentyl	4-amidinobenzyl	497
1526-12	3-aminophenyl	ethyl	4-amidinobenzyl	454
1526-13	3-aminophenyl	propyl	4-amidinobenzyl	469
1526-14	3-aminophenyl	2-butyl	4-amidinobenzyl	483
1526-15	3-aminophenyl	2-(3-methylbutyl)	4-amidinobenzyl	497
1526-16	3-aminophenyl	(R)-2-butyl	4-amidinobenzyl	483
1526-17	3-aminophenyl	2-(4-methylpentyl)	4-amidinobenzyl	511
1526-19	3-aminophenyl	2-propenyl	4-amidinobenzyl	466
1526-21	3-aminophenyl	2-propynyl	4-amidinobenzyl	464
1526-23	3-aminophenyl	cyclobutyl	4-amidinobenzyl	481
1526-24	3-aminophenyl	isopropyl	4-amidinobenzyl	469
1526-25	3-aminophenyl	2-methoxyethyl	4-amidinobenzyl	485
1526-26	3-aminophenyl	2-methylpropyl	4-amidinobenzyl	483
1526-29	3-aminophenyl	(1S)-1-cyclohexylethyl	4-amidinobenzyl	537
1526-30	3-aminophenyl	2-(2R)bicyclo[2.2.1]-heptyl	4-amidinobenzyl	521
1526-33	3-aminophenyl	(2S)-oxalan-2-ylmethyl	4-amidinobenzyl	511
1526-40	3-aminophenyl	butyl	4-amidinobenzyl	483
1526-41	3-aminophenyl	cyclopropylmethyl	4-amidinobenzyl	481
1543-03	3-aminophenyl	2-(pyrrolidin-1-yl)ethyl	4-amidinobenzyl	524
1543-05	3-aminophenyl	methyl	4-amidinobenzyl	440
1543-07	3-aminophenyl	3-(1-imidazolyl)-propyl	4-amidinobenzyl	535
1543-09	3-aminophenyl	2-dimethylaminoethyl	4-amidinobenzyl	498
1543-11	3-aminophenyl	6-amidocarbonylhexyl	4-amidinobenzyl	540
1543-13	3-aminophenyl	3-hydroxypropyl	4-amidinobenzyl	485
1543-15	3-aminophenyl	2-(piperid-1-yl)ethyl	4-amidinobenzyl	538
1543-19	3-aminophenyl	2-dimethylamino-propyl	4-amidinobenzyl	512
1543-21	3-aminophenyl	4-(pyrrolidin-1-yl)butyl	4-amidinobenzyl	552
1543-25	3-aminophenyl	2-(3-diethylamino)-propyl	4-amidinobenzyl	540
1543-27	3-aminophenyl	3-(pyrrolidin-1-yl)propyl	4-amidinobenzyl	538
1543-31	3-aminophenyl	ethyl	4-amidino-2-fluorobenzyl	472
1543-33	3-aminophenyl	cyclopropyl	4-amidino-2-fluorobenzyl	484
1543-34	3-aminophenyl	cyclopentyl	4-amidino-2-fluorobenzyl	513
1543-35	3-aminophenyl	propyl	4-amidino-2-fluorobenzyl	486
1543-36	3-aminophenyl	butyl	4-amidino-2-	501

TABLE 6-continued

Structures of Pyrazinones Prepared by General Robotic and Experiental Procedures

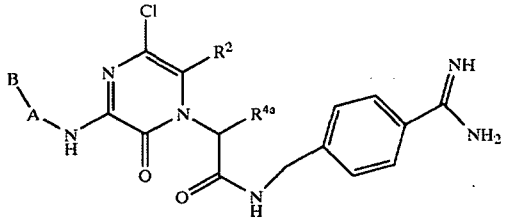


General Structure

Ex. No.	R^2	B—A—	Y^0	MW (m/z + 1)
			fluorobenzyl	
1543-37	3-aminophenyl	2-(pyrrolidin-1-yl)ethyl	4-amidino-2-fluorobenzyl	542
1543-38	3-aminophenyl	2-methylpropyl	4-amidino-2-fluorobenzyl	501
1543-39	3-aminophenyl	cyclobutyl	4-amidino-2-fluorobenzyl	499
1543-40	3-aminophenyl	isopropyl	4-amidino-2-fluorobenzyl	486
1543-41	3-aminophenyl	cyclobutyl	8-aza-1,4-dioxa-spiro[4.5]decyl	474
1543-45	3-aminophenyl	cyclobutyl	3,3-diethyl-pyrrolidin-1-yl	462
1543-46	3-aminophenyl	cyclobutyl	4-(4-amino-phenyl)pyrazinyl	497

TABLE 7

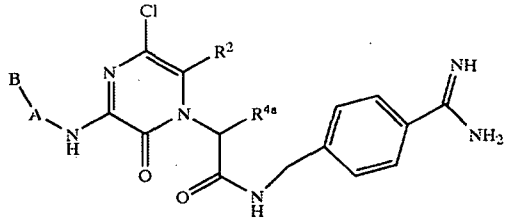
Structures of Pyrazinones Prepared by General Robotic and Experimental Procedures



Ex. No.	R^2	B-A-	R^{4a}	MW (m/z + 1)
1517-01	3-thienyl	benzyl	H	508
1517-03	phenyl	benzyl	(S)-methyl	516
1517-04	phenyl	benzyl	methyl-thiomethyl	562
1517-05	phenyl	benzyl	(R)-methyl	516
1517-06	2,6-dichlorophenyl	benzyl	H	570
1517-07	3-thienyl	cyclobutyl	H	472
1517-08	phenyl	cyclobutyl	benzyl	556
1517-09	phenyl	cyclobutyl	(S)-methyl	480
1517-10	phenyl	cyclobutyl	methyl-thiomethyl	526
1517-11	phenyl	cyclobutyl	(R)-methyl	480
1517-12	2,6-dichlorophenyl	cyclobutyl	H	534
1517-13	3-thienyl	2-phenylethyl	H	522
1517-14	phenyl	2-phenylethyl	benzyl	606
1517-15	phenyl	2-phenylethyl	(S)-methyl	530
1517-16	phenyl	2-phenylethyl	methyl-thiomethyl	576
1517-17	phenyl	2-phenylethyl	(R)-methyl	530
1517-18	2,6-dichlorophenyl	2-phenylethyl	H	584

TABLE 7-continued

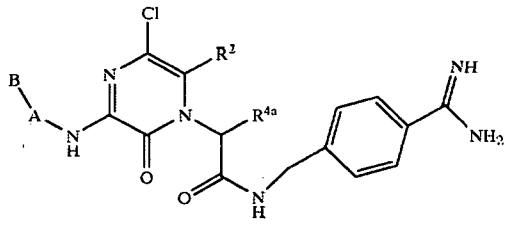
Structures of Pyrazinones Prepared by General Robotic and Experimental Procedures



Ex. No.	R^2	B-A-	R^{4a}	MW (m/z + 1)
1517-19	3-thienyl	2-(3-chlorophenyl)-ethyl	H	556
1517-20	phenyl	2-(3-chlorophenyl)-ethyl	benzyl	640
1517-23	phenyl	2-(3-chlorophenyl)-ethyl	(R)-methyl	564
1517-24	2,6-dichlorophenyl	2-(3-chlorophenyl)-ethyl	H	619
1517-25	phenyl	cyclohexyl	H	494
1517-26	phenyl	4-heptyl	H	510
1517-29	phenyl	2-hexyl	H	496
1517-31	phenyl	N-methyl N-(1-methylethyl)	H	468
1517-33	phenyl	propyl	H	453
1517-35	phenyl	butyl	H	468
1517-36	phenyl	trimethylsilylmethyl	H	498
1517-37	phenyl	2-butyl	H	468
1517-38	phenyl	prop-2-enyl	H	451
1517-39	phenyl	methyl	H	425
1517-40	phenyl	3-methylbutyl	H	482
1517-41	phenyl	3,3-dimethylbutyl	H	496
1517-43	phenyl	cyclopropylmethyl	H	465

TABLE 7-continued

Structures of Pyrazinones Prepared by General Robotic and Experimental Procedures



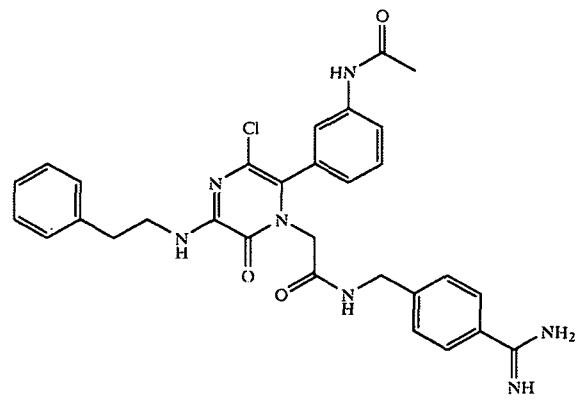
Ex. No.	R^2	B-A-	R^{4a}	MW (m/z + 1)
1517-44	phenyl	isopropyl	H	453
1517-46	phenyl	ethyl	H	439
1517-47	phenyl	3-heptyl	H	524
1517-48	phenyl	pentyl	H	482

Formula (I) compounds of this invention possessing hydroxyl, thiol, and amine functional groups can be converted to a wide variety derivatives. Alternatively, derivatized Formula (I) compounds can be obtained by first derivatizing one or more intermediates in the processes of preparation before further transforming the derivatized intermediate to compounds of Formula (I). A hydroxyl group in the form of an alcohol or phenol can be readily converted to esters of carboxylic, sulfonic, carbamic, phosphonic, and phosphoric acids. Acylation to form a carboxylic acid ester is readily effected using a suitable acylating reagent such as an aliphatic acid anhydride or acid chloride. The corresponding aryl and heteroaryl acid anhydrides and acid chlorides can also be used. Such reactions are generally carried out using an amine catalyst such as pyridine in an inert solvent. Similarly, carbamic acid esters (urethanes) can be obtained by reacting a hydroxyl group with isocyanates and carbamoyl chlorides. Sulfonate, phosphonate, and phosphate esters can be prepared using the corresponding acid chloride and similar reagents. Compounds of Formula (I) that have at least one thiol group present can be converted to the corresponding thioesters derivatives analogous to those of alcohols and phenols using the same reagents and comparable reaction conditions. Compounds of Formula (I) that have at least one primary or secondary amine group present can be converted to the corresponding amide derivatives. Amides of carboxylic acids can be prepared using the appropriate acid chloride or anhydrides with reaction conditions analogous to those used with alcohols and phenols. Ureas of the corresponding primary or secondary amine can be prepared using isocyanates directly and carbamoyl chlorides in the presence of an acid scavenger such as triethylamine or pyridine. Sulfonamides can be prepared from the corresponding sulfonyl chloride in the presence of aqueous sodium hydroxide or a tertiary amine. Suitable procedures and methods for preparing these derivatives can be found in House's Modern Synthetic Reactions, W. A. Benjamin, Inc., Shriner, Fuson, and Curtin in The Systematic Identification of Organic Compounds, 5th Edition, John Wiley & Sons, and Fieser and Fieser in Reagents for Organic Synthesis, Volume 1, John Wiley & Sons. Reagents of a wide variety that can be used to derivatize hydroxyl, thiol, and amines of compounds of Formula (I) are available from commercial sources or the references cited above, which are incorporated herein by reference.

Formula (I) compounds of this invention possessing hydroxyl, thiol, and amine functional groups can be alkylated to a wide variety of derivatives. Alternatively, alkylated Formula (I) compounds can be obtained by first alkylating one or more intermediates in the processes of preparation before further transforming the alkylated intermediate to compounds of Formula (I). A hydroxyl group of compounds of Formula (I) can be readily converted to ethers. Alkylation to form an ether is readily effected using a suitable alkylating reagent such as an alkyl bromide, alkyl iodide or alkyl sulfonate. The corresponding aralkyl, heteroaralkyl, alkoxyalkyl, aralkyloxyalkyl, and het eroaralkyloxyalkyl bromides, iodides, and sulfonates can also be used. Such reactions are generally carried out using an alkoxide forming reagent such as sodium hydride, potassium t-butoxide, sodium amide, lithium amide, and n-butyl lithium using an inert polar solvent such as DMF, DMSO, THF, and similar, comparable solvents. amine catalyst such as pyridine in an inert solvent. Compounds of Formula (I) that have at least one thiol group present can be converted to the corresponding thioether derivatives analogous to those of alcohols and phenols using the same reagents and comparable reaction conditions. Compounds of Formula (I) that have at least one primary, secondary or tertiary amine group present can be converted to the corresponding secondary, tertiary or quaternary ammonium derivative. Quaternary ammonium derivatives can be prepared using the appropriate bromides, iodides, and sulfonates analogous to those used with alcohols and phenols. Conditions involve reaction of the amine by warming it with the alkylating reagent with a stoichiometric amount of the amine (i.e., one equivalent with a tertiary amine, two with a secondary; and three with a primary). With primary and secondary amines, two and one equivalents, respectively, of an acid scavenger are used concurrently. Secondary or tertiary amines can be prepared from the corresponding primary or secondary amine. A primary amine can be dialkylated by reductive amination using an aldehyde, such as formaldehyde, and sodium cyanoborohydride in the presence of glacial acetic acid. A primary amine can be monoalkylated by first monoprotecting the amine with a ready cleaved protecting group, such as trifluoroacetyl. An alkylating agent, such as dimethylsulfate, in the presence of a non-nucleophilic base, such as Barton's base (2-tert-butyl-1,1,3,3-tetramethylguanidine), gives the monomethylated protected amine. Removal of the protecting group using aqueous potassium hydroxide gives the desired monoalkylated amine. Additional suitable procedures and methods for preparing these derivatives can be found in House's Modern Synthetic Reactions, W. A. Benjamin, Inc., Shriner, Fuson, and Curtin in The Systematic Identification of Organic Compounds, 5th Edition, John Wiley & Sons, and Fieser and Fieser in Reagents for Organic Synthesis published by John Wiley & Sons. Perfluoroalkyl derivatives can be prepared as described by DesMarteau in J. Chem. Soc. Chem. Commun. 2241 (1998). Reagents of a wide variety that can be used to derivative hydroxyl, thiol, and amines of compounds of Formula (I) are available from commercial sources or the references cited above, which are incorporated herein by reference.

The examples of synthetic approaches to the preparation pyrazinones derivatized in a nucleophilic substituent such as may be present in B, R^1, R^2 and Y^0 are shown in specific Examples 100 through 104 below. The specific examples recited below should be considered a being merely illustrative of the wide variety possible and not as limiting to one of ordinary skill in the art.

Example 100

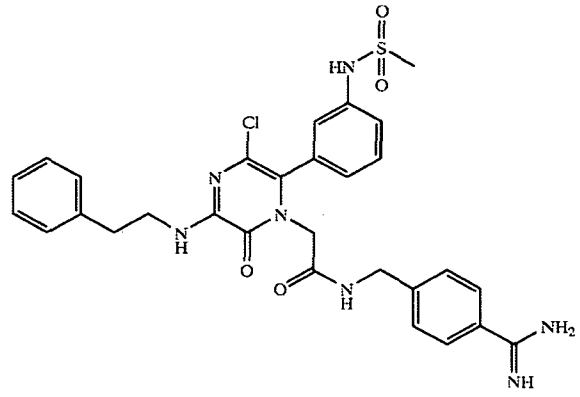


By following the method of Example 1 and substituting 3-nitrobenzaldehyde for benzaldehyde, 1-benzyloxycarbonylmethyl-3,5-dichloro-6-(3-nitrophenyl) pyrazinone (EX-100A) was obtained. The pyrazinone, 1-benzyl oxycarbonyl methyl-3,5-dichloro(3-nitrophenyl) pyrazinone (EX-100A), (15.01 g, 34.6 mmol) was taken up in 325 mL of 50% EtOH (w/w) and heated to 75° C. EtOAc was added until the solution was homogeneous (about 80 mL). Iron powder (9.4 g, 168 mmol) was added, followed by 0.57 mL of 12 M HCl (6.8 mmol) in about 0.6 mL of 50% EtOH. The reaction was monitored by TLC (80% EtOAc/hexanes) and was complete within 40 minutes. The reaction mixture was cooled to room temperature, and the iron was removed by filtration through Celite. The yellow solution was diluted with 600 mL of EtOAc and 300 mL of water. Saturated NaCl was added to help separate the layers. The organic phase was washed with saturated $NaHCO_3$ (2×250 mL), saturated NaCl (1×250 mL), dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. The residue was taken up in 20–25 mL of 3.4 M HCl in EtOAc. Additional EtOAc (about 25 mL) was added, and the mixture was heated to dissolve all of the compound. The volatile components were removed under reduced pressure. The residue (crusty solid) was taken up in EtOAc and slowly dripped into hexanes. The pale yellow solid that precipitated was filtered and dried under vacuum at room temperature to yield 12.19 g (80% yield) of 1-benzyloxycarbonylmethyl-3,5-dichloro-6-(3-aminophenyl)pyrazinone hydrochloride (EX-100B) as a pale yellow solid: ^{1}H NMR (300 MHz, CD_3OD) d 4.61 (AB q, 2 H, J=17 Hz), 5.20 (AB q, 2H, J=12 Hz), 7.31–7.51 (m, 7H), 7.63–7.67 (m, 2H); HPLC purity (retention time): 91% (3.0 min); LRMS m/z 404 (M^++H).

The pyrazinone, 1-benzyloxycarbonylmethyl-3,5-dichloro-6-(3-aminophenyl)pyrazinone hydrochloride (EX-100B), (78.2 mg, 0.18 mmol) was taken up in 5 mL of dichloromethane. Pyridine (32 mL, 0.40 mmol) was added, followed by acetyl chloride (26 mL, 0.36 mmol) in 1 mL of dichloromethane. The reaction was stirred at ambient temperature until the reaction was complete by TLC and LC/MS after 24 hours. The reaction solution was then washed with saturated $NaHCO_3$ (4×5 mL), saturated NaCl (1×5 mL), dried over $MgSO_4$ and concentrated to give 68.9 mg (86% yield) of the product 1-benzyloxycarbonylmethyl-3,5-dichloro-6-(3-acetamidophenyl)pyrazinone (EX-100C): ^{1}H NMR (300 MHz, $CDCl_3$) d 2.21 (s, 3H), 4.55 (AB q, 2H, J=16.6 Hz), 5.17 (s, 2H), 6.96 (d, 1H, J=7.7 Hz), 7.26–7.40 (m, 5H), 7.57 (s, 1H), 7.74–7.79 (m, 1H), 8.19–8.24 (br m, 1H), 8.65 (br s, 1H).

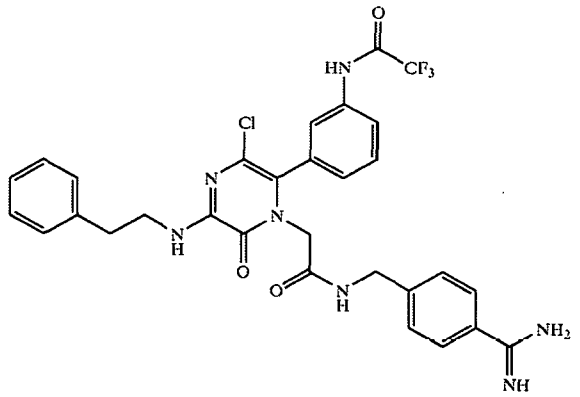
Following the necessary final steps of the procedure of Example 1, EX-100C was converted to the product: HPLC purity (retention time): 100% (2.9 min); LRMS m/z 572.5 (M^++H).

Example 101



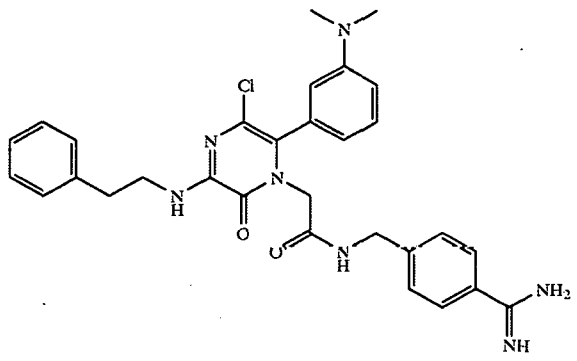
By following the method of Example 100 and substituting methanesulfonyl chloride for acetyl chloride the product was prepared: HPLC purity (retention time): 100% (2.9 min), LRMS m/z 608.2 (M^++H).

Example 102



By following the method of Example 100 and substituting trifluoroacetic anhydride for acetyl chloride, the product was prepared: HPLC purity (retention time): 100% (3.3 min); LRMS m/z 626.3 (M^++H).

Example 103

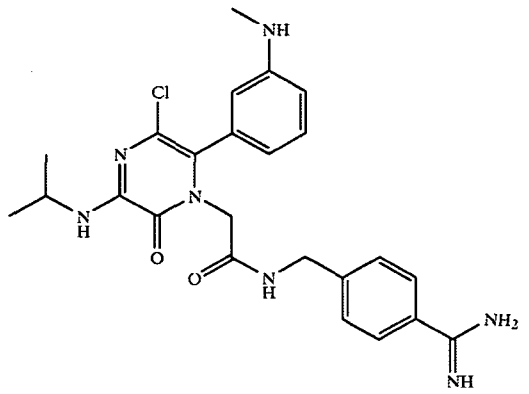


By following the method of Example 1 and substituting 3-nitrobenzaldehyde for benzaldehyde, 1-benzyloxycarbonylmethyl-3,5-dichloro-6-(3-aminophenyl)pyrazinone was obtained.

The 1-benzyloxycarbonylmethyl-3,5-dichloro-6-(3-aminophenyl)pyrazinone (210.6 mg, 0.48 mmol) was taken up in 9 mL of acetonitrile. Polyamine resin (1.05 g, 4.9 mmol) was added, along with about 10 mL of dichioromethane. After agitating about 10 mins the resin was filtered, rinsed with acetonitrile, and the solvents concentrated to about 10 mL. Formaldehyde (37%) (0.4 mL, 4.9 mmol) was added, followed by $NaCNBH_3$ (1.0 M in THF, 1.5 mL, 1.5 mmol) and the dropwise addition of two 50 mL portions of glacial acetic acid (17.4 M, 1.74 mmol). The reaction was monitored by LC/MS. A third 50 mL portion of glacial acetic acid was added after 3.5 h to force the reaction to completion. The solution was diluted with about 40 mL of diethyl ether and washed with 1.2 M NaOH (3×5 mL), saturated NaCl (1×5 mL), dried over $MgSO_4$, and the solvents were removed under reduced pressure to give 0.17 g (82% yield) of 1-benzyloxycarbonylmethyl-3,5-dichloro-6-(3-[N,N-dimethylamino]phenyl)pyrazinone (EX-103A): ^1H NMR (300 MHz, $CDCl_3$): d 2.96 (s, 6H), 4.59 (s, 2H), 5.19 (s, 2H), 6.55 (m, 2H), 6.82 (d, 1H), 7.25–7.40 (m, 6H).

Following the necessary final steps of the procedure of Example 1, EX-103A was converted to the product: HPLC purity (retention time): 94% (2.6 min); LRMS m/z 558.4 (M^++H).

Example 104



By following the method of Example 100 and replacing phenethylamine with isopropylamine, 1-benzyloxycarbonylmethyl-3-isopropylamino-5-chloro-6-(3-aminophenyl)pyrazinone was obtained.

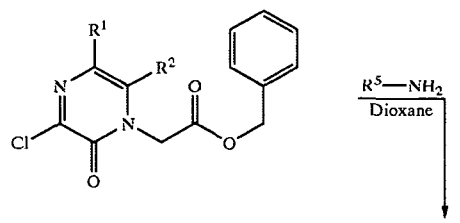
The 1-benzyloxycarbonylmethyl-3-isopropylamino-5-chloro-6-(3-aminophenyl)pyrazinone (1.01 g, 2.4 mmol) was dissolved in 25 mL of THF. Pyridine (0.37 mL, 4.6 mmol) was added, followed by pentafluoropyridine trifluoroacetate (0.79 mL, 4.6 mmol). After 2 h, polyamine resin (3.1 g, 8.7 mmol) and 25 mL of dichloromethane was added, and the mixture was vigorously stirred for 1–2 h. The resin was filtered, rinsed with dichloromethane (3×5 mL), and the volatiles were removed under reduced presssure to give the desired product EX-104A in quantitative yield: ^1H NMR (300 MHz, $CDCl_3$) d 1.30 (d, 3H, J=1.4 Hz), 1.32 (d, 3H, J=1.4 Hz), 4.24 (m, 1H), 4.47 (AB q, 2H, J=16.9 Hz), 5.15 (s, 2H), 6.22 (d, 1H, J=8.2Hz), 7.12 (d, 1H, J=7.7Hz), 7.25–7.42 (m, 5H), 7.54 (s, 1H), 7.73–7.81 (m, 1H), 8.62 (d, 1H, J=4.2 Hz), 9.10 (br s, 1H).

The 1-benzyloxycarbonylmethyl-3-isopropylamino-5-chloro-6-(3-[N-trifluoroacetamido]phenyl)pyrazinone (EX-104A) (0.63 g, 1.2 mmol) was dissolved in 20 mL of dichioromethane. Barton's base (2-tert-butyl-1,1,3,3-tetramethylguanidine) (0.5 mL, 2.5 mmol) and dimethylsulfate (0.66 mL, 7 mmol) wee added, and the reaction was stirred at ambient temperature overnight. The reaction was monitored by LC/MS, and after completion the solution was washed with aqueous NH_4OH (2×10 mL) and 5% HCl (1×10 mL). The combined aqueous washes were extracted with dichloromethane (1×10 mL). The combined organic phases were washed with saturated NaCl (1×10 mL), dried over $MgSO_4$, filtered, and the volatiles were removed under reduced pressure to give 0.51 g (80% yield) of the desired product (EX-104B): HPLC purity (retention time): 97% (4.4 min); LRMS m/z 537.5 (M^++H).

Following the necessary final steps of the procedure of Example 1, EX-104B was converted to the product: ^1H NMR (300 MHz, CD_3OD) d 1.31 (s, 3H), 1.33 (s, 3H), 2.94 (s, 3H), 4.22 (m, 1H), 4.40–4.52 (m, 4H), 7.01–7.05 (m, 2H), 7.17–7.19 (m, 1H), 7.42–7.45 (m, 1H), 7.49 (d, 2H, J=8.3 Hz) 7.80 (d, 2H, J=8.3 Hz); HPLC purity (retention time): 100% (2.1 min); LRMS m/z 481.6 (M^++H).

Pyrazinones, wherein a B-A substituent is introduced by reaction of a 3-amino group of an intermediate pyrazinone with an electrophilic reagent, can be prepared using the general procedures and processes shown in Scheme 9 and Scheme 10 and as illustrated below in specific Examples 105–109.

Scheme 9
Introduction of B—A—N(R^5) into Pyrazidone Intermediates and the Resulting Products



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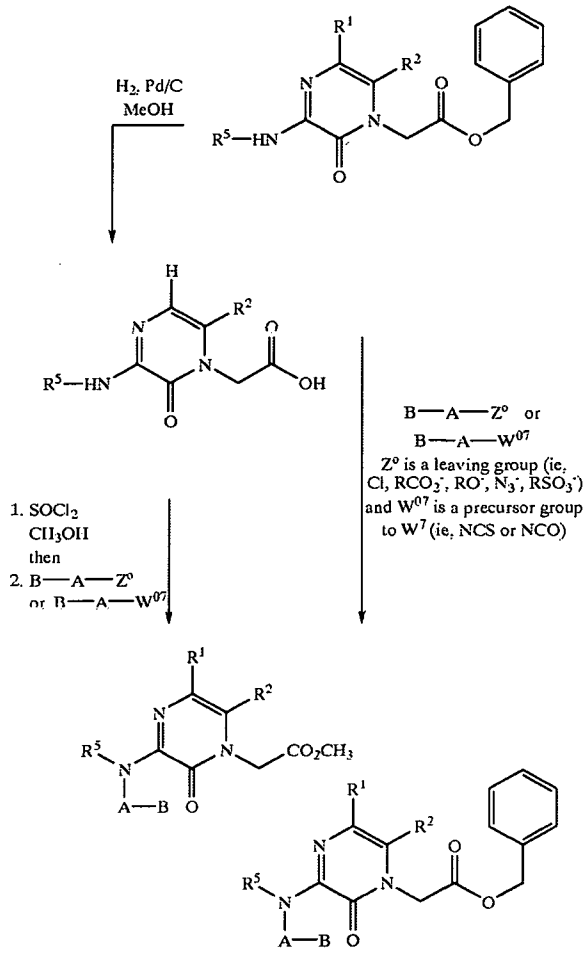
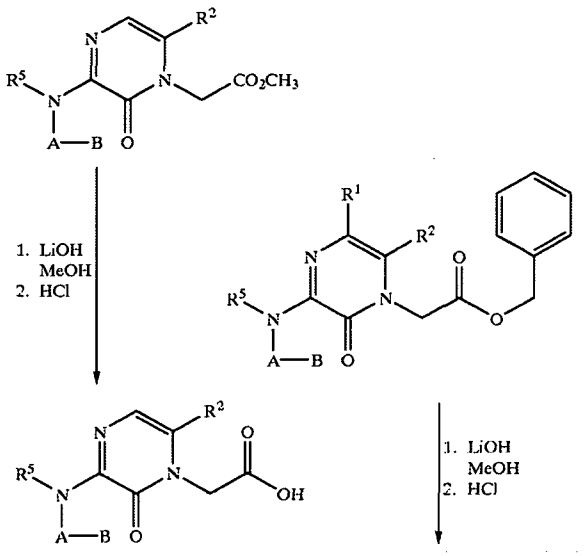


Scheme 10

Introduction of B—A—N(R^5) into Pyrazidone Intermediates and the Resulting Products (Concluded)



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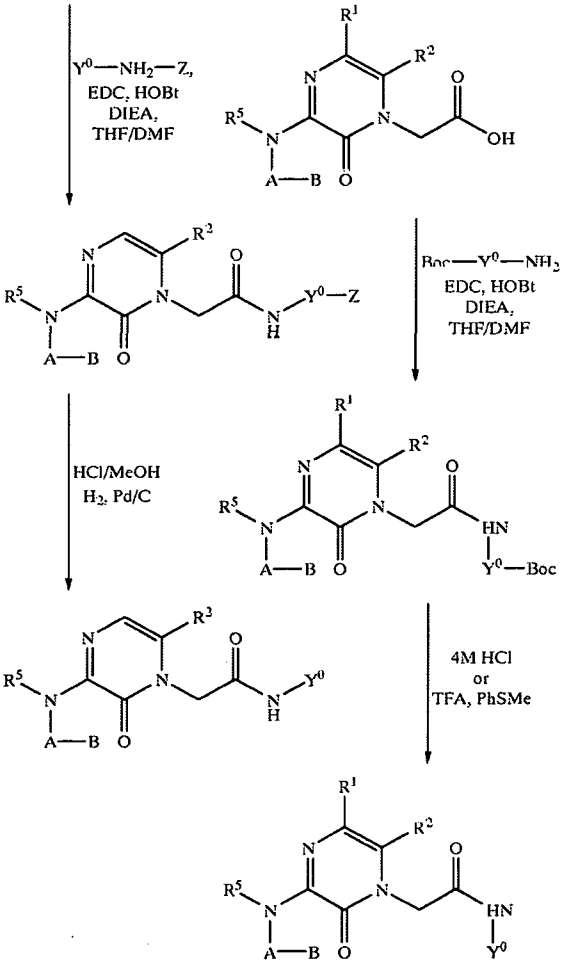
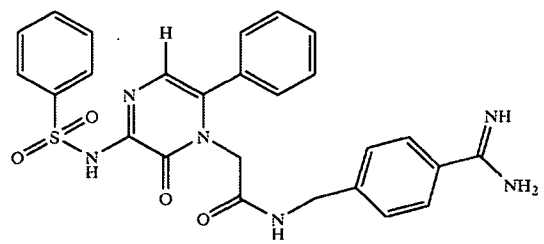
-continued



The examples of synthetic approaches to the preparation pyrazinones in which the substituents represented by B-A are introduced by reaction of a 3-amino group of the pyrazinone with an electrophilic reagent are shown in specific Examples 105 through 109 below. The specific examples recited below should be considered a being merely illustrative of the wide variety possible and not construed as limiting to one of ordinary skill in the art.

Example 105



1-Benzyloxycarbonylmethyl-3,5-dichloro-6-phenylpyrazinone (EX-1B) (0.8 g, 2.06 mmol) was mixed with 20 ml 0.5 M ammonia in dioxane in a sealed tube. The tube was heated to 100° C. for 12 hours. After removing the dioxane under reduced pressure, the residue was dissolved

in ethyl acetate. The ethyl acetate solution was washed with water and brine and dried over anhydrous Na_2SO_4. After removing the solvent, the product was recrystallized in acetone to yield the pure amino pyrazinone EX-105A as a white crystal solid (0.76 g, 99%): HPLC-MS (0 to 95% AcCN/6 min @ 1.0 mL/Min @ 254 nm @ 50° C.): retention time 3.75 min, $M+H^+$=370.0 for formula $C_{19}H_{17}ClN_3O_3$. ^1H NMR (400 MHz, $CDCl_3$): d 4.43 (s, 2H), 5.13 (s, 2H), 5.78 (b, 2H), 7.21–7.27 (m, 5H), 7.35–7.39 (m, 5H).

EX-105A (4.7 g, 12.73 mmol) was mixed with 1.34 g 10% Pd/C in 100 ml methanol. The mixture was stirred under hydrogen atmosphere that was introduced via a balloon for 48 hours. After filtration and removing the solvent, a white crystal solid was obtained as the carboxylic acid product EX-105B (3.0 g, 97%): HPLC-MS (0 to 95% AcCN/6 min @ 1.0 mL/Min @ 254 nm @ 50° C.): retention time 1.45 min, $M+H^+$=246.0 for formula $C_{12}H_{12}N_3O_3$.

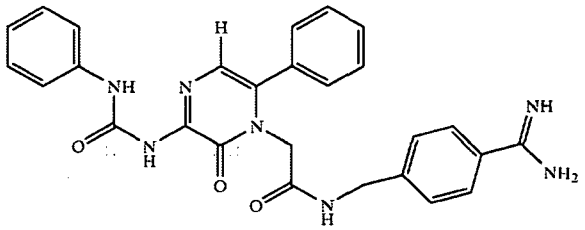
EX-105B (3.0 g, 12.2 mmol) in 100 ml methanol was cooled down to −50° C. $SOCl_2$ (1.4 ml, 19.1 mmol) was added to the solution. After stirring at room temperature for four hours, the mix was heated to reflux for three hours. After removing the solvent, the residue was subjected to a silica gel plug using ethyl acetate to elute. The pure product was obtained by recrystallization in methanol as a white crystal solid EX-105C (2.22 g, 68%): HPLC-MS (0 to 95% AcCN/6 min @ 1.0 mL/Min @ 254 nm @ 50° C.): retention time 1.94 min, $M+H^+$=260.0 for formula $C_{13}H_{14}N_3O_3$.

EX-105C (0.258 g, 1 mmol) was mixed with benzenesulfonyl chloride (0.353 g, 2 mmol) in 3 ml pyridine. The reaction mixture was heated at 90° C. for 2 hours. After removing the pyridine, the crude product was obtained by an aqueous work-up procedure. The crude product EX-105D was dissolved in 10 ml methanol and treated with 10 ml 1M LiOH solution for 15 minutes. After the solution was acidified with 2 N HCl to a pH of about 2 and the methanol removed under reduced pressure, a yellow precipitate was obtained via filtration and washing with water. The pure sulfonamide EX-105E is a yellow crystalline solid (0.267 g, 70%): HPLC-MS (0 to 95% AcCN/6 min @ 1.0 mL/Min @ 254 nm @ 50° C.): retention time 2.88 min, $M+H^+$=386.0 for formula $C_{18}H_{16}N_3O_5S$. ^1H NMR (400 MHz, methanol-d_4): d 4.44 (s, 2H), 6.77 (s, 1H), 7.32 (dd, J=8.0, 1.6 Hz, 2H), 7.42–7.48 (m, 3H), 7.54 (t, J=8.0 Hz, 2H), 7.60–7.64 (m, 1H), 8.09 (d, J=8.0, 2H). ^{13}C NMR (101 MHz, methanol-d_4): d 48.4, 129.2, 129.9, 130.0, 130.6, 131.0, 132.6, 134.4, 141.4, 146.1, 157.0, 159.0, 160.0, 170.3.

EX-105E (0.106 g, 0.275 mmol) was mixed with EDC (0.055 g, 0.289 mmol) and HOBt (0.044 g, 0.289 mmol) in 2 ml DMF. The mixture was stirred for 10 minutes. To this mixture was then added the protected amidine, 4-(N-benzyloxycarbonylamidino)benzylamine hydrogen chloride salt (0.289 mmol), and DIEA (0.144 ml, 0.825 mmol) in 1 ml DMF. The reaction solution was stirred for 2 hours at room temperature. The DMF was removed under reduced pressure. The remaining residue was triturated in 1 N HCl and washed with water to yield the product EX-105F as an off-white amorphous solid (0.152 g, 85%): HPLC-MS (0 to 95% AcCN/6 min @ 1.0 mL/Min @ 254 nm @ 50° C.): retention time 3.14 min, $M+H^+$=651.3 for formula $C_{34}H_{30}N_5O_7S$. ^1H NMR (400 MHz, methanol-d_4): d 4.42 (s, 2H), 4.51 (s, 2H), 5.40 (s, 2H), 6.76 (s, 1H), 7.35–7.62 (m, 15H), 7.75 (d, J=8.0 Hz, 2H), 8.08 (d, J=8.0 Hz, 2H). ^{13}C NMR (101 MHz, methanol-d_4): d 43.6, 49.7, 70.7, 111.6, 118.2, 119.7, 127.3, 128.7, 129.0, 129.1, 129.8, 129.9, 130.0, 130.8, 131.0, 132.6, 134.4, 135.8, 136.2, 141.5, 146.3, 147.6, 153.0, 154.5, 167.9, 169.0.

EX-105F (0.148 g, 0.228 mmol), p-toluenesulfonic acid mono hydrate (0.045 g, 0.24 mmol) and 10% Pd on activated carbon (0.012 g, 0.007 mmol) were mixed with 5 ml methanol. The mixture was stirred for 2 hours under an atmosphere of hydrogen that was introduced through a rubber balloon. After filtering off the catalyst and removing the methanol, the remaining residue was triturated in a solvent of 2:1 ether to methanol to yield a white amorphous solid as the product (0.105 g, 95%) as the mono-salt of p-toluenesulfonic acid: HPLC-MS (0 to 95% AcCN/6 min @ 1.0 mL/Min @ 254 nm @ 50° C.): retention time 2.64 min, $M+H^+$=517.5 for formula $C_{26}H_{25}N_6O_4S$. ^1H NMR (400 MHz, methanol-d_4): d 2.35 (s, 3H), 4.40 (s, 2H), 4.52 (s, 2H), 6.77 (s, 1H), 7.21 (d, J=7.6 Hz, 2H), 7.34 (d, J=7.2 Hz, 2H), 7.41–7.51 (m, 3H), 7.55 (t, J=7.6 Hz, 2H), 7.64 (t, J=7.2 Hz, 1H), 7.79 (d, J=8.0 Hz, 2H), 7.74 (d, J=8.0 Hz, 2H). ^{13}C NMR (101 MHz, methanol-d_4): d 21.2, 43.5, 70.7, 119.5, 126.8, 128.0, 128.7, 128.9, 129.0, 129.7, 129.8, 129.9, 130.6, 130.9, 132.4, 134.3, 136.0, 141.3, 141.6, 146.2, 146.4, 152.9, 167.9, 168.7.

Example 106



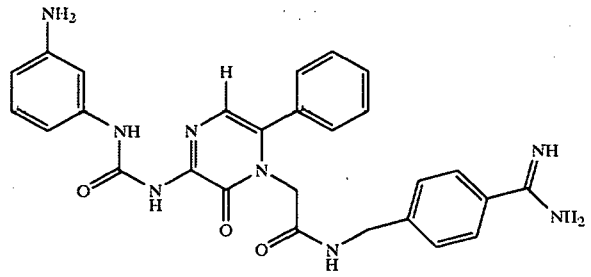
Following, the method of Example 105, EX-105C (0.0932 g, 0.36 mmol) was treated with phenyl isocyanate (0.128 g, 1.08 mmol) and 0.2 ml pyridine in 2 ml acetonitrile at 80° C. for 3 hours instead of benzenesulfonyl chloride. After the reaction mixture was kept in a freezer for two days, a nice crystal solid formed as the pure pyrazinone urea EX-106A (0.129 g, 95%): HPLC-MS (0 to 95% AcCN/6 min @ 1.0 mL/Min @ 254 nm @ 50° C.): retention time 3.73 min, $M+H^+$=379.3 for formula $C_{20}H_{19}N_4O_4$. ^1H NMR (400 MHz, $CDCl_3$): d 3.75 (s, 3H), 4.55 (s, 2H), 6.97 (s, 1H), 7.10 (t, J=7.6 Hz, 1H), 7.32–7.38 (m, 4H), 7.46–7.52 (m, 3H) 7.58 (d, J=8.0 Hz, 2H), 8.28 (s, 1H), 11.1 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): d 47.4, 52.8, 119.6, 120.2, 123.9, 128.9, 129.1, 129.4, 130.1, 130.9, 133.8, 137.8, 145.7, 150.8, 150.9, 167.3.

Saponification of compound EX-106A manner similar to the procedure as described in the synthesis of EX-105D yielded compound EX-106B. HPLC-MS (0 to 95% AcCN/6 min @ 1.0 mL/Min @ 254 nm @ 50° C.): retention time 3.34 min. $M+H^+$=365.1 for formula $C_{19}H_{16}N_4O_4$. Compound EX-106B was coupled with 4-(N-benzyloxycarbonylamidino)benzylamine hydrogen chloride salt using EDC, HOBt and DIEA as described before to yield the protected product EX-106C as an off-white solid: HPLC-MS (0 to 95% AcCN/6 min @ 1.0 mL/Min @ 254 nm @ 50° C.): retention time 3.58 min, $M+H^+$=630.0 for formula $C_{35}H_{32}N_7O_5$. ^1H NMR (400 MHz, methanol-d_4): d 4.49 (s, 2H), 4.61 (s, 2H), 5.40 (s, 2H), 7.06 (s, 1H), 7.11 (t, J=7.2 Hz, 1H), 7.32–7.56 (m, 16H), 7.76 (d, J=8 Hz, 2H).

EX-106C was converted to the HCl salt of the product by hydrogenation in methanol in the presence of HCl with Pd/C as the catalyst. The product was an off-white amorphous solid: HPLC-MS (0 to 95% AcCN/6 min @ 1.0 mL/Min @ 254 nm @ 50° C.): retention time 3.01 min, $M+H^+$=496.4 for formula $C_{27}H_{26}N_7O_3$. ^1H NMR (400 MHz, methanol-

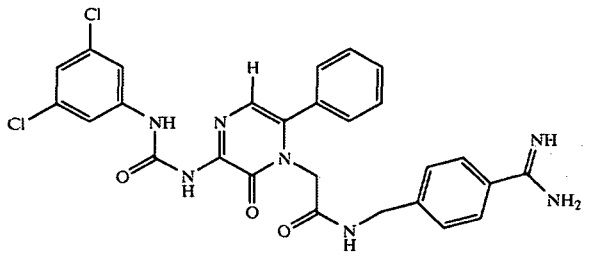
d_4): d 4.47 (s, 2H), 4.65 (s, 2H), 6.97 (s, 1H), 7.15 (t, J=7.2 Hz, 1H), 7.27–7.54 (m, 9H), 7.57 (d, J=7.2 Hz, 2H) 7.78 (d, J=8.0 Hz, 2H), 8.76 (s, 1H), 9.26 (s, 1H). HRMS m/z MH^+496.2036, calcd for $C_{27}H_{26}N_7O_3$ 496.2097.

Example 107



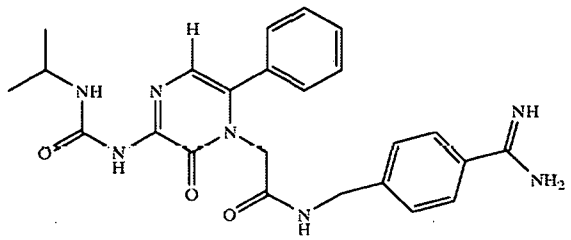
Using the procedure of Example 106 and substituting 3-(benzyloxycarbonylamido)phenyl isocyanate for phenyl isocyanate, the product was obtained as the HCl salt: HPLC-MS (0 to 95% AcCN/6 min @ 1.0 mL/Min @ 254 nm @ 50° C.): retention time 1.84 min, $M+H^+$=511.6 for formula $C_{27}H_{27}N_8O_3$. ^1H NMR (400 MHz, methanol-d_4): d 4.46 (s, 2H), 4.65 (s, 2H), 6.97 (s, 1H), 7.17 (d, J=6.8 Hz, 1H), 7.45–7.60 (m, 8H), 7.78 (m, 3H) 7.94 (s, 1H), 8.77 (s, 1H), 9.26 (s, 1H). HRMS m/z MH^+ 511.2251, calcd for $C_{27}H_{27}N_8O_3$ 511.2206.

Example 108



Using the procedure of Example 106 and substituting 3,5-dichlorophenyl isocyanate for phenyl isocyanate, the product was obtained as the HCl salt: HPLC-MS (0 to 95% AcCN/6 min @ 1.0 mL/Min @ 254 nm @ 50° C.): retention time 3.41 min, $M+H^+$=564.4 for formula $C_{27}H_{24}Cl_2N_7O_3$. ^1H NMR (400 MHz, methanol-d_4): d 4.47 (s, 2H), 4.63 (s, 2H), 7.04 (s, 1H), 7.18 (t, J=1.6 Hz, 1H), 7.45–7.56 (m, 7H), 7.64 (d, J=2 Hz, 2H) 7.78 (d, J=8.0 Hz, 2H), 8.77 (s, 1H), 9.26 (s, 1H). HRMS m/z MH^+ 564.1351, calcd for $C_{27}H_{24}Cl_2N_7O_3$ 564.1318.

Example 109



Using the procedure of Example 106 and substituting isopropyl isocyanate for phenyl isocyanate, the product was obtained as the HCl salt: HPLC-MS (0 to 95% AcCN/6 min @ 1.0 mL/Min @ 254 nm @ 50° C.): retention time 2.43 min, $M+H^+$=462.4 for formula $C_{24}H_{28}N_7O_3$. ^1H NMR (400 MHz, methanol-d_4): d 1.25 (d, J=6.4 Hz, 6H), 3.99(m, 1 H), 4.45 (s, 2H), 4.64 (s, 2H), 6.82 (s, 1H), 7.43–7.53 (m, 5H), 7.60 (m, 1H) 7.67 (t, J=6.4 Hz, 1H), 7.78 (d, J=8.0 Hz, 2H), 8.77 (s, 1H), 9.26 (s, 1H). HRMS m/z MH^+ 462.2230, calcd for $C_{24}H_{28}N_7O_3$ 462.2254.

Assays for Biological Activity

TF-VIIa Assay

In this assay 100 nM recombinant soluble tissue factor and 2 nM recombinant human factor VIIa are added to a 96-well assay plate containing 0.4 mM of the substrate, N-Methylsulfonyl-D-phe-gly-arg-p-nitroaniline and either inhibitor or buffer (5 mM $CaCl_2$,50 mM Tris-HCl, pH 8.0, 100 mM NaCl, 0.1% BSA). The reaction, in a final volume of 100 ul is measured immediately at 405 nm to determine background absorbance. The plate is incubated at room temperature for 60 min, at which time the rate of hydrolysis of the substrate is measured by monitoring the reaction at 405 nm for the release of p-nitroaniline. Percent inhibition of TF-VIIa activity is calculated from $OD_{405\ nm}$ value from the experimental and control sample.

Xa Assay

Human factor Xa (0.3 nM) and 0.15 mM N-α-Benzyloxycarbonyl-D-arginyl-L-glycyl-L-arginine-p-nitroaniline-dihydrochloride (S-2765) are added to a 96-well assay plate containing either inhibitor or buffer (50 mM Tris-HCl, pH 8.0, 100 mM NaCl, 0.1% BSA). The reaction, in a final volume of 100 ul is measured immediately at 405 nm to determine background absorbance. The plate is incubated at room temperature for 60 min, at which time the rate of hydrolysis of the substrate is measured by monitoring the reaction at 405 nm for the release of p-nitroaniline. Percent inhibition of Xa activity is calculated from $OD_{405\ nm}$ value from the experimental and control sample.

Thrombin Assay

Human thrombin (0.28 nM)and 0.06 mM H-D-Phenylalanyl-L-pipecolyl-L-arginine-p-nitroaniline dihydrochloride are added to a 96-well assay plate containing either inhibitor or buffer (50 mM Tris-HCl, pH 8.0, 100 mM NaCl, 0.1% BSA). The reaction, in a final volume of 100 ul is measured immediately at 405 nm to determine background absorbance. The plate is incubated at room temperature for 60 min, at which time the rate of hydrolysis of the substrate is measured by monitoring the reaction at 405 nm for the release of p-nitroaniline.

Percent inhibition of thrombin activity is calculated from $OD_{405\ nm}$ value from the experimental and control sample.

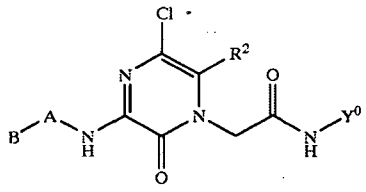
Trypsin Assay

Trypsin (5 ug/ml; type IX from porcine pancreas) and 0.375 mM N-α-Benzoyl-L-arginine-p-nitroanilide (L-BAPNA) are added to a 96-well assay plate containing either inhibitor or buffer (50 mM Tris-HCl, pH 8.0, 100 mM NaCl, 0.1% BSA). The reactions, in a final volume of 100 ul are measured immediately at 405 nm to determine background absorbance. The plate is incubated at room temperature for 60 min, at which time the rate of hydrolysis of the substrate is measured by monitoring the reaction at 405 nm for the release of p-nitroaniline. Percent inhibition of trypsin activity is calculated from $OD_{405\ nm}$ value from the experimental and control sample.

Recombinant soluble TF, consisting of amino acids 1–219 of the mature protein sequence was expressed in *E. coli* and purified using a Mono Q Sepharose FPLC. Recombinant human VIIa was purchased from American Diagnostica, Greenwich Conn. and chromogenic substrate N-Methylsulfonyl-D-phe-gly-arg-p-nitroaniline was prepared by American Peptide Company, Inc., Sunnyvale, Calif. Factor Xa was obtained from Enzyme Research Laboratories, South Bend Ind., thrombin from Calbiochem, La Jolla, Calif., and trypsin and L-BAPNA from Sigma, St. Louis Mo. The chromogenic substrates S-2765 and S-2238 were purchased from Chromogenix, Sweden.

Using bioassay procedures described herein, the biological activity of the compounds of Examples 1 through Example 109 and Tables 1 through Table 7 are summarized in Table 8 and Table 9.

TABLE 8

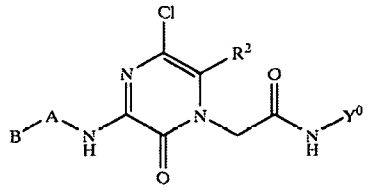


General Structure

Inhibitory Activity of Pyrazinones toward TF-VIIA, Thrombin II, Factor Xa, And Trypsin II.

Ex. No.	IC50 or % Inhibition TF-VIIa (30 uM)	IC50 or % Inhibition Thrombin II (30 uM)	IC50 or % Inhibition Factor Xa (30 uM)	IC50 or % Inhibition Trpysin II (30 uM)
1	1	1	>100	0.2
2	5	0.4	>100	1
3	0.2	<0.04	1	0.4
4	0.3	0.1	3	0.5
5	7	1	4	1
6	0.1	<0.04	1	0.4
7	0.2	0.1	3	0.4
8	3	0.2	1	0.4
9	>30	30	>0	>30
10	>30	>0	>0	>30
11	91	<0.1	>100	1
12	>100	7	>100	1
13	>100	48	>100	14
14	>100	29	>100	0.3
15	>100	>100	>100	1
16	>100	13	>100	1
17	0.71	15.32	41%	0.24
18	47%	20%	0	1.13

TABLE 8-continued

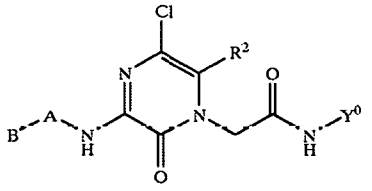


General Structure

Inhibitory Activity of Pyrazinones toward TF-VIIA, Thrombin II, Factor Xa, And Trypsin II.

Ex. No.	IC50 or % Inhibition TF-VIIa (30 uM)	IC50 or % Inhibition Thrombin II (30 uM)	IC50 or % Inhibition Factor Xa (30 uM)	IC50 or % Inhibition Trpysin II (30 uM)
19	0.8	0.22	22% @ 30	0.27
20	41% @ 30	4	6% @ 30	7
21	8% @ 30	26.8	21% @ 30	2
22	0% @ 30	47% @ 30	13% @ 30	1.7
23	1.7	17	38% @ 30	0.32
24	0% @ 30	46% @ 30	22% @ 30	1.3
25	7%	3%	4%	9%
26	1%	4%	5%	3%
27	12.5	>30	>30	16
28	3	>30	>30	0.23
29	pending	pending	pending	pending
30	pending	pending	pending	pending
31	22%	4%	4%	20%
32	12	0	0	0
33	4%	30	0	3.6
34	20%	0.59	0	1.3
35	29%	5%	10%	2.88
36	5%	31%	0	30%
37	1.8	1.9	0	0.3
38	0.9	0.58	22%	0.4
39	1.7	0.26	0	0.28
40	0.06	0	0	0.1
41	0.02	8	0	0.1
42	0.5	17%	0	0.53
43	0.25	43%	0	0.15
44	2.1	40%	4%	0.54
45	0.89	13	9%	0.25
46	0.98	18.7	10%	0.23
47	0.66	1.14	10.6	0.20
48	0.57	6.4	20%	0.38
49	0.57	6.4	28.9	0.19
50	0.50	14.2	39%	0.24
51	0.65	2.14	9.68	0.17
52	0.59	7.0	24.0	0.15
53	0.30	11.1	7%	0.15
54	11.3	0%	0%	0%
55	0.15	0.12	0%	0.18
56	16.7	3.13	0%	0.738
57	1.4	0.15	0%	0.22
58	0%	1%	1%	4%
59	0%	0%	2%	7%
60	0.901	<0.04	5.65	0.192
61	1%	0%	0%	10%
62	5.6	4%	10%	2.2
63	28%	6%	0	7
64	0.78	2	19%	0.07
65	0.36	2.8	12%	0.3
66	0.34	40%	0	0.28
67	0.20	4.25	0	0.14
68	32%	0%	6%	4.8
69	0.06	2.6	2.6	0.07
73	0.03	4.4	0	0.1
74	3.25	1.78	13%	0.15
75	0.21	2	9%	0.04
76	0.12	0	0	0.28
77	2.52	0.98	>30	1.13
78	0.43	0.3	16% @ 30	0.23
79	4.14	0.3	30% @ 30	0.15
80	1.29	4.55	29% @ 30	0.16

TABLE 8-continued

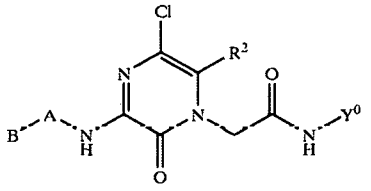


General Structure

Inhibitory Activity of Pyrazinones
toward TF-VIIA, Thrombin II, Factor Xa, And Trypsin II.

Ex. No.	IC50 or % Inhibition TF-VIIa (30 uM)	IC50 or % Inhibition Thrombin II (30 uM)	IC50 or % Inhibition Factor Xa (30 uM)	IC50 or % Inhibition Trpysin II (30 uM)
81	1	0.89	33% @ 30	0.22
82	20	4.67	32% @ 30	0.17
83	0.75	0.84	>30	0.36
84	3.03	0.5	>30	0.2
85	0.88	0.92	42% @ 30	0.19
86	0.07	0.9	26% @ 30	78% @ 1
87	0.07	1.5	>30	0.26
88	0.1	15	>30	0.27
89	5% @ 30	3% @ 30	5% @ 30	9% @ 30
90	0.02	8	16% @ 30	0.1
91	0.07	0.4	7	0.5
92	0.053	17.7	18% @ 30	0.25
93	0.07	15.4	>30	0.16
94	0.04	48% @ 30	>30	0.24
95	0.6	0.58	>30	0.21
96	0.26	6.39	>30	0.12
97	0.04	29% @ 30	>30	0.24
98	0.09	20% @ 30	10% @ 30	0.07
99	6% @ 30	0% @ 30	8% @ 30	7% @ 30
100	1.6	0.1	>30	62% @ 1
101	0.6	0.1	>30	83% @ 1
102	1.2	1	43% @ 30	0.39
103	0.3	1.3	11% @ 30	0.45
104	1.2	19	>30	0.7
105	0	17%	5%	0.49
106	1.11	28.8	30%	0.25
107	0.57	48%	35%	0.24
108	4.13	16%	20%	0.5
109	6.17	46%	10%	0.22
1471-1	8.17	2.57	10%	0.79
1471-2	3.62	86% @ .04	10%	0
1471-3	13.59	6.31	0	1.29
1471-4	29.4	18.3	0	3.1
1471-5	8.69	0.09	12%	1.79
1471-6	2.85	63% @ .04	14%	0.68
1471-7	4.28	0.06	4%	0.87
1471-8	3.86	70% @ .04	27%	0.65
1471-9	0.77	7.63	29%	0.24
1471-10	0.6	69% @ .04	45%	0.18
1471-11	1.69	12.03	9%	0.93
1471-12	7.97	37% @ 30	9%	0.93
1471-13	1.47	0.33	0%	0.53
1471-14	0.18	62% @ .04	23	0.05
1471-15	0.63	0.16	10%	0.24
1471-16	0.82	0.1	23%	0.28
1471-17	11.01	3.76	16	0.24
1471-18	11.21	0.15	26%	0.8
1471-19	33%	16.86	26%	1.6
1471-20	42%	9.46	34%	0.57
1471-21	8.18	0.08	30	0.24
1471-22	14.56	0.32	28%	0.5
1471-23	8.88	0.2	36%	0.28
1471-24	10.05	0.05	23	0.27
1471-25	2.45	24.47	31%	0.36
1471-27	4.19	40%	16%	0.59
1471-28	7.22	26.99	8%	0.39
1471-29	2.18	0.67	21%	0.47
1471-30	0.83	0.13	41%	0.08
1471-31	1.98	0.72	17%	0.47

TABLE 8-continued

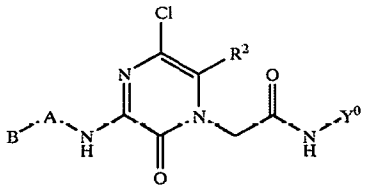


General Structure

Inhibitory Activity of Pyrazinones
toward TF-VIIA, Thrombin II, Factor Xa, And Trypsin II.

Ex. No.	IC50 or % Inhibition TF-VIIa (30 uM)	IC50 or % Inhibition Thrombin II (30 uM)	IC50 or % Inhibition Factor Xa (30 uM)	IC50 or % Inhibition Trpysin II (30 uM)
1471-32	1.19	0.17	25%	0.23
1471-33	31%	34%	22%	0.36
1471-34	17.47	0.74	24%	0.25
1471-35	37%	40%	22%	0.27
1471-36	11%	15%	6%	0.74
1471-37	39%	6.02	7%	0.43
1471-38	24.38	3.92	18%	0.34
1471-39	23.45	4.06	11%	0.29
1471-40	40%	4.03	11%	0.47
1471-41	18.33	25.8	34%	0.33
1471-42	10.45	0.55	15%	0.45
1471-43	25.26	34%	18%	0.44
1471-44	34%	25%	13%	0.53
1471-45	13.22	1.19	24%	0.27
1471-46	13.02	1.76	21%	0.37
1471-47	12.59	2.24	22%	0.41
1471-48	15.7	0.92	17%	0.42
1471-57	4.73	0.9	11%	0.67
1471-58	12.44	76% @ .04	0%	4.03
1471-59	7.52	1.95	0%	1.03
1471-60	13.01	2.97	0%	1.52
1471-61	5	0.04	0%	1.2
1471-62	4%	24%	0%	>30
1471-63	3.45	56% @ .04	2%	0.84
1471-64	3.02	78% @ .04	2%	0.61
1471-67	12%	27%	16%	0.82
1471-70	10%	33%	12%	1.01
1471-71	6%	24%	0%	2.58
1471-72	15%	12.2	22%	0.72
1507-01	6.3	18.9	16%	0.9
1507-02	9.4	36%	9%	1.1
1507-03	3.6	21	21%	0.8
1507-04	29.5	9.5%	>30	9% @ 1
1507-05	4.7	22	10%	
1507-06	20	0.5	>30	8% @ 1
1507-07	25%	27	>30	7% @ 1
1507-08	7%	10%	1%	
1507-09	22.6	0.97	13%	0.7
1507-10	24%	39.5%	>30	7% @ 1
1507-11	3	<0.04	>30	27% @ 1
1507-12	6.7	0.6	>30	12% @ 1
1507-13	26.7	6%	>30	8% @ 1
1507-15	12	25%	>30	11% @ 1
1507-16	5.8	21.3	18%	1
1507-17	27.4	0.9	16%	2.8
1507-18	10.6	10.6	>30	6% @ 1
1507-19	12.9	45%	4%	
1507-20	20.9	10.5%	>30	11% @ 1
1507-21	0.4	4.6	23%	0.36
1507-22	45%	1.5%	>30	8% @ 1
1507-23	28.9	11%	>30	11% @ 1
1507-24	0%	7.5%	15%	25% @ 30
1507-25	1.6	22.4	>30	60% @ 1
1507-26	20.5	11.5%	>30	11% @ 1
1507-28	38%	1.5	>30	1% @ 1
1507-29	5.8	27%	4%	
1507-30	13.4	18.5	>30	0% @ 1
1507-31	3.7	21.5%	>30	2% @ 1
1507-32	21.3	16.5%	>30	0% @ 1

TABLE 8-continued

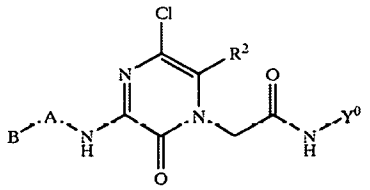


General Structure

Inhibitory Activity of Pyrazinones toward TF-VIIA, Thrombin II, Factor Xa, And Trypsin II.

Ex. No.	IC50 or % Inhibition TF-VIIa (30 uM)	IC50 or % Inhibition Thrombin II (30 uM)	IC50 or % Inhibition Factor Xa (30 uM)	IC50 or % Inhibition Trpysin II (30 uM)
1507-33	28.4	8.5%	>30	2% @ 1
1507-34	8.5	20%	>30	0% @ 1
1507-35	19.9	15.9	28%	0.49
1507-36	13.8	18%	0%	
1507-38	16	34.5%	>30	0% @ 1
1507-40	5.7	30	11%	
1507-41	48%	10.5%	17%	13.9
1507-42	11.6	23.5%	>30	0% @ 1
1507-43	4.1	7.1	21%	0.97
1507-44	6	0.5	9%	
1507-45	7.3	1	>30	0% @ 1
1507-46	4.3	36%	8%	
1507-47	17.6	37%	19%	1.6
1507-48	18.3	14%	>30	11% @ 1
1512-01	18	18%	4%	
1512-02	19.2	19%	3%	
1512-04	10.8	17%	8%	
1512-05	16.7	1.7	10%	
1512-06	12.6	23.6	4%	
1512-07	3.6	30	4%	
1512-11	30	22%	5%	
1512-12	11.3	10.5	5%	
1512-14	3.2	27.9	7%	
1512-15	20.9	23%	6%	
1512-16	6.5	34%	10%	
1512-17	39%	6%	4%	
1512-19	14.3	17%	3%	
1512-20	11.2	9%	8%	
1512-23	14.6	34%	6%	
1512-26	26.9	7%	5%	
1512-27	16.5	13%	3%	
1512-29	47%	8%	4%	
1512-31	43%	9%	14%	
1512-32	21.9	10%	5%	
1512-35	22.5	23%	4%	
1512-36	3.8	48%	9%	
1512-39	6	47%	4%	
1512-40	40%	9%	3%	
1512-41	30	4.4	4%	
1512-42	25	15%	1%	
1512-43	11	27%	9%	
1512-44	43%	20%	6%	
1512-45	27%	16%	11%	
1512-46	11.7	27.2	10%	
1512-47	3.5	0.3	13%	
1515-01	7	25%	>30	2.3
1515-02	3.8	26%	>30	1.5
1515-03	1.9	40%	>30	2.9
1515-04	5.2	43%	>30	2.8
1515-05	4	9.8	>30	0.9
1515-06	1.7	6.2	>30	1.1
1515-07	14.2	3.8	>30	1.2
1515-08	11%	9%	>30	2
1515-09	4.1	44%	>30	1.1
1515-10	5.7	38%	>30	1.1
1515-11	4.3	44%	>30	1.9
1515-12	6.3	9%	>30	8.2
1515-13	1.4	37%	>30	1.3
1515-14	2.9	7%	>30	4

TABLE 8-continued

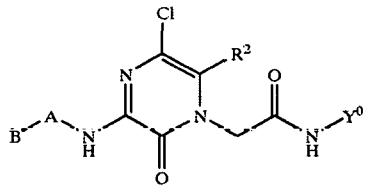


General Structure

Inhibitory Activity of Pyrazinones toward TF-VIIA, Thrombin II, Factor Xa, And Trypsin II.

Ex. No.	IC50 or % Inhibition TF-VIIa (30 uM)	IC50 or % Inhibition Thrombin II (30 uM)	IC50 or % Inhibition Factor Xa (30 uM)	IC50 or % Inhibition Trpysin II (30 uM)
1515-15	2.6	1%	>30	11.7
1515-16	8.8	3%	>30	17.3
1515-17	4.4	43%	>30	3.2
1515-18	0.6	4.4	>30	1.1
1515-19	24.2	9.4	>30	8.4
1515-20	32%	36%	>30	1.2
1515-22	4.2	25%	>30	2.7
1515-23	6.2	18%	>30	8.5
1515-24	1.6	22%	>30	6.7
1515-25	2.9	3.5	>30	1.4
1515-26	1.6	3.3	>30	1.3
1515-27	1.1	2	>30	2
1515-28	3	2.1	>30	2.4
1515-29	5.2	1	>30	2.2
1515-30	1.2	0.4	>30	1.2
1515-31	8.1	0.1	>30	1.2
1515-32	25%	6.3	>30	1.4
1515-33	2.3	1.1	>30	1
1515-34	4.4	2.4	>30	1.3
1515-35	1.8	1.2	>30	1.1
1515-36	2.7	8.6	>30	5.4
1515-37	3.6	4	>30	1.6
1515-38	1.8	2.5	>30	1.4
1515-39	1.6	1.7	>30	2.3
1515-40	4.4	1.7	>30	2.4
1515-41	2.6	0.4	>30	1
1515-42	1.8	0.5	>30	1.4
1515-43	6.8	0.1	>30	1.1
1515-44	30%	7.7	>30	1.4
1515-45	2.9	1	>30	1.2
1515-46	4.8	2	>30	1.3
1515-47	3.1	1.6	>30	1.8
1515-48	4.1	6.2	>30	4.1
1517-01	1.2	1.8	0	0.38
1517-03	9	36%	0	2
1517-04	5.7	14.5	0	4.5
1517-05	4.6	29.8	0	1.2
1517-06	2.5	11.9	0	1.6
1517-07	0.4	1.1	0	0.32
1517-08	43%	30%	0	3.8
1517-09	2.6	30%	0	1.5
1517-10	2	38%	0	2.1
1517-11	3	22%	0	1.9
1517-12	0.8	18.1	0	2.1
1517-13	0.6	0.1	0	0.28
1517-14	30%	20%	0	8.4
1517-15	3.1	5.3	0	1.5
1517-16	3.4	26.1	0	5.1
1517-17	1.8	4.1	0	0.85
1517-18	1.3	1	0	0.98
1517-19	0.9	0.1	0	0.4
1517-20	22%	25%	0	7.3
1517-23	2.3	4.3	0	1.4
1517-24	1.8	1	0	0.84
1517-25	1.4	16.5	0	0.72
1517-26	1.8	2.1	0	0.32
1517-29	0.9	1.2	0	0.3
1517-31	9.1	19.9	0	0.69
1517-33	0.4	5.2	0	0.21

TABLE 8-continued

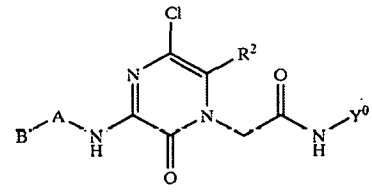


General Structure

Inhibitory Activity of Pyrazinones toward TF-VIIA, Thrombin II, Factor Xa, And Trypsin II.

Ex. No.	IC50 or % Inhibition TF-VIIa (30 uM)	IC50 or % Inhibition Thrombin II (30 uM)	IC50 or % Inhibition Factor Xa (30 uM)	IC50 or % Inhibition Trpysin II (30 uM)
1517-35	33%	9%	0	23.6
1517-36	3	28.1	0	0.61
1517-37	0.4	3.7	0	0.28
1517-38	0.7	8.7	0	0.33
1517-39	0.7	20.4	0	0.43
1517-40	1.2	6.4	0	0.37
1517-41	2.2	16.6	0	0.59
1517-43	25%	4%	0	43%
1517-44	0.2	4	0	0.22
1517-46	0.4	11.3	0	0.36
1517-47	9.8	5.2	0	0.65
1517-48	1.2	2.4	0	0.29
1522-02	0.5	20	>30	0.2
1522-05	0.6	10	>30	0.2
1522-06	5.5	20	>30	0.3
1522-07	0.47	1	>30	0.15
1522-08	0.27	1	>30	0.1
1522-09	0.2	3	>30	0.2
1522-11	0.43	1	>30	0.2
1522-12	0.81	8	>30	0.3
1522-13	0.75	8	>30	0.2
1522-14	0.84	8	>30	0.2
1522-15	0.54	4	>30	0.2
1522-17	0.62	1	>30	0.35
1522-18	1.7	20	>30	0.2
1522-19	13	>30	>30	0.3
1522-20	5	>30	>30	0.2
1522-21	0.72	3	>30	0.2
1522-23	2.2	20	>30	0.3
1522-27	6.3	20	>30	0.35
1522-28	>30	>30	>30	2
1522-31	6.4	8	>30	0.35
1522-33	0.88	10	>30	0.2
1522-34	0.5	8	>30	0.2
1522-35	4	10	>30	0.35
1522-36	1	10	>30	0.3
1522-37	2	0.08	>30	0.3
1522-38	1	0.1	>30	0.3
1522-40	0.5	0.8	>30	0.2
1522-41	0.5	10	>30	0.2
1522-42	1	2	>30	0.15
1522-43	0.8	20	>30	0.3
1522-44	0.8	10	>30	0.2
1522-46	1	10	>30	0.2
1522-47	3	15	>30	2
1526-01	0.02	13.13	>30	0.15
1526-03	0.06	17.3	>30	0.15
1526-04	0.03	18.08	>30	0.16
1526-05	0.1	15	>30	0.19
1526-06	0.17	12.04	>30	0.21
1526-07	0.08	20.91	>30	0.19
1526-09	0.03	11.23	>30	0.14
1526-11	0.05	3.21	>30	0.15
1526-12	0.04	28.41	>30	0.2
1526-13	0.06	22.42	>30	0.2
1526-14	0.04	7.63	>30	0.14
1526-15	0.06	6.88	>30	0.15
1526-16	0.04	5.6	>30	0.13
1526-17	0.08	2.21	>30	0.17

TABLE 8-continued



General Structure

Inhibitory Activity of Pyrazinones toward TF-VIIA, Thrombin II, Factor Xa, And Trypsin II.

Ex. No.	IC50 or % Inhibition TF-VIIa (30 uM)	IC50 or % Inhibition Thrombin II (30 uM)	IC50 or % Inhibition Factor Xa (30 uM)	IC50 or % Inhibition Trpysin II (30 uM)
1526-19	0.04	16.97	>30	0.15
1526-21	0.05	20.03	>30	0.18
1526-23	0.03	9.45	>30	0.15
1526-24	0.04	11.06	>30	0.17
1526-25	0.14	40%	>30	0.19
1526-26	0.06	14.27	>30	0.16
1526-29	0.12	50%	>30	0.22
1526-30	0.08	21.42	>30	0.2
1526-33	0.26	29%	>30	0.24
1526-40	0.1	17.85	>30	0.22
1526-41	0.07	24.04	>30	0.16
1543-03	0.64	26%	34%	0.06
1543-05	0.06	27%	14%	0.07
1543-07	0.21	24.56	19%	0.09
1543-09	0.69	14%	12%	0.18
1543-11	0.07	16.56	24%	0.04
1543-13	0.09	41%	12%	0.06
1543-15	0.95	45%	41%	0.14
1543-19	0.22	37%	11%	0.08
1543-21	0.29	17.12	27%	0.06
1543-25	0.28	8.12	26%	0.05
1543-27	0.38	24.6	27%	0.06
1543-31	0.04	24.26	8%	0.06
1543-33	0.03	19.34	14%	0.05
1543-34	0.08	17.32	20%	0.06
1543-35	0.07	23.61	8%	0.07
1543-36	0.08	12.57	15%	0.05
1543-37	1.23	16%	16%	0.12
1543-38	0.09	18.26	14%	0.06
1543-39	0.04	12.77	14%	0.05
1543-40	0.04	11.45	10%	0.04
1543-41	3%	0%	9%	6%
1543-45	1%	0%	5%	8%
1543-46	22%	0%	11%	18%

TABLE 9

Inhibitory Activity of Pyrazinones toward Factor Xa, TF-VIIA, Thrombin II, and Trypsin II.

Example Number	% Inhibition TF-VIIa (100 vM)	% Inhibition Thrombin II (100 vM)	% Inhibition Factor Xa (100 vM)	% Inhibition Trpysin II (100 vM)
E-0001	0	0	1	0
E-0002	0	0	0	0
E-0003	0	10	0	0
E-0004	0	6	0	0
E-0005	0	0	0	0
E-0006	2	0	0	1
E-0007	0	0	0	0
E-0008	0	-0.2	0	0
E-0009	0	8	1	1
E-0010	0	5	0	0
E-0011	0	0	0	0

TABLE 9-continued

Inhibitory Activity of Pyrazinones toward Factor Xa, TF-VIIA, Thrombin II, and Trypsin II.

Example Number	% Inhibition TF-VIIa (100 vM)	% Inhibition Thrombin II (100 vM)	% Inhibition Factor Xa (100 vM)	% Inhibition Trpysin II (100 vM)
E-0012	0	0	0	0
E-0013	0	2	0	1
E-0014	0	6	0	0
E-0015	0	3	0	3
E-0016	0	10	0	4
E-0017	0	10	0	1
E-0018	1	10	0	4
E-0019	0	9	0	2
E-0020	0	13	1	4
E-0021	0	9	1	5
E-0022	0	12	0	2
E-0023	0	5	0	1
E-0024	0	0	0	1
E-0025	0	13	0	3
E-0026	0	13	0	3
E-0027	0	10	0	2
E-0028	0	8	0	3
E-0029	0	8	0	2
E-0030	0	8	0	4
E-0031	0	4	0	1
E-0032	0	6	0	3
E-0033	0	6	0	5
E-0034	0	7	6	3
E-0035	4	12	0	2
E-0036	0	1	0	0
E-0037	0	5	0	2
E-0038	0	9	0	3
E-0039	0	9	1	2
E-0040	0	7	0	4
E-0041	0	8	0	2
E-0042	0	8	0	5
E-0043	0	12	0	3
E-0044	0	9	0	3
E-0045	0	7	0	4
E-0046	0	7	0	4
E-0047	0	9	0	2
E-0048	0	1	0	0
E-0049	2	0	0	0
E-0050	0	0	0	0
E-0051	0	0	0	0
E-0052	0	0	0	0
E-0053	0	0	0	0
E-0054	0	0	0	0
E-0055	0	0	0	0
E-0056	0	0	0	0
E-0057	0	0	6	0
E-0058	0	0	0	0
E-0059	0	0	0	0
E-0060	0	0	0	0
E-0061	0	0	0	0
E-0062	0	0	0	0
E-0063	0	0	0	0
E-0064	0	0	0	0
E-0065	0	0	0	0
E-0066	0	-0.2	0	0
E-0067	0	1	0	0
E-0068	0	3	0	0
E-0069	0	0	0	0
E-0070	0	0	0	0
E-0071	0	0	0	0
E-0072	0	0	0	0
E-0073	0	0	2	6
E-0074	0	0	0	8
E-0075	0	0	0	7
E-0076	0	0	1	10
E-0077	0	0	3	7
E-0078	0	3	1	10
E-0079	0	0	4	11
E-0080	1	0	4	5
E-0081	0	24	5	8

TABLE 9-continued

Inhibitory Activity of Pyrazinones toward Factor Xa, TF-VIIA, Thrombin II, and Trypsin II.

Example Number	% Inhibition TF-VIIa (100 vM)	% Inhibition Thrombin II (100 vM)	% Inhibition Factor Xa (100 vM)	% Inhibition Trpysin II (100 vM)
E-0082	4	0	4	3
E-0083	2	53	3	6
E-0084	0	0	0	8
E-0085	0	5	0	9
E-0086	0	0	4	11
E-0087	0	0	0	10
E-0088	0	0	3	9
E-0089	3	0	4	8
E-0090	0	0	2	11
E-0091	1	0	4	8
E-0092	1	0	3	9
E-0093	0	14	0	10
E-0094	2	0	2	7
E-0095	2	0	4	9
E-0096	0	5	0	10
E-0097	0	0	3	11
E-0098	0	0	2	8
E-0099	0	0	1	10
E-0100	7	0	6	12
E-0101	11	2	10	11
E-0102	0.4	0	3	13
E-0103	2	0	3	11
E-0104	3	0	5	9
E-0105	0	0	3	12
E-0106	5	0	3	9
E-0107	4	0	6	12
E-0108	0	0	4	12
E-0109	2	0	3	12
E-0110	0	0	3	14
E-0111	4	0	1	14
E-0112	11	0	1	13
E-0113	14	0	3	11
E-0114	10	0	3	14
E-0115	15	0	3	11
E-0116	13	0	4	10
E-0117	9	0	1	9
E-0118	12	0	3	9
E-0119	13	0	5	10
E-0120	8	0	1	9
E-0121	0	8	0.1	0
E-0122	0	8	0.1	0
E-0123	0	6	0.1	1
E-0124	0	6	0.1	0
E-0125	0	4	0.1	0
E-0126	0	4	0.1	0
E-0127	0	5	0.1	0
E-0128	0	7	0.1	0
E-0129	0	5	0.1	0
E-0130	0	2	0.1	0
E-0131	0	0	0.1	1
E-0132	0	0	0.1	0
E-0133	0	5	0.1	0
E-0134	0	5	0.1	1
E-0135	0	3	0.1	2
E-0136	0	3	0.1	1
E-0137	2	3	0.1	0
E-0138	1	4	0.1	3
E-0139	0	4	0.1	3
E-0140	0	4	0.1	2
E-0141	0	4	0.1	2
E-0142	1	5	0.1	3
E-0143	1	2	0.1	1
E-0144	0	0	0.1	1
E-0145	0	5	0.1	0
E-0146	0	8	0.1	0
E-0147	0	3	0.1	1
E-0148	0	5	0.1	3
E-0149	0	4	0.1	0
E-0150	0	6	0.1	2
E-0151	0	6	0.1	3

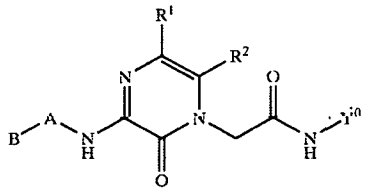
TABLE 9-continued

Inhibitory Activity of Pyrazinones toward Factor Xa, TF-VIIA, Thrombin II, and Trypsin II.

Example Number	% Inhibition TF-VIIa (100 vM)	% Inhibition Thrombin II (100 vM)	% Inhibition Factor Xa (100 vM)	% Inhibition Trpysin II (100 vM)
E-0152	0	6	0.1	4
E-0153	0	3	0.1	1
E-0154	0	5	0.1	3
E-0155	2	6	0.1	4
E-0156	0	-0.4	0.1	1
E-0157	0	5	0.1	0
E-0158	0	3	0.1	6
E-0159	0	4	0.1	1
E-0160	0	6	0.1	2
E-0161	0	6	0.1	1
E-0162	0	7	0.1	4
E-0163	0	5	0.1	0
E-0164	0	5	0.1	0
E-0165	0	7	0.1	0
E-0166	0	6	0.1	1
E-0167	0	4	0.1	1
E-0168	7	5	0.1	0
E-0169	0	2	0.1	1
E-0170	0	7	0.1	0
E-0171	0	9	0.1	2
E-0172	0	6	0.1	0
E-0173	0	5	0.1	1
E-0174	0	5	0.1	1
E-0175	0	6	0.1	2
E-0176	0	7	0.1	0
E-0177	0	6	0.1	0
E-0178	0	3	0.1	2
E-0179	0	10	0.1	0
E-0180	0	3	0.1	0
E-0181	0	5	0.1	3
E-0182	0	5	0.1	0
E-0183	0	5	0.1	2
E-0184	0	2	0.1	0
E-0185	0	3	0.1	2
E-0186	0	5	0.1	0
E-0187	0	8	0.1	1
E-0188	0	2	0.1	8
E-0189	0	6	0.1	1
E-0190	0	4	0.1	3
E-0191	0	6	0.1	0
E-0192	0	0	0.1	0
E-0193	0	5	0.1	0
E-0194	0	14	0.2	0
E-0195	0	1	0.1	0
E-0196	0	1	0.1	0
E-0197	0	3	0.1	1
E-0198	0	0	0.1	3
E-0199	0	1	0.1	2
E-0200	0	33	0.2	2
E-0201	0	1	0.1	1
E-0202	0	1	0.1	1
E-0203	0	5	0.1	2
E-0204	0	1	0.1	1
E-0205	0	1	0.1	2
E-0206	0	2	0.1	1
E-0207	0	2	0.1	1
E-0208	0	4	0.1	1
E-0209	1	3	0.1	3
E-0210	0	6	0.1	2

What we claim is:

1. A compound having the Formula:



or a pharmaceutically acceptable salt thereof, wherein;

B is selected from the group consisting of hydrido, trialkylsilyl, C2–C4 alkyl, C3–C5 alkylenyl, C3–C4 alkenyl, C3–C4 alkynyl, and C2–C4 haloalkyl, wherein each member of group B is optionally substituted at any carbon up to and including 3 atoms from the point of attachment of B to A with one or more of the group consisting of R^{32}, R^{33}, and R^{34};

R^{32}, R^{33}, and R^{34} are independently selected from the group consisting of hydrido, acetamido, haloacetamido, amidino, guanidino, alkoxy, hydroxy, amino, alkoxyamino, lower alkylamino, alkylthio, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, alkyl, halo, haloalkyl, haloalkoxy, hydroxyalkyl, carboalkoxy, carboxy, carboxamido, and cyano;

A is $(CH(R^{15}))_{pa}$—$N(R^7)$ wherein pa is an integer selected from 1 through 2 and R^7 is selected from the group consisting of hydrido and alkyl;

R^{15} is selected from the group consisting of hydrido, halo, alkyl, and haloalkyl;

R^1 is selected from the group consisting of hydrido, alkyl, cyano, halo, and haloalkyl;

R^2 is Z^0—Q;

Z^0 is a covalent single bond;

Q is selected from the group consisting of aryl and heteroaryl, wherein (a) a ring carbon in a first alpha position relative to the ring carbon at the point of attachment is optionally substituted by R^9, (b) a ring carbon in a second alpha position relative to the ring carbon at the point of attachment is optionally substituted by R^{13}, (c) a ring carbon, in a first beta position relative to the ring carbon at the point of attachment and in an alpha position relative to the ring atom optionally substituted by R^9, is optionally substituted by R^{10}, (d) a ring carbon, in a second beta position relative to the ring carbon at the point of attachment and in an alpha position relative to the ring atom optionally substituted by R^{13}, is optionally substituted by R^{12}, and (e) a ring carbon, if present, in the gamma position relative to the ring carbon at the point of attachment and in an alpha position relative to each of the ring atoms optionally substituted by R^{10} and R^{12}, respectively, is optionally substituted by R^{11};

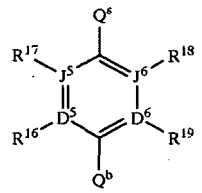
R^9, R^{11}, and R^{13} are independently selected from the group consisting of hydrido, hydroxy, amino, amidino, guanidino, lower alkylamino, alkylthio, alkylsulfonamido, alkylsulfinyl, alkylsulfonyl, amidosulfonyl, monoalkyl amidosulfonyl, alkyl, alkoxy, halo, haloalkyl, haloalkoxy, hydroxyalkyl, carboxy, carboxamido, and cyano;

R^{10} and R^{12} are independently selected from the group consisting of hydrido, acetamido, haloacetamido, amidino, guanidino, alkyl, alkoxy, hydroxy, amino,

alkoxyamino, lower alkylamino, alkylsulfonamido, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, hydroxyalkyl, aminoalkyl, carboalkoxy, carboxy, carboxyalkyl, amidocarbonyl, halo, haloalkyl, and cyano;

Y^0 is formula (IV):

(IV)



wherein D^5, D^6, J^5, and J^6 are independently selected from the group consisting of C, N, O, S and a covalent bond with the provisos that no more than one is a covalent bond, no more than one of D^5, D^6, J^5, and J^6 is O, no more than one of D^5, D^6, J^5, and J^6 is S, one of D^5, D^6, J^5, and J^6 must be a covalent bond when two of D^5, D^6, J^5, and J^6 are O and S, and no more than four of D^5, D^6, J^5, and J^6 are N, with the provisos that R^{16}, R^{17}, R^{18}, and R^{19} are each independently selected to maintain the tetravalent nature of carbon, trivalent nature of nitrogen, the divalent nature of sulfur, and the divalent nature of oxygen;

R^{16}, R^{17}, R^{18}, and R^{19} are independently selected from the group consisting of hydrido, amidino, guanidino, carboxy, haloalkylthio, alkoxy, hydroxy, amino, lower alkylamino, alkylthio, alkylsulfinyl, alkylsulfonyl, alkanoyl, haloalkanoyl, alkyl, halo, haloalkyl, haloalkoxy, hydroxyalkyl, aminoalkyl, and cyano;

Q^b is selected from the group consisting of $NR^{20}R^{21}$, hydrido, $C(NR^{25})NR^{23}R^{24}$, and $N(R^{26})C(NR^{25})N(R^{23})(R^{24})$, with the provisos that no more than one of R^{20} and R^{21} is hydroxy and that no more than one of R^{23} and R^{24} is hydroxy;

R^{20}, R^{21}, R^{23}, R^{24}, R^{25}, and R^{26} are independently selected from the group consisting of hydrido, alkyl, and hydroxy; and

Q^s is selected from the group consisting of a single covalent bond, CH_2, and CH_2CH_2.

2. The compound as recited in claim 1 or a pharmaceutically acceptable salt thereof, wherein;

B is selected from the group consisting of ethyl, 2-propenyl, 2-propynyl, propyl, isopropyl, trimethylene, tetramethylene, butyl, 2-butenyl, 3-butenyl, 2-butynyl, sec-butyl, tert-butyl, isobutyl, 2-methylpropenyl, 2,2,2-trifluoroethyl, 3,3,3-trifluoropropyl, and 2,2-difluoropropyl, wherein each member of group B is optionally substituted at any carbon up to and including 3 atoms from the point of attachment of B to A with one or more of the group consisting of R^{32}, R^{33}, and R^{34};

R^{32}, R^{33}, and R^{34} are independently selected from the group consisting of hydrido, amidino, guanidino, carboxy, methoxy, ethoxy, isopropoxy, propoxy, hydroxy, amino, methoxyamino, ethoxyamino, acetamido, trifluoroacetamido, N-methylamino, dimethylamino, N-ethylamino, methylthio, ethylthio, isopropylthio, trifluoromethyl, pentafluoroethyl, 2,2,2-trifluoroethyl, trifluoromethoxy, 1,1,2,2-tetrafluoroethoxy, fluoro, chloro, bromo, amidosulfonyl, N-methylamidosulfonyl, N,N-dimethylamidosulfonyl, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 2,2,2-trifluoro-1-hydroxyethyl, methoxycarbonyl, ethoxycarbonyl, amidocarbonyl, N-methylamidocarbonyl, N,N-dimethylamidocarbonyl, and cyano;

A is $CH_2N(CH_3)$, $CH_2N(CH_2CH_3)$, $CH_2CH_2N(CH_3)$, or $CH_2CH_2N(CH_2CH_3)$;

R^1 is selected from the group consisting of hydrido, methyl, ethyl, propyl, trifluoromethyl, pentafluoroethyl, 2,2,2-trifluoroethyl, 2,2,3,3,3-pentafluoropropyl, fluoro, chloro, and bromo;

R^2 is Z^0—Q;

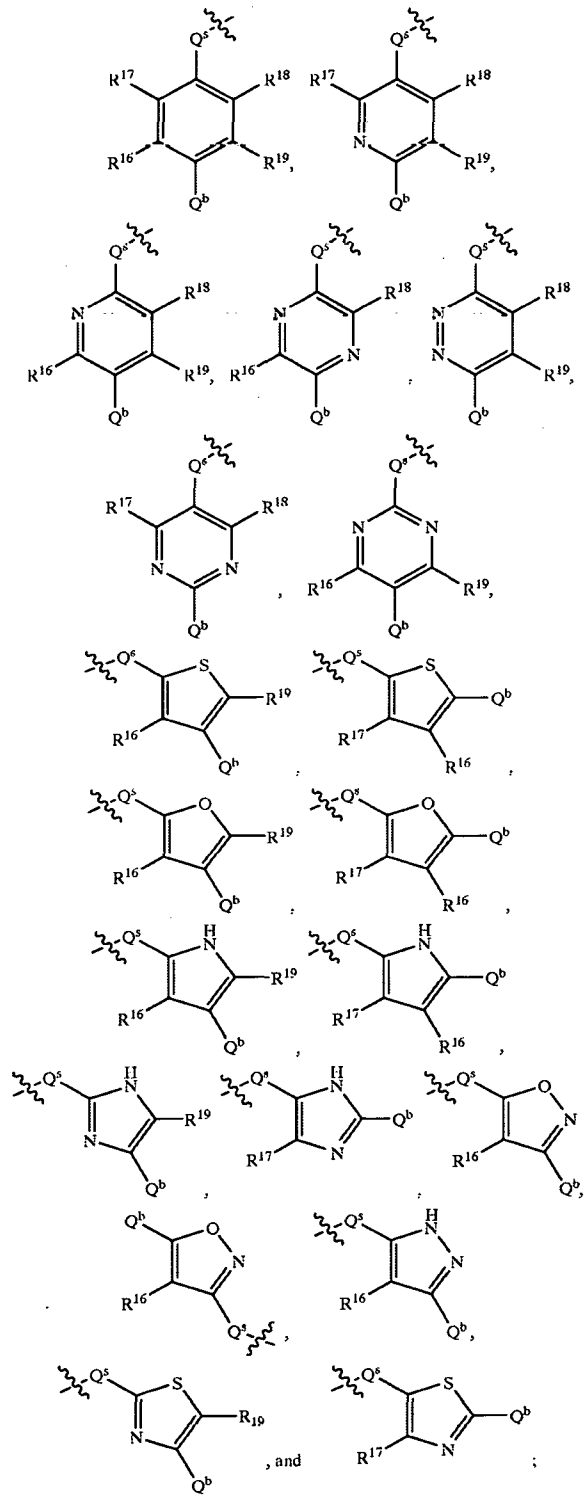
Z^0 is a covalent single bond;

Q is selected from the group consisting of phenyl and 2-thienyl, 3-thienyl, 2-furyl, 3-furyl, 2-pyrrolyl, 3-pyrrolyl, 2-imidazolyl, 4-imidazolyl, 3-pyrazolyl, 4-pyrazolyl, 2-thiazolyl, 3-isoxazolyl, 5-isoxazolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrazinyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 3-pyridazinyl, 4-pyridazinyl, and 1,3,5-triazin-2-yl heteroaryl rings, wherein (a) a ring carbon in a first alpha position relative to the ring carbon at the point of attachment is optionally substituted by R^9, (b) a ring carbon in a second alpha position relative to the ring carbon at the point of attachment is optionally substituted by R^{13}, (c) a ring carbon, in a first beta position relative to the ring carbon at the point of attachment and in an alpha position relative to the ring atom optionally substituted by R^9, is optionally substituted by R^{10}, (d) a ring carbon, in a second beta position relative to the ring carbon at the point of attachment and in an alpha position relative to the ring atom optionally substituted by R^{13}, is optionally substituted by R^{12}, and (e) a ring carbon, if present, in the gamma position relative to the ring carbon at the point of attachment and in an alpha position relative to each of the ring atoms optionally substituted by R^{10} and R^{12}, respectively, is optionally substituted by R^{11};

R^9, R^{11}, and R^{13} are independently selected from the group consisting of hydrido, amidino, guanidino, carboxy, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, isopropoxy, propoxy, hydroxy, amino, N-methylamino, N,N-dimethylamino, N-ethylamino, methylthio, ethylthio, isopropylthio, trifluoromethyl, pentafluoroethyl, 2,2,2-trifluoroethyl, 2,2,3,3,3-pentafluoropropyl, trifluoromethoxy, 1,1,2,2-tetrafluoroethoxy, fluoro, chloro, bromo, methanesulfonamido, amidosulfonyl, N-methylamidosulfonyl, N,N-dimethylamidosulfonyl, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 2,2,2-trifluoro-1-hydroxyethyl, amidocarbonyl, N-methylamidocarbonyl, N,N-dimethylamidocarbonyl, and cyano;

R^{10} and R^{12} are independently selected from the group consisting of hydrido, amidino, guanidino, carboxy, carboxymethyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, isopropoxy, propoxy, hydroxy, amino, methoxyamino, ethoxyamino, acetamido, trifluoroacetamido, aminomethyl, 1-aminoethyl, 2-aminoethyl, N-methylamino, dimethylamino, N-ethylamino, methanesulfonamido, amidosulfonyl, N-methylamidosulfonyl, N,N-dimethylamidosulfonyl, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 2,2,2-trifluoro-1-hydroxyethyl, methoxycarbonyl, ethoxycarbonyl, amidocarbonyl, N-methylamidocarbonyl, N,N-dimethylamidocarbonyl, fluoro, chloro, bromo, and cyano;

Y^0 is selected from the group consisting of:



, and

R^{16}, R^{17}, R^{18}, and R^{19} are independently selected from the group consisting of hydrido, methyl, ethyl, isopropyl, propyl, carboxy, amidino, guanidino, methoxy, ethoxy, isopropoxy, propoxy, hydroxy, amino, aminomethyl, 1-aminoethyl, 2-aminoethyl, N-methylamino, dimethylamino, N-ethylamino, methylthio, ethylthio, isopropylthio, trifluoromethylthio, methylsulfinyl, ethylsulfinyl, methylsulfonyl, ethylsulfonyl, trifluoromethyl, pentafluoroethyl, 2,2,2-trifluoroethyl, 2,2,3,3,3-pentafluoropropyl, trifluoromethoxy, 1,1,2,2-tetrafluoroethoxy, fluoro, chloro, bromo, amidosulfonyl, N-methylamidosulfonyl, N,N-dimethylamidosulfonyl, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 2,2,2-trifluoro-1-hydroxyethyl, and cyano;

Q^b is selected from the group consisting of $NR^{20}R^{21}$, hydrido, $C(NR^{25})NR^{23}R^{24}$, and $N(R^{26})C(NR^{25})N(R^{23})(R^{24})$, with the provisos that no more than one of R^{20}, R^{21}, R^{23}, and R^{24} can be hydroxy, when any two of the group consisting of R^{20}, R^{21}, R^{23}, and R^{24} are bonded to the same atom;

R^{20}, R^{21}, R^{23}, R^{24}, R^{25}, and $R^{25}$are independently selected from the group consisting of hydrido, methyl, ethyl, propyl, butyl, isopropyl, and hydroxy; and

Q^s is selected from the group consisting of a single covalent bond, CH_2, and CH_2CH_2.

3. The compound as recited in claim **1**, or a pharmaceutically acceptable salt thereof, wherein;

A is selected from the group consisting of $CH_2N(CH_3)$, $CH_2N(CH_2CH_3)$, $CH_2CH_2N(CH_3)$, and $CH_2CH_2N(CH_2CH_3)$;

R^1 is selected from the group consisting of hydrido, methyl, ethyl, trifluoromethyl, pentafluoroethyl, 2,2,2-trifluoroethyl, fluoro, chloro, and bromo;

R^2 is Z^0—Q;

Z^0 is a covalent single bond;

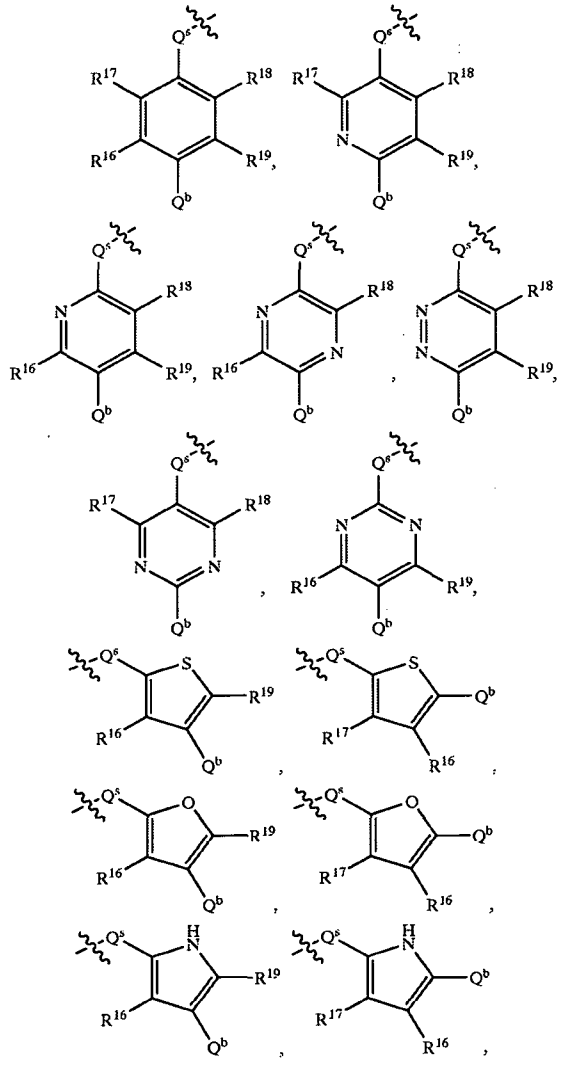
Q is selected from the group consisting of phenyl and 2-thienyl, 3-thienyl, 2-furyl, 3-furyl, 2-pyrrolyl, 3-pyrrolyl, 2-imidazolyl, 4-imidazolyl, 3-pyrazolyl, 4-pyrazolyl, 2-thiazolyl, 3-isoxazolyl, 5-isoxazolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrazinyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 3-pyridazinyl, 4-pyridazinyl, and 1,3,5-triazin-2-yl heteroaryl rings, wherein (a) a ring carbon in a first alpha position relative to the ring carbon at the point of attachment is optionally substituted by R^9, (b) a ring carbon in a second alpha position relative to the ring carbon at the point of attachment is optionally substituted by R^{13}, (c) a ring carbon, in a first beta position relative to the ring carbon at the point of attachment and in an alpha position relative to the ring atom optionally substituted by R^9, is optionally substituted by R^{10}, (d) a ring carbon, in a second beta position relative to the ring carbon at the point of attachment and in an alpha position relative to the ring atom optionally substituted by R^{13}, is optionally substituted by R^{12}, and (e) a ring carbon, if present, in the gamma position relative to the ring carbon at the point of attachment and in an alpha position relative to each of the ring atoms optionally substituted by R^{10} and R^{12}, respectively, is optionally substituted by R^{11};

R^9, R^{11}, and R^{13} are independently selected from the group consisting of hydrido, amidino, guanidino, carboxy, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, isopropoxy, propoxy, hydroxy, amino, N-methylamino, N,N-dimethylamino, N-ethylamino, methylthio, ethylthio, isopropylthio, trifluoromethyl, pentafluoroethyl, 2,2,2-trifluoroethyl, 2,2,3,3,3-pentafluoropropyl, trifluoromethoxy, 1,1,2,2-tetrafluoroethoxy, fluoro, chloro, bromo,

methanesulfonamido, amidosulfonyl, N-methylamidosulfonyl, N,N-dimethylamidosulfonyl, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 2,2,2-trifluoro-1-hydroxyethyl, amidocarbonyl, N-methylamidocarbonyl, N,N-dimethylamidocarbonyl, and cyano;

R^{10} and R^{12} are independently selected from the group consisting of hydrido, amidino, guanidino, carboxy, carboxymethyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, isopropoxy, propoxy, hydroxy, amino, methoxyamino, ethoxyamino, acetamido, trifluoroacetamido, aminomethyl, 1-aminoethyl, 2-aminoethyl, N-methylamino, dimethylamino, N-ethylamino, methanesulfonamido, amidosulfonyl, N-methylamidosulfonyl, N,N-dimethylamidosulfonyl, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 2,2,2-trifluoro-1-hydroxyethyl, methoxycarbonyl, ethoxycarbonyl, amidocarbonyl, N-methylamidocarbonyl, N,N-dimethylamidocarbonyl, fluoro, chloro, bromo, and cyano;

Y^0 is selected from the group consisting of:



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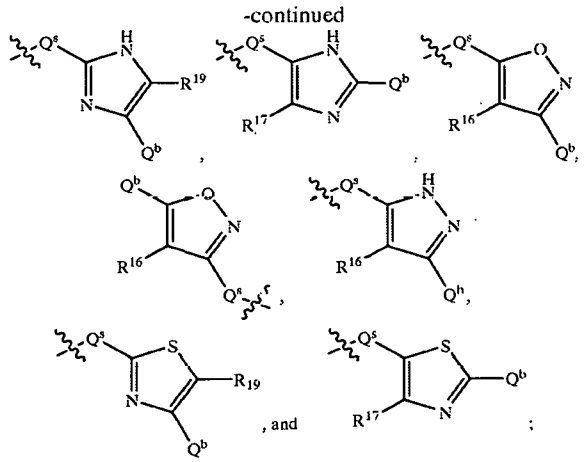


, and

;

R^{16}, R^{17}, R^{18}, and R^{19} are independently selected from the group consisting of hydrido, methyl, ethyl, isopropyl, propyl, amidino, guanidino, methoxy, ethoxy, isopropoxy, propoxy, hydroxy, amino, aminomethyl, 1-aminoethyl, 2-aminoethyl, N-N-methylamino, dimethylamino, N-ethylamino, methylthio, ethylthio, isopropylthio, trifluoromethylthio, methylsulfinyl, ethylsulfinyl, methylsulfonyl, ethylsulfonyl, trifluoromethyl, pentafluoroethyl, 2,2,2-trifluoroethyl, 2,2,3,3,3-pentafluoropropyl, trifluoromethoxy, 1,1,2,2-tetrafluoroethoxy, fluoro, chloro, bromo, amidosulfonyl, N-methylamidosulfonyl, N,N-dimethylamidosulfonyl, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 2,2,2-trifluoro-1-hydroxyethyl, and cyano;

Q^b is selected from the group consisting of $NR^{20}R^{21}$, $C(NR^{25})NR^{23}R^{24}$, and $N(R^{26})C(NR^{25})N(R^{23})(R^{24})$, with the provisos that no more than one of R^{20}, R^{21}, R^{23}, and R^{24} can be hydroxy when any two of the group consisting of R^{20}, R^{21}, R^{23}, and R^{24} are bonded to the same atom;

R^{20}, R^{21}, R^{23}, R^{24}, R^{25}, and R^{26} are independently selected from the group consisting of hydrido, methyl, ethyl, propyl, butyl, isopropyl, and hydroxy; and

Q^s is selected from the group consisting of a single covalent bond, CH_2, and CH_2CH_2.

4. The compound as-recited in claim **3** or a pharmaceutically acceptable salt thereof, wherein;

A is selected from the group consisting of $CH_2N(CH_3)$, $CH_2N(CH_2CH_3)$, $CH_2CH_2N(CH_3)$, and $CH_2CH_2N(CH_2CH_3)$;

R^1 is selected from the group consisting of hydrido, methyl, ethyl, propyl, trifluoromethyl, pentafluoroethyl, 2,2,2-trifluoroethyl, fluoro, chloro, and bromo;

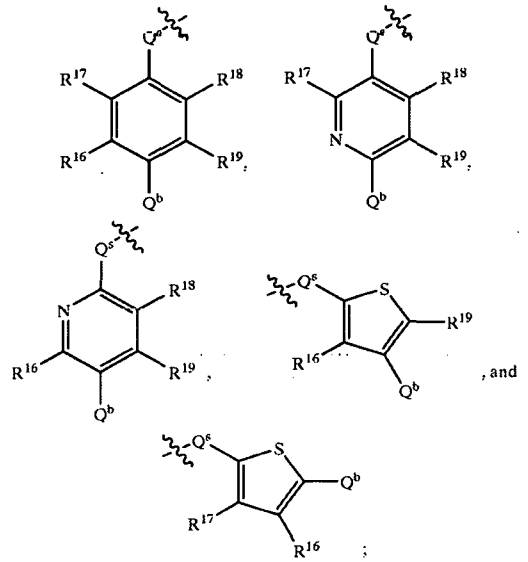
R^2 is Z^0—Q;

Z^0 is a covalent single bond;

Q is selected from the group consisting of 5-amino-3-amidocarbonylphenyl, 5-amino-2-fluorophenyl, 3-amino-5-hydroxymethylphenyl, 5-amino-3-methoxycarbonylphenyl, 3-amidinophenyl, 3-amino-2-methylphenyl, 5-amino-2-methylthiophenyl, 3-aminophenyl, benzyl, 3-carboxyphenyl, 3-carboxy-5-hydroxyphenyl, 3-carboxy-5-aminophenyl, 3-chlorophenyl, 2-chlorophenyl, 3-cyanophenyl, 3-dimethylaminophenyl, 2-fluorophenyl,

3-fluorophenyl, 2-hydroxyphenyl, 3-hydroxyphenyl, 3-methanesulfonylaminophenyl, 2-methoxyphenyl, 3-methoxyphenyl, 3-methoxyaminophenyl, 3-methoxycarbonylphenyl, 2-methylaminophenyl, 3-methylaminophenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, phenyl, 3-trifluoroacetamidophenyl, 3-trifluoromethylphenyl, 2-trifluoromethylphenyl, 5-amino-2-thienyl, 5-amino-3-thienyl, 3-bromo-2-thienyl, 3-pyridyl, 4-pyridyl, 2-thienyl, and 3-thienyl;

Y^0 is selected from the group consisting of:



, and

R^{16} and R^{19} are independently selected from the group consisting of: hydrido, amidino, amino, aminomethyl, methoxy, methylamino, hydroxy, hydroxymethyl, fluoro, chloro, and cyano;

R^{17} and R^{18} are independently selected from the group consisting of hydrido, fluoro, chloro, hydroxy, hydroxymethyl, amino, carboxy, and cyano;

Q^b is selected from the group consisting of hydrido and $C(NR^{25})NR^{23}R^{24}$;

R^{23}, R^{24}, and $R^{25}$are independently selected from the group consisting of hydrido and methyl; and

Q^s is CH_2.

5. A compound, or a pharmaceutically acceptable salt thereof, where said compound is selected from the group consisting of:

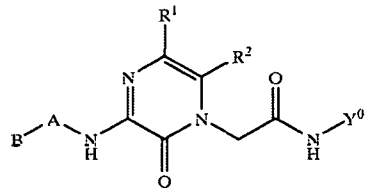
6-[3-aminophenyl]-5-chloro-N-[[4-iminomethylphenyl] methyl]-3-[N,N-dimethylhydrazino]-2-oxo-1(2H)-pyrazineacetamide;

6-[3-aminophenyl]-5-chloro-3-[N-ethyl-N-methylhydrazino]-N-[[4-iminomethylphenyl]methyl]-2-oxo-1(2H)-pyrazineacetamide;

6-[3-aminophenyl]-5-chloro-3-[N,N-diethylhydrazino]-N-[[4-iminomethylphenyl]methyl]-2-oxo-1(2H)-pyrazineacetamide; and

6-[3-aminophenyl]-3-[N-(azetidin-1-yl)amino]-5-chloro-N-[[4-iminomethylphenyl]methyl]-2-oxo-1(2H)-pyrazineacetamide.

6. A compound having the Formula:



or a pharmaceutically acceptable salt thereof, wherein;

B is selected from the group consisting of hydrido C2–C8 alkyl, C3–C8 alkenyl, C3–C8 alkynyl, and C2–C8 haloalkyl, wherein each member of group B is optionally substituted at any carbon up to and including 6 atoms from the point of attachment of B to A with one or more of the group consisting of R^{32}, R^{33}, R^{34}, R^{35}, and R^{36};

R^{32}, R^{33}, R^{34}, R^{35}, and R^{36} are independently selected from the group consisting of hydrido, acetamido, haloacetamido, amidino, guanidino, alkoxy, hydroxy, amino, alkoxyamino, lower alkylamino, alkylthio, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, alkyl, halo, haloalkyl, haloalkoxy, hydroxyalkyl, carboalkoxy, carboxy, carboxamido, cyano, and Q^b;

Q^b is selected from the group consisting of $NR^{20}R^{21}$, hydrido, $C(NR^{25})NR^{23}R^{24}$, and $N(R^{26})C(NR^{25})N(R^{23})(R^{24})$, with the provisos that no more than one of R^{20} and R^{21} is hydroxy and that no more than one of R^{23} and R^{24} is hydroxy;

R^{20}, R^{21}, R^{23}, R^{24}, R^{25}, and R^{26} are independently selected from the group consisting of hydrido, alkyl, and hydroxy;

A is selected from the group consisting of single covalent bond and $(CH(R^{15}))_{pa}$—$(W^7)_{rr}$ wherein rr is an integer selected from 0 through 1, pa is an integer selected from 0 through 3, and W^7 is selected from the group consisting of $(R^7)NC(O)$ and $N(R^7)$;

R^7 is selected from the group consisting of hydrido, hydroxy and alkyl;

R^{15} is selected from the group consisting of hydrido, halo, alkyl, and haloalkyl;

R^1 is selected from the group consisting of hydrido, alkyl, cyano, haloalkyl, and halo;

R^2 is Z^0—Q;

Z^0 is a covalent single bond;

Q is selected from the group consisting of aryl and heteroaryl wherein (a) a ring carbon in a first alpha position relative to the ring carbon at the point of attachment is optionally substituted by R^9, (b) a ring carbon in a second alpha position relative to the ring carbon at the point of attachment is optionally substituted by R^{13}, (c) a ring carbon, in a first beta position relative to the ring carbon at the point of attachment and in an alpha position relative to the ring atom optionally substituted by R^9, is optionally substituted by R^{10}, (d) a ring carbon, in a second beta position relative to the ring carbon at the point of attachment and in an alpha position relative to the ring atom optionally substituted by R^{13}, is optionally substituted by R^{12}, and (e) a ring carbon, if present, in the gamma position relative to the ring carbon at the point of attachment and in an alpha position relative to each of the ring atoms optionally

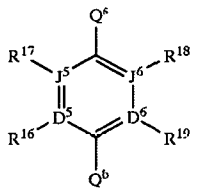
substituted by R^{10} and R^{12}, respectively, is optionally substituted by R^{11};

R^9, R^{11}, and R^{13} are independently selected from the group consisting of hydrido, hydroxy, amino, amidino, guanidino, lower alkylamino, alkylthio, alkylsulfonamido, alkylsulfinyl, alkylsulfonyl, amidosulfonyl, monoalkyl amidosulfonyl, alkyl, alkoxy, halo, haloalkyl, haloalkoxy, hydroxyalkyl, carboxy, carboxamido, and cyano;

R^{10} and R^{12} are independently selected from the group consisting of hydrido, acetamido, haloacetamido, amidino, guanidino, alkyl, alkoxy, hydroxy, amino, alkoxyamino, lower alkylamino, alkylsulfonamido, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, hydroxyalkyl, aminoalkyl, carboalkoxy, carboxy, carboxyalkyl, amidocarbonyl, halo, haloalkyl, and cyano;

Y^0 is formula (IV):

(IV)



wherein D^5, D^6, J^5, and J^6 are independently selected from the group consisting of C, N, O, S and a covalent bond with the provisos that no more than one is a covalent bond, no more than one of D^5, D^6, J^5, and J^6 is O, no more than one of D^5, D^6, J^5, and J^6 is S, one of D^5, D^6, J^5, and J^6 must be a covalent bond when two of D^5, D^6, J^5, and J^6 are O and S, and no more than four of D^5, D^6, J^5, and J^6 are N;

R^{16}, R^{17}, R^{18}, and R^{19} are independently selected from the group consisting of hydrido, amidino, guanidino, carboxy, haloalkylthio, alkoxy, hydroxy, amino, lower alkylamino, alkylthio, alkylsulfinyl, alkylsulfonyl, alkanoyl, haloalkanoyl, alkyl, halo, haloalkyl, haloalkoxy, hydroxyalkyl, aminoalkyl, and cyano; and

Q^s is selected from the group consisting of a single covalent bond, CH_2, and CH_2CH_2.

7. The compound as recited in claim 6 or a pharmaceutically acceptable salt thereof, wherein;

B is selected from the group consisting of hydrido, ethyl, 2-propynyl, 2-propenyl, propyl, isopropyl, butyl, 2-butenyl, 3-butenyl, 2-butynyl, sec-butyl, tert-butyl, isobutyl, 2-methylpropenyl, 1-pentyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 2-pentynyl, 3-pentynyl, 2-pentyl, 1-methyl-2-butenyl, 1-methyl-3-butenyl, 1-methyl-2-butynyl, 3-pentyl, 1-ethyl-2-propenyl, 2-methylbutyl, 2-methyl-2-butenyl, 2-methyl-3-butenyl, 2-methyl-3-butynyl, 3-methylbutyl, 3-methyl-2-butenyl, 3-methyl-3-butenyl, 1-hexyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, 2-hexyl, 1-methyl-2-pentenyl, 1-methyl-3-pentenyl, 1-methyl-4-pentenyl, 1-methyl-2-pentynyl, 1-methyl-3-pentynyl, 3-hexyl, 1-ethyl-2-butenyl, 1-ethyl-3-butenyl, 1-propyl-2-propenyl, 1-ethyl-2-butynyl, 1-heptyl, 2-heptenyl, 3-heptenyl, 4-heptenyl, 5-heptenyl, 6-heptenyl, 2-heptynyl, 3-heptynyl, 4-heptynyl, 5-heptynyl, 2-heptyl, 1-methyl-2-hexenyl, 1-methyl-3-hexenyl, 1-methyl-4-hexenyl, 1-methyl-5-hexenyl, 1-methyl-2-hexynyl, 1-methyl-3-hexynyl, 1-methyl-4-hexynyl, 3-heptyl, 1-ethyl-2-pentenyl, 1-ethyl-3-pentenyl, 1-ethyl-4-pentenyl, 1-butyl-2-propenyl, 1-ethyl-2-pentynyl, 1-ethyl-3-pentynyl, 2,2,2-trifluoroethyl, 2,2-difluoropropyl, 4-trifluoromethyl-5,5,5-trifluoropentyl, 4-trifluoromethylpentyl, 5,5,6,6,6-pentafluorohexyl, and 3,3,3-trifluoropropyl, wherein each member of group B is optionally substituted at any carbon up to and including 5 atoms from the point of attachment of B to A with one or more of the group consisting of R^{32}, R^{33}, R^{34}, R^{35}, and R^{36};

R^{32}, R^{33}, R^{34}, R^{35}, and R^{36} are independently selected from the group consisting of hydrido, amidino, guanidino, carboxy, methoxy, ethoxy, isopropoxy, propoxy, hydroxy, amino, methoxyamino, ethoxyamino, acetamido, trifluoroacetamido, N-methylamino, dimethylamino, N-ethylamino, methylthio, ethylthio, isopropylthio, trifluoromethyl, pentafluoroethyl, 2,2,2-trifluoroethyl, 2,2,3,3,3-pentafluoropropyl, trifluoromethoxy, 1,1,2,2-tetrafluoroethoxy, fluoro, chloro, bromo, amidosulfonyl, N-methylamidosulfonyl, N,N-dimethylamidosulfonyl, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 2,2,2-trifluoro-1-hydroxyethyl, methoxycarbonyl, ethoxycarbonyl, amidocarbonyl, N-methylamidocarbonyl, N,N-dimethylamidocarbonyl, cyano, and Q^b;

Q^b is selected from the group consisting of $NR^{20}R^{21}$, hydrido, $C(NR^{25})NR^{23}R^{24}$, and $N(R^{26})C(NR^{25})N(R^{23})(R^{24})$, with the provisos that no more than one of R^{20} and R^{21} is hydroxy and that no more than one of R^{23} and R^{24} is hydroxy;

R^{20}, R^{21}, R^{23}, R^{24}, R^{25}, and R^{26} are independently selected from the group consisting of hydrido, methyl, ethyl, propyl, butyl, isopropyl, and hydroxy;

A is selected from the group consisting of single covalent bond, NH, $N(CH_3)$, N(OH), CH_2, CH_3CH, CF_3CH, NHC(O), $N(CH_3)C(O)$, C(O)NH, $C(O)N(CH_3)$, CH_2CH_2, $CH_2CH_2CH_2$, CH_3CHCH_2, and CF_3CHCH_2;

R^1 is selected from the group consisting of hydrido, methyl, ethyl, propyl, trifluoromethyl, pentafluoroethyl, 2,2,2-trifluoroethyl, 2,2,3,3,3-pentafluoropropyl, fluoro, chloro, and bromo;

R^2 is Z^0—Q;

Z^0 is a covalent single bond;

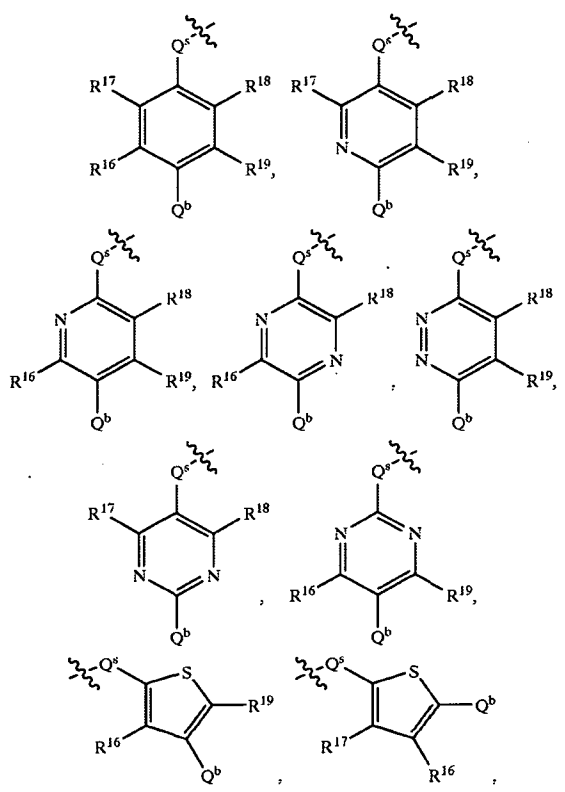
Q is selected from the group consisting of phenyl and 2-thienyl, 3-thienyl, 2-furyl, 3-furyl, 2-pyrrolyl, 3-pyrrolyl, 2-imidazolyl, 4-imidazolyl, 3-pyrazolyl, 4-pyrazolyl, 2-thiazolyl, 3-isoxazolyl, 5-isoxazolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrazinyl, 2pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 3-pyridazinyl, 4-pyridazinyl, and 1,3,5-triazin-2-yl heteroaryl rings, wherein (a) a ring carbon in a first alpha position relative to the ring carbon at the point of attachment is optionally substituted by R^9, (b) a ring carbon in a second alpha position relative to the ring carbon at the point of attachment is optionally substituted by R^{13}, (c) a ring carbon, in a first beta position relative to the ring carbon at the point of attachment and in an alpha position relative to the ring atom optionally substituted by R^9, is optionally substituted by R^{10}, (d) a ring carbon, in a second beta position relative to the ring carbon at the point of attachment and in an alpha position relative to the ring atom optionally substituted by R^{13}, is optionally substituted by R^{12}, and (e) a ring carbon, if present, in the gamma position relative to the ring carbon at the point of attachment and in an alpha

position relative to each of the ring atoms optionally substituted by R^{10} and R^{12}, respectively, is optionally substituted by R^{11};

R^9, R^{11}, and R^{13} are independently selected from the group consisting of hydrido, amidino, guanidino, carboxy, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, isopropoxy, propoxy, hydroxy, amino, N-methylamino, N,N-dimethylamino, N-ethylamino, methylthio, ethylthio, isopropylthio, trifluoromethyl, pentafluoroethyl, 2,2,2-trifluoroethyl, 2,2,3,3,3-pentafluoropropyl, trifluoromethoxy, 1,1,2,2-tetrafluoroethoxy, fluoro, chloro, bromo, methanesulfonamido, amidosulfonyl, N-methylamidosulfonyl, N,N-dimethylamidosulfonyl, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 2,2,2-trifluoro-1-hydroxyethyl, amidocarbonyl, N-methylamidocarbonyl, N,N-dimethylamidocarbonyl, and cyano;

R^{10} and R^{12} are independently selected from the group consisting of hydrido, amidino, guanidino, carboxy, carboxymethyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, isopropoxy, propoxy, hydroxy, amino, methoxyamino, ethoxyamino, acetamido, trifluoroacetamido, aminomethyl, 1-aminoethyl, 2-aminoethyl, N-methylamino, dimethylamino, N-ethylamino, methanesulfonamido, amidosulfonyl, N-methylamidosulfonyl, N,N-dimethylamidosulfonyl, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 2,2,2-trifluoro-1-hydroxyethyl, methoxycarbonyl, ethoxycarbonyl, amidocarbonyl, N-methylamidocarbonyl, N,N-dimethylamidocarbonyl, fluoro, chloro, bromo, and cyano;

Y^0 is selected from the group consisting of:



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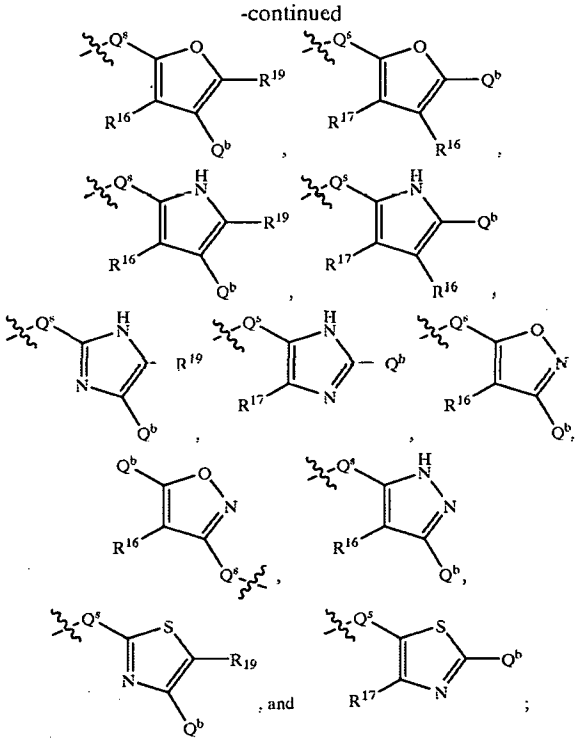


R^{16}, R^{17}, R^{18}, R^{19} are independently selected from the group consisting of hydrido, methyl, ethyl, isopropyl, propyl, carboxy, amidino, guanidino, methoxy, ethoxy, isopropoxy, propoxy, hydroxy, amino, aminomethyl, 1-aminoethyl, 2-aminoethyl, N-methylamino, dimethylamino, N-ethylamino, methylthio, ethylthio, isopropylthio, trifluoromethylthio, methylsulfinyl, ethylsulfinyl, methylsulfonyl, ethylsulfonyl, trifluoromethyl, pentafluoroethyl, 2,2,2-trifluoroethyl, 2,2,3,3,3-pentafluoropropyl, trifluoromethoxy, 1,1,2,2-tetrafluoroethoxy, fluoro, chloro, bromo, amidosulfonyl, N-methylamidosulfonyl, N,N-dimethylamidosulfonyl, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 2,2,2-trifluoro-1-hydroxyethyl, and cyano; and

Q^s is selected from the group consisting of a single covalent bond, CH_2, and CH_2CH_2.

8. The compound as recited in claim **7** or a pharmaceutically acceptable salt thereof, wherein;

B is selected from the group consisting of hydrido,ethyl, 2-propenyl, 2-propynyl, propyl, isopropyl, butyl, 2-butyl, (R)-2-butyl,(S)-2-butyl, tert-butyl, isobutyl, 1-pentyl, 3-pentyl, 2-methylbutyl, 2,2,2-trifluoroethyl, 6-amidocarbonylhexyl, 4-methyl-2-pentyl, 3-hydroxypropyl, 3-methoxy-2-propyl, 2-methoxyethyl, 2-methyl-2-butyl, 3-methyl-2-butyl, 2-dimethylaminopropyl, 2-cyanoethyl, 6-hydroxyhexyl, 2-hydroxyethyl, 2-amidinoethyl, 2-guanidinoethyl, 3-guanidinopropyl, 4-guanidinobutyl, 3-hydroxypropyl, 4-hydroxybutyl, 6-cyanohexyl, 2-dimethylaminoethyl, 3-methylbutyl, 2-methylbutyl, (S)-2-methylbutyl, 3-aminopropyl, 2-hexyl, and 4-aminobutyl;

A is selected from the group consisting of single covalent bond,CH_2, NHC(O), CH_2CH_2, $CH_2CH_2CH_2$, and CH_3CHCH_2;

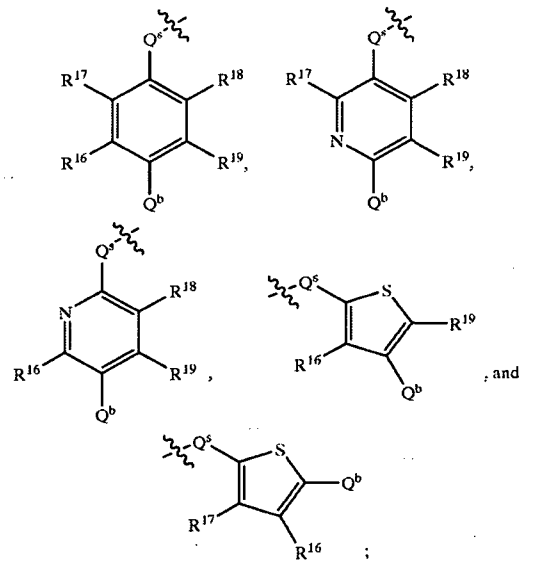
R^1 is selected from the group consisting of hydrido, methyl, ethyl, propyl, trifluoromethyl, pentafluoroethyl, 2,2,2-trifluoroethyl, fluoro, chloro, and bromo;

R^2 is Z^0—Q;

Z^0 is a covalent single bond;

Q is selected from the group consisting of 5-amino-3-amidocarbonylphenyl, 5-amino-2-fluorophenyl, 3-amino-5-hydroxymethylphenyl, 5-amino-3-methoxycarbonylphenyl, 3-amidinophenyl, 3-amino-2-methylphenyl, 5-amino-2-methylthiophenyl, 3-aminophenyl, benzyl, 3-carboxyphenyl, 3-carboxy-5-aminophenyl, 3-carboxy-5-hydroxyphenyl, 3-carboxymethyl-5-aminophenyl, 3-carboxymethyl-5-hydroxyphenyl, 3-carboxymethylphenyl, 3-chlorophenyl, 2-chlorophenyl, 2,6-dichlorophenyl, 3-cyanophenyl, 3-dimethylaminophenyl, 2-fluorophenyl, 3-fluorophenyl, 2,5-difluorophenyl, 2-hydroxyphenyl, 3-hydroxyphenyl, 3-methanesulfonylaminophenyl, 2-methoxyphenyl, 3-methoxyphenyl, 3-methoxyaminophenyl, 3-methoxycarbonylphenyl, 2-methylaminophenyl, 3-methylaminophenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, phenyl, 3-trifluoroacetamidophenyl, 3-trifluoromethylphenyl, 2-trifluoromethylphenyl, 5-amino-2-thienyl, 5-amino-3-thienyl, 3-bromo-2-thienyl, 3-pyridyl, 4-pyridyl, 2-thienyl, and 3-thienyl;

Y^0 is selected from the group consisting of:



, , , , and ;

R^{16} and R^{19} are independently selected from the group consisting of: hydrido, amidino, amino, aminomethyl, methoxy, methylamino, hydroxy, hydroxymethyl, fluoro, chloro, and cyano;

R^{17} and R^{18} are independently selected from the group consisting of hydrido, fluoro, chloro, hydroxy, hydroxymethyl, amino, carboxy, and cyano;

Q^b is selected from the group consisting of hydrido and $C(NR^{25})NR^{23}R^{24}$;

R^{23}, R^{24}, and R^{25} are independently selected from the group consisting of hydrido and methyl; and

Q^s is CH_2.

9. The compound as recited in claim 6, or a pharmaceutically acceptable salt thereof, wherein;

B is selected from the group consisting of hydrido, C2–C8 alkyl, C3–C8 alkenyl, C3–C8 alkynyl, and C2–C8 haloalkyl, wherein each member of group B is optionally substituted at any carbon up to and including 6 atoms from the point of attachment of B to A with one or more of the group consisting of R^{32}, R^{33}, R^{34}, R^{35}, and R^{36};

R^{32}, R^{33}, R^{34}, R^{35}, and R^{36} are independently selected from the group consisting of hydrido, acetamido, haloacetamido, amidino, guanidino, alkoxy, hydroxy, amino, alkoxyamino, lower alkylamino, alkylthio, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, alkyl, halo, haloalkyl, haloalkoxy, hydroxyalkyl, carboalkoxy, carboxy, carboxamido, cyano, and Q^b;

Q^b is selected from the group consisting of $NR^{20}R^{21}$, hydrido, $N(R^{26})C(NR^{25})N(R^{23})(R^{24})$, and $C(NR^{25})NR^{23}R^{24}$;

R^{20}, R^{21}, R^{23}, R^{24}, R^{25}, and R^{26} are independently selected from the group consisting of hydrido and alkyl;

A is selected from the group consisting of single covalent bond and $(CH(R^{15}))_{pa}$—$(W^7)_{rr}$ wherein rr is an integer selected from 0 through 1, pa is an integer selected from 0 through 3, and W^7 is $N(R^7)$;

R^7 is selected from the group consisting of hydrido and alkyl;

R^{15} is selected from the group consisting of hydrido, halo, alkyl, and haloalkyl;

R^1 is selected from the group consisting of hydrido, cyano, haloalkyl, and halo;

R^2 is Z^0—Q;

Z^0 is a covalent single bond;

Q is selected from the group consisting of aryl and heteroaryl wherein (a) a ring carbon in a first alpha position relative to the ring carbon at the point of attachment is optionally substituted by R^9, (b) a ring carbon in a second alpha position relative to the ring carbon at the point of attachment is optionally substituted by R^{13}, (c) a ring carbon, in a first beta position relative to the ring carbon at the point of attachment and in an alpha position relative to the ring atom optionally substituted by R^9, is optionally substituted by R^{10}, (d) a ring carbon, in a second beta position relative to the ring carbon at the point of attachment and in an alpha position relative to the ring atom optionally substituted by R^{13}, is optionally substituted by R^{12}, and (e) a ring carbon, if present, in the gamma position relative to the ring carbon at the point of attachment and in an alpha position relative to each of the ring atoms optionally substituted by R^{10} and R^{12}, respectively, is optionally substituted by R^{11};

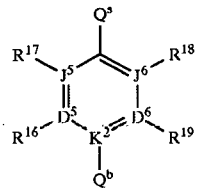
R^9, R^{11}, and R^{13} are independently selected from the group consisting of hydrido, hydroxy, amino, amidino, guanidino, lower alkylamino, alkylthio, alkoxy, alkylsulfinyl, alkylsulfonyl, amidosulfonyl, monoalkylamidosulfonyl, alkyl, halo, haloalkyl, haloalkoxy, hydroxyalkyl, carboxy, carboxamido, and cyano;

R^{10} and R^{12} are independently selected from the group consisting of hydrido, acetamido, haloacetamido, amidino, guanidino, alkyl, alkoxy, alkoxyamino, aminoalkyl, hydroxy, amino, lower alkylamino,

alkylsulfonamido, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, hydroxyalkyl, aminoalkyl, halo, haloalkyl, carboalkoxy, carboxy, carboxyamido, carboxyalkyl, and cyano;

Y^0 is formula (IV):

(IV)



wherein D^5, D^6, J^5, and J^6 are independently selected from the group consisting of C, N, O, S and a covalent bond with the provisos that no more than one is a covalent bond, no more than one of D^5, D^6, J^5, and J^6 is O, no more than one of D^5, D^6, J^5, and J^6 is S, one of D^5, D^6, J^5, and J^6 must be a covalent bond when two of D^5, D^6, J^5, and J^6 are O and S, and no more than four of D^5, D^6, J^5, and J^6 are N;

R^{16}, R^{17}, R^{18}, and R^{19} are independently selected from the group consisting of hydrido, amidino, guanidino, carboxy, haloalkylthio, alkoxy, hydroxy, amino, lower alkylamino, alkylthio, alkylsulfinyl, alkylsulfonyl, alkanoyl, haloalkanoyl, alkyl, halo, haloalkyl, haloalkoxy, hydroxyalkyl, aminoalkyl, and cyano; and

Q^s is CH_2.

10. The compound as recited in claim **6** or a pharmaceutically acceptable salt thereof, wherein;

B is selected from the group consisting of hydrido, ethyl, 2-propenyl, 2-propynyl, propyl, isopropyl, butyl, 2-butenyl, 2-butynyl, sec-butyl, tert-butyl, isobutyl, 2-methylpropenyl, 1-pentyl, 2-pentenyl, 3-pentenyl, 2-pentynyl, 3-pentynyl, 2-pentyl, 3-pentyl, 2-methylbutyl, 2-methyl-2-butenyl, 3-methylbutyl, 3-methyl-2-butenyl, 1-hexyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, 2-hexyl, 1-methyl-2-pentenyl, 1-methyl-3-pentenyl, 1-methyl-2-pentynyl, 1-methyl-3-pentynyl, 3-hexyl, 1-ethyl-2-butenyl, 1-heptyl, 2-heptenyl, 3-heptenyl, 4-heptenyl, 5-heptenyl, 2-heptynyl, 3-heptynyl, 4-heptynyl, 5-heptynyl, 2-heptyl, 1-methyl-2-hexenyl, 1-methyl-3-hexenyl, 1-methyl4-hexenyl, 1-methyl-2-hexynyl, 1-methyl-3-hexynyl, 1-methyl-4-hexynyl, 3-heptyl, 1-ethyl-2-pentenyl, 1-ethyl-3-pentenyl, 1-ethyl-2-pentynyl, 1-ethyl-3-pentynyl, 2,2,2-trifluoroethyl, 2,2-difluoropropyl, 4-trifluoromethyl-5,5,5-trifluoropentyl, 4-trifluoromethylpentyl, 5,5,6,6,6-pentafluorohexyl, and 3,3,3-trifluoropropyl, wherein each member of group B is optionally substituted at any carbon up to and including 5 atoms from the point of attachment of B to A with one or more of the group consisting of R^{32}, R^{33}, R^{34}, R^{35}, and R^{36};

R^{32}, R^{33}, R^{34}, R^{35}, and R^{36} are independently selected from the group consisting of hydrido, amidino, guanidino, methyl, ethyl, methoxy, ethoxy, hydroxy, amino, N-methylamino, dimethylamino, methylthio, ethylthio, trifluoromethyl, pentafluoroethyl, 2,2,2-trifluoroethyl, fluoro, chloro, bromo, amidosulfonyl, N-methylamidosulfonyl, hydroxymethyl, amidocarbonyl, carboxy, cyano, and Q^b;

R^{20}, R^{21}, R^{23}, R^{24}, R^{25}, and R^{26} are independently selected from the group consisting of hydrido, methyl, and ethyl;

A is selected from the group consisting of:

(i) a single covalent bond, NH, $N(CH_3)$, CH_2, CH_3CH, and CH_2CH_2; and

(ii) $CH_2N(CH_3)$, $CH_2N(CH_2CH_3)$, $CH_2CH_2N(CH_3)$, and $CH_2CH_2N(CH_2CH_3)$ with the proviso that B is hydrido;

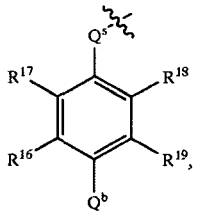
R^1 is selected from the group consisting of hydrido, trifluoromethyl, pentafluoroethyl, fluoro, and chloro;

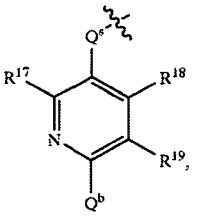
R^2 is selected from the group consisting of phenyl and 2-thienyl, 2-furyl, 2-pyrrolyl, 2-imidazolyl, 2-thiazolyl, 3-isoxazolyl, 2-pyridyl, and 3-pyridyl heteroaryl rings, wherein (a) a ring carbon in a first alpha position relative to the ring carbon at the point of attachment is optionally substituted by R^9, (b) a ring carbon in a second alpha position relative to the ring carbon at the point of attachment is optionally substituted by R^{13}, (c) a ring carbon, in a first beta position relative to the ring carbon at the point of attachment and in an alpha position relative to the ring atom optionally substituted by R^9, is optionally substituted by R^{10}, (d) a ring carbon, in a second beta position relative to the ring carbon at the point of attachment and in an alpha position relative to the ring atom optionally substituted by R^{13}, is optionally substituted by R^{12}, and (e) a ring carbon, if present, in the gamma position relative to the ring carbon at the point of attachment and in an alpha position relative to each of the ring atoms optionally substituted by R^{10} and R^{12}, respectively, is optionally substituted by R^{11};

R^9, R^{11}, and R^{13} are independently selected from the group consisting of hydrido, methyl, ethyl, methoxy, ethoxy, hydroxy, amino, N-methylamino, N,N-dimethylamino, methylthio, trifluoromethyl, pentafluoroethyl, 2,2,2-trifluoroethyl, fluoro, chloro, bromo, amidosulfonyl, N-methylamidosulfonyl, N,N-dimethylamidosulfonyl, hydroxymethyl, 1-hydroxyethyl, amidocarbonyl, N-methylamidocarbonyl, carboxy, and cyano;

R^{10} and R^{12} are independently selected from the group consisting of hydrido, amidino, amidocarbonyl, N-methylamidocarbonyl, guanidino, methyl, ethyl, methoxy, ethoxy, hydroxy, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, carboxy, carboxymethyl, amino, acetamido, trifluoromethyl, pentafluoroethyl, 2,2,2-trifluoroethyl, trifluoroacetamido, aminomethyl, N-methylamino, dimethylamino, amidosulfonyl, N-methylamidosulfonyl, N,N-dimethylamidosulfonyl, methoxycarbonyl, fluoro, chloro, bromo, and cyano;

Y^0 is selected from the group consisting of:





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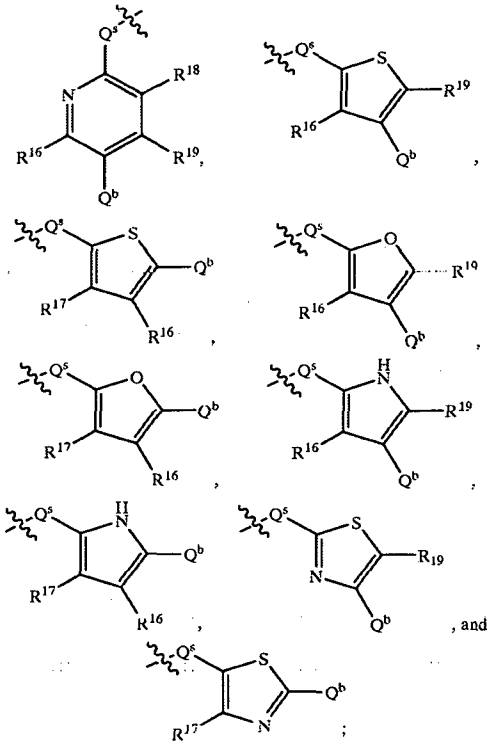


R^{16}, R^{17}, R^{18}, and R^{19} are independently selected from the group consisting of hydrido, methyl, ethyl, amidino, guanidino, methoxy, hydroxy, amino, aminomethyl, 1-aminoethyl, 2-aminoethyl, *N-methylamino, dimethylamino, methylthio, ethylthio,* trifluoromethylthio, methylsulfinyl, methylsulfonyl, trifluoromethyl, pentafluoroethyl, 2,2,2-trifluoroethyl, trifluoromethoxy, fluoro, chloro, amidosulfonyl, N-methylamidosulfonyl, hydroxymethyl, carboxy, and cyano.

Q^b is selected from the group consisting of $NR^{20}R^{21}$, $C(NR^{25})NR^{23}R^{24}$, and $N(R^{26})C(NR^{25})N(R^{23})(R^{24})$;

R^{20}, R^{21}, R^{23}, R^{24}, R^{25}, and R^{26} are independently selected from the group consisting of hydrido, methyl, and ethyl; and

Q^s is CH_2.

11. The compound as recited in claim **10** or a pharmaceutically acceptable salt thereof, wherein;

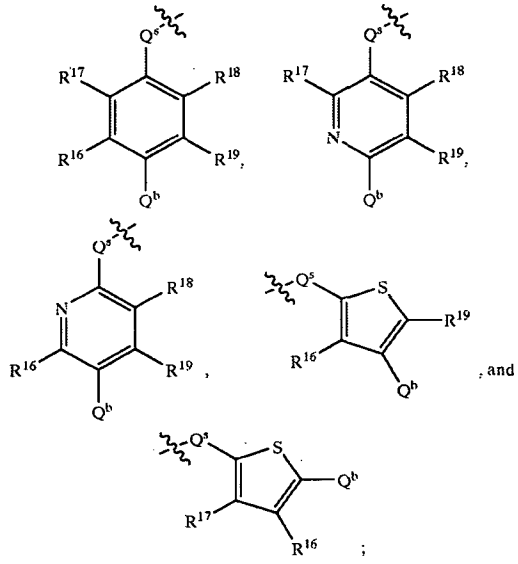
B is selected from the group consisting of hydrido,ethyl, 2-propenyl, 2-propynyl, propyl, isopropyl, butyl, 2-butyl, (R)-2-butyl,(S)-2-butyl, tert-butyl, isobutyl, 1-pentyl, 3-pentyl, 2-methylbutyl, 2,2,2-trifluoroethyl, 6-amidocarbonylhexyl, 4-methyl-2-pentyl, 3-hydroxypropyl, 3-methoxy-2-propyl, 2-methoxyethyl, 2-methyl-2-butyl, 3-methyl-2-butyl, 2-dimethylaminopropyl, 2-cyanoethyl, 6-hydroxyhexyl, 2-hydroxyethyl, 2-amidinoethyl, 2-guanidinoethyl, 3-guanidinopropyl, 4-guanidinobutyl, 3-hydroxypropyl, 4-hydroxybutyl, 6-cyanohexyl, 2-dimethylaminoethyl, 3-methylbutyl, 2-methylbutyl, (S)-2-methylbutyl, 3-aminopropyl, 2-hexyl, and 4-aminobutyl;

A is selected from the group consisting of single covalent bond, CH_2, CH_3CH, and CH_2CH_2;

R^1 is selected from the group consisting of hydrido, trifluoromethyl, fluoro, and chloro;

R^2 is selected from the group consisting of 5-amino-3-amidocarbonylphenyl, 5-amino-2-fluorophenyl, 3-amino-5-hydroxymethylphenyl, 5-amino-3-methoxycarbonylphenyl, 3-amidinophenyl, 3-amino-2-methylphenyl, 5-amino-2-methylthiophenyl, 3-aminophenyl, benzyl, 3-carboxyphenyl, 3-carboxy-5-aminophenyl, 3-carboxy-5-hydroxyphenyl, 3-carboxymethyl-5-aminophenyl, 3-carboxymethyl-5-hydroxyphenyl, 3-carboxymethylphenyl, 3-chlorophenyl, 2-chlorophenyl, 2,6-dichlorophenyl, 3-cyanophenyl, 3-dimethylaminophenyl, 2-fluorophenyl, 3-fluorophenyl, 2,5-difluorophenyl, 2-hydroxyphenyl, 3-hydroxyphenyl, 3-methanesulfonylaminophenyl, 2-methoxyphenyl, 3-methoxyphenyl, 3-methoxyaminophenyl, 3-methoxycarbonylphenyl, 2-methylaminophenyl, 3-methylaminophenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, phenyl, 3-trifluoroacetamidophenyl, 3-trifluoromethylphenyl, 2-trifluoromethylphenyl, 5-amino-2-thienyl, 5-amino-3-thienyl, 3-bromo-2-thienyl, 3-pyridyl, 4-pyridyl, 2-thienyl, and 3-thienyl;

Y^o is selected from the group consisting of:



R^{16} and R^{19} are independently selected from the group consisting of: hydrido, amidino, amino, aminomethyl, methoxy, methylamino, hydroxy, hydroxymethyl, fluoro, chloro, and cyano;

R^{17} and R^{18} are independently selected from the group consisting of hydrido, fluoro, chloro, hydroxy, hydroxymethyl, amino, carboxy, and cyano;

Q^b is selected from the group consisting of hydrido and $C(NR^{25})NR^{23}R^{24}$;

R^{23}, R^{24}, and R^{25} are independently selected from the group consisting of hydrido and methyl; and

Q^s is CH_2.

12. The compound as recited in claim **11** or a pharmaceutically acceptable salt thereof, wherein;

B is selected from the group consisting of hydrido,ethyl, 2-propenyl, 2-propynyl, propyl, isopropyl, butyl, 2-butyl, (R)-2-butyl,(S)-2-butyl, tert-butyl, isobutyl, 1-pentyl, 3-pentyl, 2-methylbutyl, 2,2,2-trifluoroethyl, 6-amidocarbonylhexyl, 4-methyl-2-pentyl,

3-hydroxypropyl, 3-methoxy-2-propyl, 2-methoxyethyl, 2-methyl-2-butyl, 3-methyl-2-butyl, 2-dimethylaminopropyl, 2-cyanoethyl, 6-hydroxyhexyl, 2-hydroxyethyl, 2-amidinoethyl, 2-guanidinoethyl, 3-guanidinopropyl, 4-guanidinobutyl, 3-hydroxypropyl, 4-hydroxybutyl, 6-cyanohexyl, 2-dimethylaminoethyl, 3-methylbutyl, 2-methylbutyl, (S)-2-methylbutyl, 3-aminopropyl, 2-hexyl, and 4-aminobutyl;

A is selected from the group consisting of single covalent bond, CH_2, CH_3CH, and CH_2CH_2;

R^1 is selected from the group consisting of hydrido and chloro;

R^2 is selected from the group consisting of 5-amino-2-fluorophenyl, 3-amino-2-methylphenyl, 5-amino-2-methylthiophenyl, 3-aminophenyl, 3-carboxyphenyl, 3-cyanophenyl, 3-methoxycarbonylphenyl, phenyl, and 3-pyridyl;

Y^0 is selected from the group consisting of 5-amidino-2-thienylmethyl, 4-amidinobenzyl, 2-fluoro-4-amidinobenzyl, and 3-fluoro-4-amidinobenzyl.

13. A compound as recited in claim **6**, or a pharmaceutically acceptable salt thereof, wherein:

R^2 is 3-aminophenyl, B is 2,2,2-trifluoroethyl, A is single bond, Y^0 is 4-amidinobenzyl, and R^1 is chloro;

R^2 is 3-aminophenyl, B is (S)-2-butyl, A is single bond, Y^0 is 4-amidinobenzyl, and R^1 is chloro;

R^2 is 5-amino-2-fluorophenyl, B is isopropyl, A is single bond, Y^0 is 4-amidinobenzyl, and R^1 is chloro;

R^2 is 2-methyl-3-aminophenyl, B is isopropyl, A is single bond, Y^0 is 4-amidinobenzyl, and R^1 is chloro;

R^2 is 3-aminophenyl, B is ethyl, A is single bond, Y^0 is 4-amidinobenzyl, and R^1 is chloro;

R^2 is 3-aminophenyl, B is ethyl, A is single bond, Y^0 is 4-amidino-2-fluorobenzyl, and R^1 is chloro;

R^2 is 3-aminophenyl, B is 2-propenyl, A is single bond, Y^0 is 4-amidinobenzyl, and R^1 is chloro;

R^2 is 3-aminophenyl, B is isopropyl, A is single bond, Y^0 is 4-amidino-2-fluorobenzyl, and R^1 is chloro;

R^2 is 3-aminophenyl, B is isopropyl, A is single bond, Y^0 is 4-amidinobenzyl, and R^1 is chloro;

R^2 is 3-aminophenyl, B is 2-butyl, A is single bond, Y^0 is 4-amidinobenzyl, and R^1 is chloro;

R^2 is 3-aminophenyl, B is (R)-2-butyl, A is single bond, Y^0 is 4-amidinobenzyl, and R^1 is chloro;

R^2 is 3-aminophenyl, B is 2-propynyl, A is single bond, Y^0 is 4-amidinobenzyl, and R^1 is chloro;

R^2 is 3-aminophenyl, B is 3-pentyl, A is single bond, Y^0 is 4-amidinobenzyl, and R^1 is hydrido;

R^2 is 3-aminophenyl, B is hydrido, A is CH_2, Y^0 is 4-amidinobenzyl, and R^1 is chloro;

R^2 is 3-aminophenyl, B is ethyl, A is CH_2, Y^0 is 4-amidinobenzyl, and R^1 is chloro;

R^2 is 3-aminophenyl, B is 2-methypropyl, A is single bond, Y^0 is 4-amidinobenzyl, and R^1 is chloro;

R^2 is 3-aminophenyl, B is 2-propyl, A is CH_3CH, Y^0 is 4-amidinobenzyl, and R^1 is chloro;

R^2 is 3-aminophenyl, B is propyl, A is single bond, Y^0 is 4-amidino-2-fluorobenzyl, and R^1 is chloro;

R^2 is 3-aminophenyl, B is 6-amidocarbonylhexyl, A is single bond, Y^0 is 4-amidinobenzyl, and R^1 is chloro;

R^2 is 3-aminophenyl, B is tert-butyl, A is single bond, Y^0 is 4-amidinobenzyl, and R^1 is hydrido;

R^2 is 3-aminophenyl, B is tert-butyl, A is single bond, Y^0 is 4-amidinobenzyl, and R^1 is chloro;

R^2 is 3-aminophenyl, B is 3-hydroxypropyl, A is single bond, Y^0 is 4-amidinobenzyl, and R^1 is chloro;

R^2 is 3-aminophenyl, B is 2-methylpropyl, A is single bond, Y^0 is 4-amidino-2-fluorobenzyl, and R^1 is chloro;

R^2 is 3-aminophenyl, B is butyl, A is single bond, Y^0 is 4-amidinobenzyl, and R^1 is chloro;

R^2 is 3-aminophenyl, B is 3-methoxy-2-propyl, A is single bond, Y^0 is 4-amidinobenzyl, and R^1 is chloro;

R^2 is 3-aminophenyl, B is 3-methoxy-2-propyl, A is single bond, Y^0 is 4-amidinobenzyl, and R^1 is chloro;

R^2 is 3-aminophenyl, B is 2-methoxy-2-ethyl, A is single bond, Y^0 is 4-amidinobenzyl, and R^1 is chloro;

R^2 is 3-aminophenyl, B is 2-propyl, A is single bond, Y^0 is 5-amidino-2-thienylmethyl, and R^1 is chloro;

R^2 is 3-aminophenyl, B is 2-propyl, A is single bond, Y^0 is 4-amidino-3-fluorobenzyl, and R^1 is hydrido;

R^2 is 3-carboxyphenyl, B is 2-propyl, A is single bond, Y^0 is 4-amidinobenzyl, and R^1 is hydrido; or

R^2 is 3-aminophenyl, B is 2-propyl, A is single bond, Y^0 is 4-amidino-3-fluorobenzyl, and R^1 is chloro.

14. A composition for inhibiting thrombotic conditions in blood comprising a compound of any one of claim **5** or **13** and a pharmaceutically acceptable carrier.

15. A composition for inhibiting thrombotic conditions in blood comprising a compound of any one of claims **1–4** or **6–13** and a pharmaceutically acceptable carrier.

16. A method for inhibiting thrombotic conditions in blood comprising adding to blood a therapeutically effective amount of a composition of any one of claims **1–5** or **6–13**.

17. A method for inhibiting formation of blood platelet aggregates in blood comprising adding to blood a therapeutically effective amount of a composition of any one of claims **1–5** or **6–13**.

18. A method for inhibiting thrombus formation in blood comprising adding to blood a therapeutically effective amount of a composition of any one of claims **1–5** or **6–13**.

19. A method for treating venuous thromboembolism and pulmonary embolism in a mammal comprising administering to the mammal a therapeutically effective amount of a composition of any one of claims **1–5** or **6–13**.

20. A method for treating deep vein thrombosis in a mammal comprising administering to the mammal a therapeutically effective amount of a composition of any one of claims **1–5** or **6–13**.

21. A method for treating cardiogenic thromboembolism in a mammal comprising administering to the mammal a therapeutically effective amount of a composition of any one of claims **1–5** or **6–13**.

22. A method for treating thromboembolic stroke in humans and other mammals comprising administering to the mammal a therapeutically effective amount of a composition of any one of claims **1–5** or **6–13**.

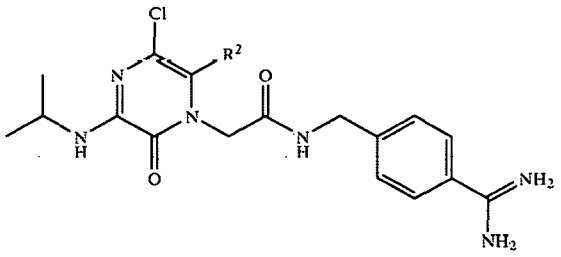
23. A method for treating thrombosis associated with cancer and cancer chemotherapy in humans and other mammals comprising administering to the mammal a therapeutically effective amount of a composition of any one of claims **1–5** or **6–13**.

24. A method for treating unstable angina in humans and other mammals comprising administering to the mammal a therapeutically effective amount of a composition of any one of claims **1–5** or **6–13**.

25. A method for inhibiting thrombus formation in blood comprising adding to blood a therapeutically effective

amount of a compound of any one of claims **1–5** or **6–13** with a therapeutically effective amount of fibrinogen receptor antagonist.

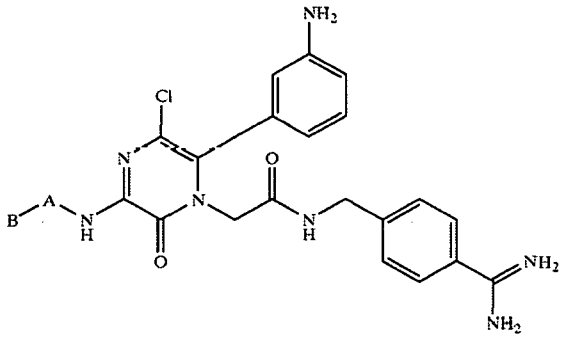
26. A compound having the Formula:



wherein

R^2 is selected from the group consisting of 3-pyridyl, 5-amino-2-methylthiophenyl, 3-(N-methylamino) phenyl, 2-methyl-3-aminophenyl and 3-aminophenyl.

27. A compound having the Formula:



wherein

A is a bond; and

B is selected from the group consisting of t-butyl, 3-pentyl, ethyl, propyl, 2-butyl, 2-(3-methylbutyl), (R)-2-butyl, 2-(4-methylpentyl), 2-propenyl, and 2-propynyl.

* * * * *

IN THE MATTER OF

Indian Patent Application 853/DELNP/2009

In the name of

BRISTOL-MYERS SQUIBB COMPANY

AND IN THE MATTER OF

A pre-grant representation by

DALVIR SINGH

D7 – US Patent 6,900,207

US006900207B2

(12) **United States Patent**
Ohmoto et al.

(10) **Patent No.: US 6,900,207 B2**
(45) **Date of Patent: May 31, 2005**

(54) **N-CONTAINING FIVE-MEMBERED RING COMPOUNDS AND PHARMACEUTICAL AGENTS COMPRISING THE SAME AS ACTIVE INGREDIENT**

(75) Inventors: **Kazuyuki Ohmoto**, Osaka (JP); **Iori Itagaki**, Nagano (JP)

(73) Assignee: **Ono Pharmaceutical Co., Ltd.**, Osaka (JP)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 52 days.

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(58) **Field of Search** 514/236.2, 326, 514/340, 381; 544/132; 546/210, 268.4; 548/251, 253

(56) **References Cited**

FOREIGN PATENT DOCUMENTS

EP 0 761 680 A2 3/1997
EP 0 900 791 A1 3/1999
JP 06192199 A * 7/1994

OTHER PUBLICATIONS

Derwent Acc. No. 1994-260477, 1994. Abstract of JP 06192199 A, 1994.*

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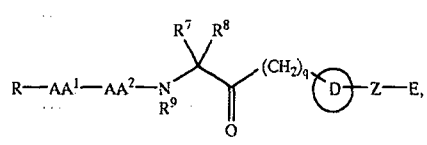
(57) **ABSTRACT**

An N-containing five-membered ring compound of formula (I)



(I)

wherein all symbols are the same as described in the specification, and a non-toxic salt thereof.

The compound of formula (I) has an inhibitory activity against cysteine protease and therefore it is useful as an agent for the prophylaxis and/or treatment of inflammatory diseases, diseases induced by apoptosis, diseases induced by disorders of immune responses, autoimmune diseases, diseases induced by decomposition of proteins which compose organism, shock, circulatory system disorders, blood coagulation systems disorders, malignant tumors, acquired immune deficiency syndrome (AIDS) and AIDS-related complex (ARC), parasitic diseases, nerve degeneration diseases, pulmonary disorders, bone resorption diseases, endocrinesthenia, etc.

13 Claims, No Drawings

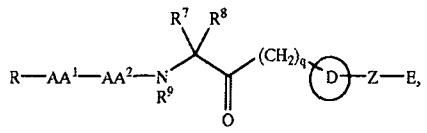
N-CONTAINING FIVE-MEMBERED RING COMPOUNDS AND PHARMACEUTICAL AGENTS COMPRISING THE SAME AS ACTIVE INGREDIENT

TECHNICAL FIELD

The present invention relates to an N-containing five-membered ring compound.

Particularly, the present invention relates to

1) an N-containing five-membered ring compound of formula (I)



(I)

wherein all symbols have the same meanings as hereafter, and a non-toxic salt thereof,

2) a method for the preparation thereof and

3) a pharmaceutical agent comprising the N-containing five-membered ring compound and non-toxic salt thereof as active ingredient.

BACKGROUND OF THE INVENTION

Cysteine protease is a generic name of proteases which have a cysteine residue in the activity center and catalyze protein degradation thereat. In animal cells, a large number of cysteine proteases are known; for example, cathepsin family, calpain family, caspase-1, etc. Cysteine protease exists in various kinds of cells extensively and plays a basic and essential role in the homeostasis, such as conversion (processing) of precursor protein into its active form and degradation of proteins which have become out of use, etc. Until now, its physiological effects are being vigorously studied, and as the studies progress and characteristics of the enzymes are revealed, cysteine protease came to be taken as a cause of really various kinds of diseases.

It is revealed that cathepsin S (See J. Immunol., 161, 2731 (1998)) and cathepsin L (See J. Exp. Med., 183, 1331 (1996)) play a role in processing of major histocompatibility antigen class-II in antigen presenting cells which play an important role in the early stage of immune responses. In an experimental inflammatory response model induced by antigens, a specific inhibitor of cathepsin S showed an inhibitory effect (see J. Clin. Invest., 101, 2351 (1998)). It is also reported that in a leishmania-infected immune response model cathepsin B inhibitor inhibited an immune response and by means of this effect it inhibited the proliferation of protozoans (See J. Immunol., 161, 2120 (1998)). In vitro, a result is given that a calpain inhibitor and a cysteine protease inhibitor E-64 inhibited apoptosis which is induced by stimuli on T cell receptors (see J. Exp. Med., 178, 1693 (1993)). Therefore, it is conceivable that cysteine protease is much concerned with the progress of immune responses.

It is speculated that caspase-1 or a cysteine protease similar thereto occupies an important position in the mechanism of cell death including apoptosis. Therefore it is expected for a cysteine protease inhibitor to be used as an agent for the prophylaxis and/or treatment of those diseases concerning apoptosis, such as infectious diseases, deterioration or sthenia of immune function and brain function,

tumors, etc. Diseases concerning apoptosis are, acquired immune deficiency syndrome (AIDS), AIDS-related complex (ARC), adult T cell leukemia, hairy cell leukemia, spondylopathy, respiratory apparatus disorder, arthitis, HIV or HTLV-1 related diseases such as uveitis, virus-related diseases such as hepatitis C, cancer, collagenosis (systemic lupus erythematosus, rheumatoid arthritis, etc.), autoimmune diseases (ulcerative colitis, Sjögren's syndrome, primary biliary cirrhosis, spontaneous thrombocytopenic purpura, autoimmune hemolytic anemia, myasthenia gravis, insulin dependent (type I) diabetes, etc.), diseases accompanied by thrombocytopenia (osteomyelodysplasia syndrome, periodic thrombocytopenia, aplastic anemia, spontaneous thrombocytopenia, disseminated intravascular coagulation (DIC), etc.), hepatic diseases such as viral hepatitis (type C, A, B, F, etc.) or hepatitis medicamentosus and cirrhosis, dementia (Alzheimer's diseases, Alzheimer's senile dementia, etc.), cerebrovascular injury, nerve degeneration diseases, adult acute respiratory distress syndrome, infectious diseases, prostatomegaly, hysteromyoma, bronchial asthma, arteriosclerosis, all kinds of lusus naturae, nephropathy, senile cataract, chronic fatigue syndrome, myodystrophy, peripheral neuropathy, etc.

Moreover, caspase-1 is concerned with various inflammatory diseases and those diseases caused by immune disorders, by means of interleukin-1β (IL-1β) production. A lot of diseases are shown to be involved with caspase-1 including inflammatory diseases and autoimmune diseases listed below; inflammatory bowel diseases such as ulcerative colitis, insulin-dependent (type-I) diabetes, autoimmune thyroid diseases, infectious diseases, rejection of an organ transplantation, graft versus host diseases, psoriasis, periodontitis (above, see N. Eng. J. Med., 328, 106 (1993)), pancreatitis (see J. Interferon Cytokine Res., 17, 113 (1997)), hepatitis (see J. Leuko. Biol., 58, 90 (1995)), glomerulonephritis (see Kidney Int., 47, 1303 (1995)), endocarditis (see Infect. Immun., 64, 1638 (1996)), myocarditis (see Br. Heart J., 72, 561 (1995)), systemic lupus erythematosus (see Br. J. Rheumatol., 34, 107 (1995)), Hashimoto's diseases (see Autoimmunity, 16, 141 (1993)), etc.), etc. Experimentally, it is reported that in liver injury model induced by lipopolysaccharide and D-galactosamine, a caspase-1 inhibitor depressed the symptoms, and it is expected that a caspase inhibitor shows an effect in sepsis, ischemic reperfusion and hepatitis gravis (see Am. J. Respir. Crit. Care Med., 159, 1308 (1999)).

It is also shown that cysteine protease is concerned with rheumatoid arthritis. IL-1β is shown to be concerned with this disease (see Arthritis Rheum., 39, 1092 (1996)), and in addition, as autoantibody toward calpastatin (endogenous calpain inhibitor) was found in the serum of the patients, it is considered that increase of calpain activity leads to the cause of diseases.

It is also known that cysteine protease causes a disease symptom by decomposing various proteins which compose the organism.

It is reported that cathepsin B plays a role in decomposing muscular protein in the chronic phase of sepsis (see J. Clin. Invest., 97, 1610 (1996)), and in decomposing muscular protein in myodystrophy model (see Biochem. J., 288, 643 (1992)). And it is also reported that calpain decomposes the myocyte cells protein of myodystrophy patients (see J. Biol. Chem., 270, 10909 (1995)).

In the ischemic reperfusion model, a result is given that calpain causes degeneration of brain tissues by means of degradation of protein kinase C-β (see J. Neurochem., 72,

2556 (1999)) and that a cathepsin B inhibitor inhibits nerve injury (see Eur. J. Neurosci., 10, 1723 (1998)).

In the brain ischemic model, it is known that the degradation of spectrin by calpain causes a damage and function disorder in the neurocyte (see Brain Res., 790, 1(1998)) and it is reported that an IL-1β receptor antagonist relieved the symptoms (see Brain Res. Bull., 29, 243 (1992)).

In myocardial ischemic model it is confirmed that cathepsin B activity increases in the lesion (see Biochem. Med. Metab. Biol., 45, 6 (1991)).

In the experiment utilizing ischemic liver injury model, it proved that necrosis and apoptosis of hepacyte were induced by means of protein-decomposing activity of calpain (see Gastroenterology, 116, 168 (1999)).

Besides, it is known that calpain causes cornea turbid in cataract by means of degradation of crystalline (see Biol. Chem., 268, 137 (1993)) and that in the lesion of contracted gut mucosa model it was confirmed that the activity of cathepsin B, H and L increased (see JPEN. J. Parenter. Enteral. Nutr., 19, 187 (1995)) and it is shown that cysteine protease is a cause of the diseases resulting from such protein degradation.

It has been revealed that cysteine protease is concerned with systemic disorders of organs and tissues by shock.

It is shown that IL-1β is concerned with septic shock and systemic inflammatory response syndrome (see Igakuno Ayumi, 169, 850 (1994)) and besides, it is reported that in endotoxin shock model induced by lipopolysaccharide, a calpain inhibitor prevented circulatory system disorder, disorders of liver and pancreas and acidosis by means of inhibitory effect of activation of nuclear factor κB (see Br. J. Pharmacol., 121, 695 (1997)).

Since it is reported that calpain is concerned with platelet coagulation process and a calpain inhibitor prevented the coagulation of platelets (see Am. J. Physiol., 259, C862 (1990)), it is conceivable that a cysteine protease inhibitor is useful for the disorder by blood coagulation. From the fact that calpain activity increased in the serum of the patients of purpura (thrombocytopenia) resulting from marrow transplantation, it is conceivable that calpain is concerned with the actual disease symptoms (see Bone Marrow Transplant., 24, 641 (1999)). Caspase-1 inhibitor inhibited the apoptosis of blood vessel endothelial cells, which is seen in the early phase of purpura (thrombocytopenia) and is thought to be important for the progression of the pathology afterwards (see Am. J. Hematol., 59, 279 (1998)), so it is expected that a cysteine protease inhibitor makes effect on purpura and hemolytic uremic syndrome.

The effect of cysteine protease and its inhibitor is being investigated in the field of cancer and metastasis of cancer.

Since the proliferations of pancreas cancer cells (see Cancer Res., 59, 4551 (1999)) and acute myeloid leukemia cells (see Clin. Lab. Haematol., 21, 173 (1999)) were inhibited by an inhibitor or receptor antagonist of caspase-1, it is expected that caspase-1 activity is essential for the process of proliferation of tumor cells, and that an inhibitor thereof is effective for these cancers. Cathepsin B activity increased in colon cancer metastasis model (see Clin. Exp. Metastasis, 16, 159 (1998)). Cathepsin K protein expression was recognized in human breast cancer cells and the relationship of cathepsin K and bone metastasis is shown (Cancer Res., 57, 5386 (1997)). Also, a calpain inhibitor inhibited migaration of the cells and it implied the possibility that calpain inhibition may inhibit metastasis of cancer (J. Biochem., 272, 32719 (1997)). From these, a cysteine protease inhibitor is presumed to show an inhibitory effect on the metastasis of various malignant tumors.

As to AIDS (see AIDS, 10, 1349 (1996)) and AIDS-related complex (ARC) (see Arch. Immunol. Ther. Exp. (Warsz), 41, 147 (1993)), it is shown that IL-1 is concerned with the progress of symptoms, so it is conceivable that cysteine protease inhibition leads to an effective therapy of AIDS and its complication.

Some parasites have cysteine protease activity in their body. Cysteine protease in the phagosome of malaria protozoan is an essential enzyme for supplying nutrition of the parasites. A result is given that the inhibitor of cysteine protease shows an inhibitory effect of the proliferation of the protozoan (see Blood, 87, 4448 (1996)). Thus, it is possible to apply the inhibitor of cysteine protease to malaria.

In Alzheimer-type dementia, it is said that adhesion of non-physiological protein called amyloid to brain is deeply involved with nervous function disorders. Cysteine protease has an activity of generating amyloid by decomposing its precursor protein. Clinically, it is shown that cathepsin B is an enzyme that possesses a processing activity of amyloid proteins in the brains of Alzheimer-type dementia patients (see Biochem. Biophys. Res. Commun., 177, 377 (1991)). Also, expressions of cathepsin B protein (see Virchows Arch. A. Pathol. Anat. Histpathol., 423, 185 (1993)), cathepsin S protein (see Am. J. Pathol., 146, 848 (1995)) and calpain protein (see Proc. Natl. Acad. Sci. USA, 90, 2628 (1993)) and increase of caspase-1 activity (see J. Neuropathol. Exp. Neurol., 58, 582 (1999)) were confirmed in the brain lesions. Besides, by the fact that calpain is concerned with the formation of paired helical filaments which accumulate in Alzheimer dementia patients and production of protein kinase C which stabilizes the protein by phosphorylation (see J. Neurochem., 66, 1539 (1996)) and by the knowledge that caspase is concerned with neurocyte death by β amyloid protein adhesion (see Exp. Cell Res., 234, 507 (1997)), it is implied that cysteine protease is concerned with the disease symptoms.

As to Huntington's chorea, cathepsin H activity increased in the patient's brain (see J. Neurol. Sci., 131, 65 (1995)), and the ratio of activated form of calpain increased (see J. Neurosci., 48, 181 (1997)). In Parkinson's diseases, the increase of expression of m-calpain was recognized in the mesencephalon of the patients (see Neuroscience, 73, 979 (1996)) and IL-1β protein was expressed in brain (see Neurosci. Let., 202, 17 (1995)). Therefore, it is speculated that cysteine protease is concerned with the genesis and progress of these diseases.

Besides, in the central nervous system, spectrin degradation by calpain is found in the process of injury on neurocyte observed in the traumatic brain injury model (see J. Neuropathol. Exp. Neurol., 58, 365 (1999)).

In spinal cord injured model it was recognized that in glia cells calpain messenger RNA increased and its activity increased in the lesion and the possibility was shown that calpain had much to do with the degeneration of myelin and actin after injury (see Brain Res., 816, 375 (1999)). And IL-1β was shown to be concerned with the genesis of multiple sclerosis (see Immunol. Today, 14, 260 (1993)). Therefore, it is conceivable that a cysteine protease inhibitor is promising as an agent for the treatment of these nerve-injuring diseases.

Normally, cathepsin S and cathepsin K do not exist in human arterial walls but it was confirmed that they expressed in arterial sclerosis lesion and they had an decomposing activity of alveolus elastica (see J. Clin. Invest., 102, 576 (1998)) and a calpain inhibitor and antisense of m-calpain inhibited the proliferation of human blood vessel smooth muscle cells and it is shown that m-calpain is

concerned with the proliferation of smooth muscle (see Arteioscler. Thromb. Vssc. Biol., 18, 493 (1998)), so it is conceivable that a cysteine protease inhibitor is promising for the treatment of blood vessel lesion such as arteriosclerosis, restenosis after percutaneous transluminal coronary angioplasty (PTCA), etc.

It is reported that in liver, cathepsin B is activated in the process of injuring hepatocyte by bile acid (see J. Clin. Invest., 103, 137 (1999)) and so it is expected that a cysteine protease inhibitor is effective for cholestatic cirrhosis.

In lungs and respiratory system, it is shown that cathepsin S is an enzyme that plays a role in elastin degradation by alveolus macrophages (see J. Biol. Chem., 269, 11530 (1994)), so it is probable that cysteine protease is a cause of pulmonary emphysema. And it is also shown that lung injury (see J. Clin. Invest., 97, 963 (1996)), lung fibrosis (see Cytokine, 5, 57 (1993)) and bronchial asthma (see J. Immunol., 149, 3078 (1992)) are caused by production of IL-1β by caspase-1.

It is pointed out that cysteine protease is also concerned with diseases concerning bones and cartilages. Cathepsin K is specifically recognized in osteoclast and it has a decomposing activity against bone matrix (see J. Biol. Chem., 271, 12517 (1996)), so its inhibitor is expected to show an effect against osteoporosis, arthritis, rheumatoid arthritis, osteoarthritis, hypercalcemia and osteometastasis of cancer, where pathologic bone resorption is recognized. And since IL-1β is shown to be concerned with bone resorption and cartilage degradation, and a caspase-1 inhibitor and IL-1β receptor antagonist inhibit the bone resorption and symptoms of arthritis, a caspase-1 inhibitor and IL-1β receptor antagonist are expected to be effective for arthritis (see Cytokine, 8, 377 (1996)) and osteoporosis (J. Clin. Invest., 93, 1959 (1994)). And it is reported that IL-1β is also concerned with osteoarthritis (see Life Sci., 41, 1187 (1987)).

Cysteine protease is involved with production of various hormones. Since increase of messenger RNA of cathepsin S was recognized by stimuli of thytropin on thyroid epitheliocyte strains (see J. Biol. Chem., 267, 26038 (1992)), it is conceivable that a cysteine protease inhibitor is effective for hyperthyrodism.

Since quantity and activity of cathepsin B protein increased in the gingival sulcus liquid of periodontitis patients (see J. Clin. Periodontol.,25, 34 (1998)), it is pointed out that cysteine protease is concerned with periodontitis.

Therefore, it is expected that the compound that possesses the inhibitory activity of cysteine protease is useful as an agent for the prophylaxis and/or treatment of inflammatory diseases (periodontitis, arthritis, inflammatory bowel diseases, infectious diseases, pancreatitis, hepatitis, glomerulonephritis, endocarditis, myocarditis, etc.), diseases induced by apoptosis (graft versus host diseases, rejection of an organ transplantation, acquired immune deficiency syndrome (AIDS), AIDS-related complex (ARC), adult T cell leukemia, hairy cells leukemia, spondylopathy, disorders of respiratory apparatus, arthritis, HIV or HTLV-1 related diseases such as uveitis, virus-related diseases such as hepatitis C, cancer, collagenosis (systemic lupus erythematosus, rheumatoid arthritis, etc.), ulcerative colitis, Sjögren's syndrome, primary biliary cirrhosis, spontaneous thrombocytopenic purpura, autoimmune hemolytic anemia, myasthenia gravis, autoimmune diseases such as insulin dependent (type I) diabetes, diseases accompanying thrombocytopenia (osteomyelodysplasia syndrome, periodic thrombocytopenia, aplastic anemia, spontaneous thrombocytopenia, disseminated intravascular coagulation (DIC), etc.), hepatic diseases such as viral hepatitis (type A, B, C, F, etc.) or hepatitis medicamentosus and cirrhosis, dementia such as Alzheimer's diseases and Alzheimer's senile dementia, cerebrovascular injury, nerve degeneration diseases, adult acute respiratory distress syndrome, infectious diseases, prostatomegaly, hysteromyoma, bronchial asthma, arteriosclerosis, all kinds of lusus naturae, nephropathy, senile cataract, chronic fatigue syndrome, myodystrophy, peripheral neuropathy, etc.), diseases induced by disorders of immune response (graft versus host diseases, rejection of an organ transplantation, allergic diseases (bronchial asthma, atopic dermatitis, allergic rhinitis, pollinosis, diseases induced by house dusts, irritable pneumonia, food allergy, etc.), psoriasis, rheumatoid arthritis, etc.), autoimmune diseases (insulin-dependent (type I) diabetes, systemic lupus erythematosus, Hashimoto's diseases, multiple sclerosis, etc.), disease by degradation various proteins which compose the organism (myodystrophy, cataract, periodontitis, hepatocyte disease by bile acid such as cholestatic cirrhosis, etc.), decomposition of alveolus elastica such as pulmonary emphysema, ischemic diseases (brain ischemia, brain disorders (encephalopathy) by ischemic reperfusion, myocardial infarction, ischemic hepatopathy, etc.), shock (septic shock, systemic inflammatory response syndrome, endotoxin shock, acidosis, etc.), circulatory system disorders (arteriosclerosis, restenosis after percutaneous transluminal coronary angioplasty (PTCA), etc.)), blood coagulation disorders (thrombocytopenic purpura, hemolytic uremic syndrome, etc.), malignant tumor, acquired immune deficiency syndrome (AIDS) and AIDS-related complex (ARC), parasitic diseases such as malaria, nerve degenerative diseases (Alzheimer-type dementia, Huntington's chorea, Parkinson's diseases, multiple sclerosis, traumatic encephalopathy, traumatic spondylopathy, etc.), pulmopathy such as lung fibrosis, bone resorption diseases (osteoporosis, rheumatoid arthritis, arthritis, osteoarthritis, hypercalcemia, osteometastasis of cancer, etc.), endocrinesthenia such as hyperthyroidism.

On the other hand, what is the most important for inhibitors in inhibiting the activity of proteases is, the special reaction site which interacts with the amino acid residue that is the activity center of proteases. The surrounding structure of the reaction sites are represented by - - - P3P2P1-P1'P2'P3' - - - , centering peptide binding (P1-P1') of the reaction site, and at P1 site there exist amino acid residues fitting the substance specificity of proteases which the inhibitors aim. Some reaction sites against cysteine proteases are known, for Example, in the specification of WO99/54317, the followings are described;

P1 position against calpain I, II (norvaline, phenylalanine, etc.),

P1 position against calpain I (arginine, lysine, tyrosine, valine, etc.),

P1 position against papain (homophenylalanine, arginine, etc.),

P1 position against cathepsin B (homophenylalanine, phenylalanine, tyrosine, etc.),

P1 position against cathepsin S (valine, norleucine, phenylalanine, etc.),

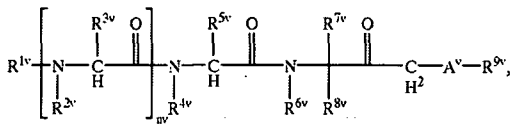
P1 position against cathepsin L (homophenylalanine, lysine, etc.),

P1 position against cathepsin K (arginine, homophenylalanine, leucine, etc.),

P1 position against caspase (aspartic acid).

On the other hand, in the specification of JP-A-H6-192199, it is disclosed that a ketone derivative of formula (V) is useful as a thiol protease inhibitor

(V)

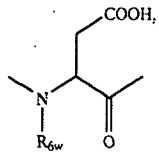


wherein R^{1V} is hydrogen atom, R^{10V}—CO—, R^{10V}—OCO—, R^{10V}—SO_2— or R^{10V}—NHCO—, (1) when A^V is —S—, —SO—, —SO_2—, R^{9V} is C6–14 aryl which may have a substituent, or —$(CH_2)_{mv}$—X^V, where in X^V is hydrogen atom, hydroxy, heteroring optionally having a substituent, etc., mv is an integer of 0 or 1 to 15, and (2) when A^V is —O—, R^{9V} is hydrogen atom or —$(CH_2)_{1V}$—X^V, wherein 1V is an integer of 1 to 15, (3) when A^V is —NR^{11V}—, R^{9V} is C6–14 aryl optionally having a substituent, or —$(CH_2)_{mv}$—X^V, R^{9V} and R^{11V} may be taken together to form a N-containing heteroring optionally having a substituent.

Also, in the specification of WO 93/09135, it is disclosed that the compound of formula (W)

$$R_W\text{-}[A_{1W}\text{—}A_{2W}]_{nw}\text{-}A_{3W}\text{—}A_{4W}\text{—}X_W\text{—}A_{5W} \quad \text{(W)}$$

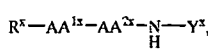
wherein R_{1V} is hydrogen atom, a protected amino, etc., nw is 0 or 1, A_{1W} is Val, Leu, Ala, Ile or trimethylsilyl-Ala, A_{2W} is Phe or Tyr, A_{3W} is a single bond, Val, Leu, Ala, Ile, trimethylsilyl-Ala, etc., A_{4W} is a single bond or —NR_{1W}—CH (Y_{1W}) —CO—, X_W is



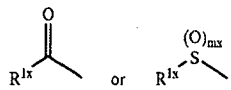
A_{5W} is hydrogen, CF_3, —CH_2—Y_{3W}, wherein Y_{3W} is heteroaryl, etc., is effective as an interleukin-1β releasing inhibitor.

Also, in the specifications of JP-A-H9-136878, WO 97/24339 and JP-A-H10-251295, it is disclosed that tetrazole compounds represented by formula (X), (Y) and (Z) respectively are effective as interleukin-1β converting enzyme inhibitors.

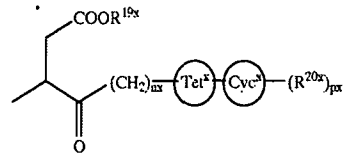
(X)



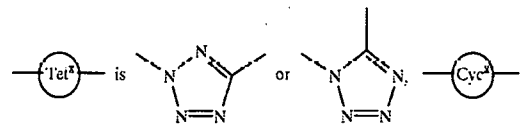
wherein R^X is



and Y^X is

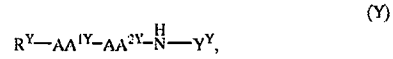


nx is an integer of 1 to 4,

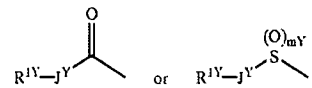


is a carboring or heteroring, and R^{20X} is hydrogen atom, C1–4 alkyl, halogen atom, etc.,

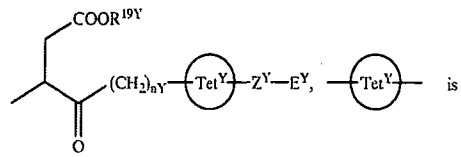
(Y)

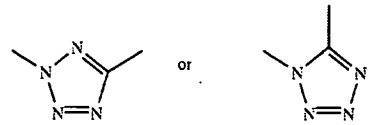


wherein R^Y is



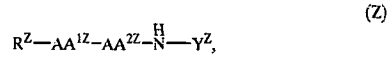
and Y^Y is



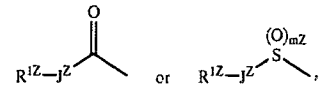


Z^Y is C1–6 alkylene, C2–6 alkenylene, O, S, etc., and E^Y is hydrogen, halogen, C1~4 alkyl, etc.,

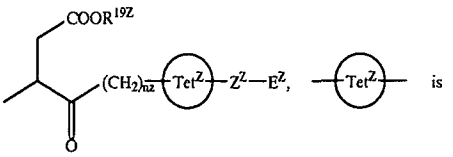
(Z)



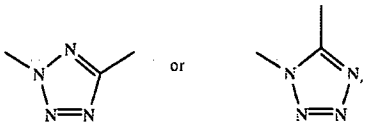
wherein R^2 is



Y^Z is



is



Z^Z is a single bond, C1–6 alkylene, C2–6 alkenylene, O, S, etc. and E^Z is hydrogen atom, halogen atom, CF_3, etc.

DISCLOSURE OF THE INVENTION

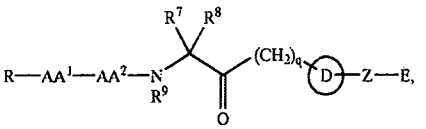
The present inventors have energetically investigated to find out such compounds that have cysteine protease inhibitory activity, and found out that the five-membered ring compound of formula (I) accomplishes the purpose.

The N-containing five-membered ring compound of formula (I) of the present invention is not known as a cysteine protease inhibitor at all.

The present invention relates to

1) a N-containing five-membered ring compound of formula (I) or a non-toxic salt thereof

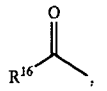
(I)



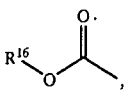
wherein R is

(i) hydrogen,
(ii) C1–8 alkyl,
(iii) CycA,
(iv) C1–8 alkyl substituted with a group selected from halogen atom, CycA, nitro, CF_3 and cyano,

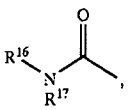
(v)



(vi)



(vii)

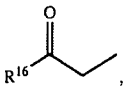


(viii)

or

-continued

(ix)



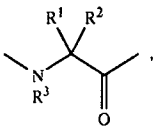
CycA is a C3 15 mono-, bi- or tri-cyclic carboring or a mono-, bi- or tri-cyclic 3–15 membered heteroring comprising 1–4 of nitrogen, 1–2 of oxygen and/or 1 of sulfur;

R^{16} is
(1) C1–8 alkyl,
(2) C2–8 alkenyl,
(3) C2–8 alkynyl,
(4) CycA or
(5) C1–8 alkyl, C2–8 alkenyl or C2–8 alkynyl substituted with a group selected from halogen atom, nitro, CF_3, cyano, CycA, $NR^{18}R^{19}$ and —NHC(O)-CycA;

R^{17}, R^{18} and R^{19} each independently represents hydrogen or C1–4 alkyl,

AA^1 is
(i) a single bond, or

(ii)



wherein R^1 and R^2 are the same or different to represent
(i) hydrogen,
(ii) C1–8 alkyl,
(iii) CycA or
(iv) C1–8 alkyl substituted with 1–5 of group selected from the following (1) to (8):
(1) $—NR^{21}R^{22}$,
(2) $—OR^{23}$,
(3) $—SR^{24}$,
(4) $—COR^{25}$,
(5) $—NR^{26}CONR^{21}R^{22}$,
(6) guanidino,
(7) CycA,
(8) $—NR^{26}SO_2R^{21}$; or

R^1 and R^2 are taken together to form C2–8 alkylene (wherein one carbon atom may be replaced by oxygen, sulfur or $—NR^{20}—$ and the alkylene may be substituted with $—NR^{21}R^{22}$ or $—OR^{23}$,

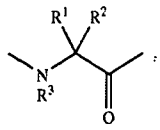
R^{20} is hydrogen, C1–4 alkyl, —COO—(C1–4 alkyl), phenyl or C1–4 alkyl substituted with phenyl,

R^{21}, R^{22}, R^{23}, R^{24} and R^{26} are the same or different to represent hydrogen, C1–4 alkyl, phenyl or C1–4 alkyl substituted with phenyl,

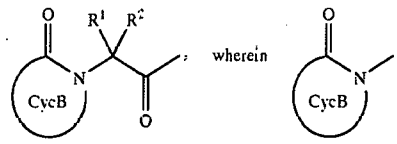
R^{25} is C1–4 alkyl, phenyl, $—NR^{21}R^{22}$, wherein all symbols have the same meaning as above, $—OR^{23}$, wherein R^{23} is the same meaning as above, or C1–4 alkyl substituted with phenyl,

R^3 is hydrogen, C1–8 alkyl, phenyl or C1–8 alkyl substituted with phenyl or

R^3 is taken together with R^1 to form C2–6 alkylene, wherein one carbon atom may be replaced by oxygen, sulfur or $—NR^{20}—$ and the alkylene may be substituted with $—NR^{21}R^{22}$ or $—OR^{23}$, or when AA^1 is



AA^1 and R may be taken together to form

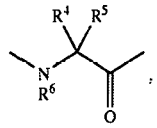


is a 5–12 membered mono- or bi-cyclic heteroring and the other symbols are the same meanings as above,

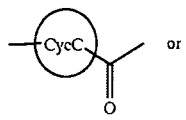
AA^2 is

(i) a single bond,

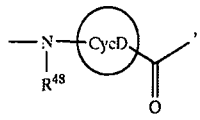
(ii)



(iii)



(iv)



wherein R^4 and R^5 are the same or different to represent

(1) hydrogen,

(2) C1–8 alkyl,

(3) CycA or

(4) C1–8 alkyl substituted with 1–5 of group selected from the following (a) to (h):

(a) $—NR^{41}R^{42}$,

(b) $—OR^{43}$,

(c) $—SR^{44}$,

(d) $—COR^{45}$,

(e) $—NR^{46}CONR^{41}R^{42}$,

(f) guanidino,

(g) CycA,

(h) $—NR46SO_2R^{41}$; or

R^4 and R^5 are taken together to form C2–8 alkylene, wherein one carbon atom may be replaced by oxygen, sulfur or $—NR^{40}—$ and the alkylene may be substituted with $—NR^{41}R^{42}$ or $—OR^{43}$,

R^{40} is hydrogen, C1–4 alkyl, —COO—(C1–4 alkyl), phenyl or C1–4 alkyl substituted with phenyl,

R^{41}, R^{42}, R^{43}, R^{44} and R^{46} are the same or different to represent hydrogen, C1–4 alkyl, phenyl or C1–4 alkyl substituted with phenyl,

R^{45} is C1–4 alkyl, phenyl, $—NR^{41}R^{42}$, wherein all symbols are the same meaning as above, $—OR^{43}$, wherein R^{43} is the same meaning as above, or C1–4 alkyl substituted with phenyl,

R^6 is hydrogen, C1–8 alkyl, phenyl or C1–8 alkyl substituted with phenyl or

R^6 is taken together with R^4 to form C2–6 alkylene, wherein one carbon atom may be replaced by oxygen, sulfur or $—NR^{40}—$ and the alkylene may be substituted with $—NR^{41}R^{42}$ or $—OR^{43}$,

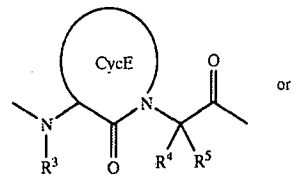
R^{48} is hydrogen, C1–4 alkyl, phenyl or C1–4 alkyl substituted with phenyl or when AA^1 is a single bond, R^{48} and R may be taken together to form C2–6 alkylene, wherein one carbon atom may be replaced by oxygen, sulfur or $—NR^{47}$, wherein R^{47} is hydrogen or C1–4 alkyl,

CycC is a 3–17 membered mono- or bi-cyclic heteroring,

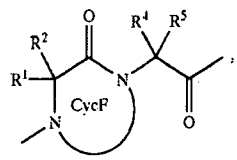
CycD is a C3–14 mono- or bi-cyclic carboring or a 3–14 membered mono- or bi-cyclic heteroring, or

AA^2 and AA^1 are taken together to form

(i)



(ii)



wherein CycE is a 4–18 membered mono- or bi-cyclic heteroring, CycF is a 5–8 membered monocyclic heteroring, and the other symbols have the same meanings as above,

R^7 and R^8 are the same or different to represent

(i) hydrogen,

(ii) C1–8 alkyl,

(iii) CycA or

(iv) C1–8 alkyl substituted with 1–5 of group selected from the following (1) to (8);

(1) $—NR^{61}R^{62}$,

(2) $—OR^{63}$,

(3) $—SR^{64}$,

(4) $—COR^{65}$,

(5) $—NR^{66}CONR^{61}R^{62}$,

(6) guanidino,

(7) CycA,

(8) $—NR^{66}SO_2R^{61}$, or

R^7 and R^8 are taken together to form C2–8 alkylene, wherein one carbon atom may be replaced by oxygen, sulfur or $—NR^{60}—$ and the alkylene may be substituted with $—NR^{61}R^{62}$ or $—OR^{63}$,

R^{60} is hydrogen, C1–4 alkyl, —COO—(C1–4 alkyl), phenyl or C1–4 alkyl substituted with phenyl,

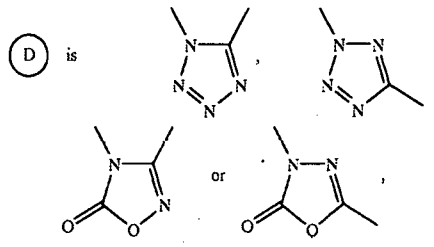
R^{61}, R^{62}, R^{63}, R^{64} and R^{66} are the same or different to represent hydrogen, C1–4 alkyl, phenyl or C1–4 alkyl substituted with phenyl,

R^{65} is C1–4 alkyl, phenyl, $—NR^{61}R^{62}$, wherein all symbols are the same meanings as above, $—OR^{63}$, wherein R^{63} is the same meaning as above, or C1–4 alkyl substituted with phenyl,

R^9 is hydrogen, C1–8 alkyl, phenyl or C1–8 alkyl substituted with phenyl or

R^9 is taken together with R^7 to form C2–6 alkylene, wherein one carbon atom may be replaced by oxygen, sulfur or $—NR^{60}—$ and the alkylene may be substituted with $—NR^{61}R^{62}$ or $—OR^{63}$,

q is an integer of 1 to 4,

D is  ,

Z is a single bond, C1–6 alkylene, C2–6 alkenylene, C2–6 alkynylene, —O—, —S—, —CO—, —SO—, —SO_2—, —NR^{10}—, or C1–6 alkylene whose one carbon atom is replaced by —O—, —S—, —CO—, —SO—, —SO_2— or —NR^{10}—,

R^{10} is hydrogen atom, C1–4 alkyl, phenyl, or C1–4 alkyl substituted with phenyl,

E is hydrogen atom, halogen atom, CF_3, diphenyl(C1-4) alkyl, tri(C1–4 alkyl) silyl, C1–4 alkyl, —$COOR^{18}$, —$CONR^{19}R^{20}$, —$NR^{19}R^{20}$, -G-$(R^{35})_r$, —CH_2—$PO(OR^{36})_2$ or —$CH(PO(OR^{36})_2)_2$,

R^{18} is hydrogen atom, C1–4 alkyl, phenyl or C1–4 alkyl substituted with phenyl,

R^{19} and R^{20} independently represent hydrogen atom, C1–4 alkyl, phenyl or C1–4 alkyl substituted with phenyl,

$R^{19}$and R^{20} are taken together with nitrogen atom to which they are attached, to represent 5–7 membered monocyclic heteroring containing 1–2 of nitrogen, 1 of nitrogen and oxygen atom, or 1 of nitrogen or sulfur atom,

G is C3–10 mono- or bi-cyclic carboring or 5–18 membered mono- or bi- or tricyclic heteroring containing 1 to 3 of nitrogen atom(s), 1 of oxygen atom and/or 1 of sulfur atom and r is an integer of 1 to 5,

R^{35} is (i) hydrogen atom, (ii) C1–8 alkyl, (iii) halogen atom, (iv) nitoro, (v) CF_3, (vi) cyano, (vii) —OR^{37}, (viii) —$NR^{37}R^{38}$, (ix) —SR^{37}, (x) —$COOR^{37}$, (xi) —COR^{37}, (xii) —CO—$NR^{19}R^{20}$, (xiii) a C3–10 mono- or bi-cyclic carboring, (xiv) a 5–18 membered mono-, bi- or tricyclic heteroring containing 1 to 3 of nitrogen atom(s), 1 of oxygen atom, and/or 1 of sulfur atom, (xv) C1–8 alkyl substituted with a 3–10 membered mono- or bi-cyclic carboring or a 5–18 membered mono-, bi- or tricyclic heteroring containing 1 to 3 of nitrogen atom(s), 1 of oxygen atom and/or 1 of sulfur atom, which ring may be substituted with 1 to 5 group(s) selected from the following groups: C1–8 alkyl, phenyl, C1–4 alkyl substituted with phenyl, halogen atom, nitro, CF_3, cyano, tetrazole, —OR^{39}, —$NR^{39}R^{40}$, —SR^{39}, —$COOR^{39}$ or —COR^{39},

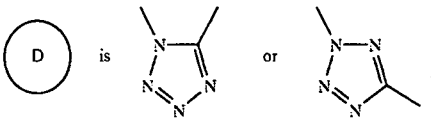
R^{36} is hydrogen atom, C1–8 alkyl, cyano, phenyl, C1–8 alkyl substituted with phenyl or cyano, C1–4 alkyl subsutituted with 1 to 3 halogen atom(s),

R^{37} is hydrogen atom, C1–4 alkyl, phenyl, C1–4 alkyl substituted with phenyl,

R^{38} is hydrogen atom, C1–4 alkyl, phenyl, C1–4 alkyl substituted with phenyl, C2–5 acyl or $COCF_3$,

R^{39} and R^{40} independently represent hydrogen atom, C1–4 alkyl, phenyl, C1–4 alkyl substituted with phenyl,

with the proviso that when (i) Z represents —SO—, E does not represent hydrogen atom and when (ii)

D is  ,

R^7 and R^8 do not represent C1 alkyl substituted with —COR^{65}, (iii) CycA included in R, R^1, R^2, R^4, R^5, R^7, R^8 and R^{16} may be the same or different and CycA, CycB, CycC, CycD, CycE and CycF, independently, may be substituted with 1 to 5 of R^{27};

R^{27} is

(1) C1–8 alkyl,

(2) halogen atom,

(3) —$NR^{11}R^{12}$,

(4) —OR^{13},

(5) a C5–10 mono-or bi-cyclic carboring,

(6) nitro,

(7) CF_3,

(8) cyano,

(9) a 5–10 membered mono- or bi-cyclic heteroring

(10) —SR^{14},

(11) —COR^{15},

(12) oxo,

(13) —SO_2R^{15},

(14) —OCF_3 or

(15) C1–8 alkyl substituted with 1 to 5 of group(s) selected from the following (a) to (m):

(a) halogen, (b) —$NR^{11}R^{12}$, (c) —OR^{13}, (d) C5–10 mono- or bi-cyclic carboring, (e) nitro, (f) CF_3, (g) cyano, (h) 5–10 membered mono- or bi-cyclic heteroring, (j) —SR^{14}, (k) —COR^{15}, (l) —SO_2R^{15}, or (m) —OCF_3,

wherein R^{11} and R^{12} are the same or different to represent hydrogen, C1–4 alkyl, —COO—(C1–4 alkyl), phenyl or C1–4 alkyl substituted with phenyl,

R^{13} and R^{14} are the same or different to represent hydrogen, C1–4 alkyl, phenyl or C1–4 alkyl substituted with phenyl,

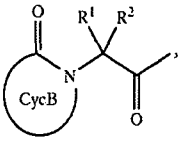
R^{15} is C1–4 alkyl, phenyl, —$NR^{11}R^{12}$, wherein all symbols have the same meanings as above, —OR^{13}, wherein R^{13} has the same meaning as above, or C1–4 alkyl substituted with phenyl,

2) a method for the preparation thereof and

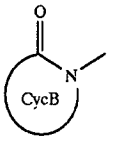
3) a pharmaceutical agent comprising the N-containing five-membered ring compound and non-toxic salt thereof as active ingredient.

DETAILED DESCRIPTION OF THE PRESENT INVENTION

In the compound of formula (I), in

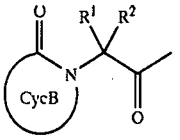


which AA^1 and R together form,



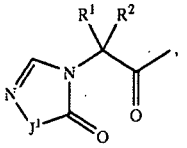
is a 5–12 membered heteroring containing 1–3 of nitrogen, 1 of oxygen, and/or 1 of sulfur (this heteroring may be substituted with 1–5 of R^{27}).

And to describe

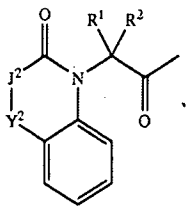


concretely, it is

(i)

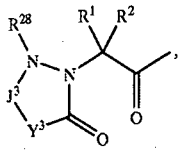


(ii)



or

(iii)



wherein J^1 is oxygen, sulfur, —NR^{29}—, wherein R^{29} is hydrogen, C1–4 alkyl, CycA or C1–4 alkyl substituted with CycA, C1–3 alkylene or C2–3 alkenylene,

J^2 is a single bond or C1–2 alkylene,

Y^2 is —N═CH—, —CH═N— or C1–2 alkylene,

J^3 is carbonyl or C1–3 alkylene,

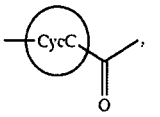
Y^3 is C1–3 alkylene, oxygen or —NR^{29}—, wherein R^{29} is the same meaning as above,

R^{28} is hydrogen, C1–4 alkyl, CycA or C1–4 alkyl substituted with CycA, or

R^{28} is taken together with R^1 to form C2–4 alkylene, and the other symbols have the same meaning as above and each ring may be substituted with 1–5 of R^{27}.

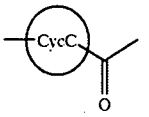
In the compound of formula (I), in

(iii)



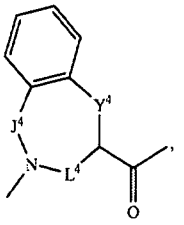
which AA^2 represents, CycC is a 3–17 membered heteroring which contains 1–2 of nitrogen, 1 of oxygen and/or 1 of sulfur (this ring may be substituted with 1–5 of R^{27}).

And to describe

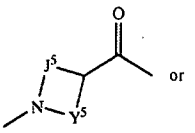


concretely,

(iii-1)

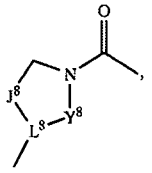


(iii-2)



or

(iii-3)



wherein J^4, Y^4 and L^4 are the same or different to represent a single bond or C1–3 alkylene, wherein J^4, Y^4 and L^4 do not represent a single bond at the same time,

J^5 is C1–6 alkylene,

Y^5 is a single bond, C1–3 alkylene or —NR^{67}—, wherein R^{67} is hydrogen,

C1–4 alkyl, phenyl or C1–4 alkyl substituted with phenyl,

J^8 is C1–5 alkylene, wherein one carbon atom may be replaced by oxygen,

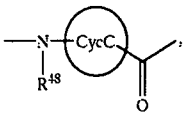
Y^8 is a single bond or C1–4 alkylene,

L^8 is —N— or —CH—,

and the other symbols have the same meaning as above and each ring may be substituted with 1–5 of R^{27}.

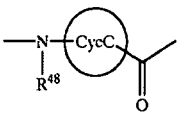
And in

(iv)



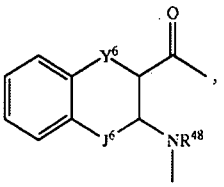
which AA^2 represents, CycD is a C3–14 mono- or bi-cyclic carboring or 3–14 membered heteroring which contains 1–2 of nitrogen, 1 of oxygen and/or 1 of sulfur (this carboring and heteroring may be substituted with 1–5 of R^{27}).

And to describe

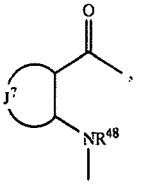


concretely, it is

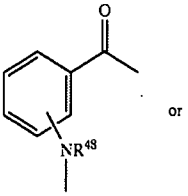
(iv-1)



(iv-2)

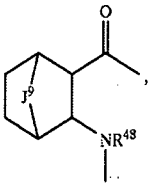


(iv-3)



or

(iv-4)



wherein J^6 and Y^6 are the same or different to represent a single bond or C1–3 alkylene, wherein J^6 and Y^6 do not represent a single bond at the same time,

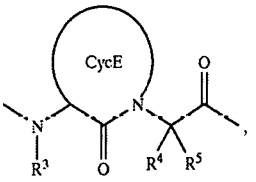
J^7 is C1–6 alkylene, wherein one carbon atom may be replaced by oxygen, sulfur or $—NR^{67}—$, wherein R^{67} has the same meaning as above,

J^9 is C1–3 alkylene, oxygen, sulfur or $—NR^{67}—$, wherein R^{67} is the same meaning as above,

and the other symbols have the same meanings as above and each ring may be replaced by 1–5 of R^{27}.

In the compounds of the formula (I), in

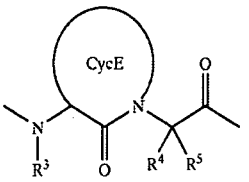
(i)



which AA^1 and AA^2 together form,

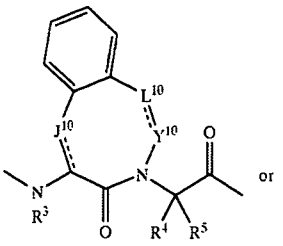
CycE is a 4–18 membered heteroring which contains 1–2 of nitrogen, 1 of oxygen and/or 1 of $—S(O)_p—$ (this heteroring may be substituted with 1–5 of R^{27}).

And to describe



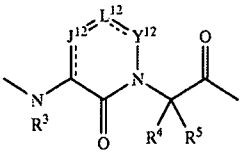
concretely, it is

(i-1)



or

(i-2)



wherein $===$ is a single bond or a double-bond,

J^{10} and Y^{10} are the same or different to represent a single bond or C1–3 alkylene,

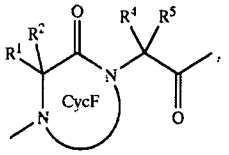
L^{10} is a single bond, C1–3 alkylene, $—NR^{57}—$, wherein R^{57} is hydrogen, C1–4 alkyl, phenyl or C1–4 alkyl substituted with phenyl, —N=, oxygen or $—S(O)_p—$, wherein p is 0 or an integer of 1 to 2,

J^{12} and Y^{12} are the same or different to represent a single bond or C1–3 alkylene,

L^{12} is C1–3 alkylene, $—NR^{57}—$, wherein R^{57} is the same meaning as above), —N=, =N—, oxygen or $—S(O)_p—$, wherein p has the same meaning as above,

and the other symbols have the same meanings as above and each ring may be substituted with 1–5 of R^{27}.

And in

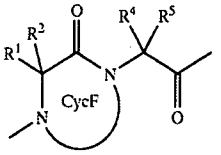


(ii)

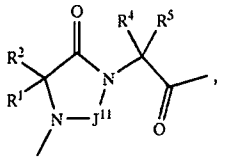
which AA^1 and AA^2 together form.

CycF is a 5–8 membered heteroring containing 2 of nitrogen.

And to describe



concretely, it is



wherein J^{11} is carbonyl or C2–4 alkylene and the other symbols have the same meaning as above and the ring therein may be substituted with 1–5 of R^{27}.

In the present specification, C1–4 alkyl is methyl, ethyl, propyl, butyl and isomers thereof.

In the present specification, C1–8 alkyl is methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl and isomers thereof.

In the present specification, C2–8 alkenyl is, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl containing 1–3 of double bond and isomers thereof. For example, vinyl, propenyl, butenyl, hexenyl, hexadienyl, octadienyl, etc. are included.

In the present specification, C2–8 alkynyl is ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl containing 1–3 of triple bond and isomers thereof. For example, ethynyl, propynyl, butynyl, pentynyl, hexynyl, heptynyl, octynyl, etc. are included.

In the present specification, C1–4 alkyl substituted with phenyl is phenylmethyl, phenylethyl, phenylpropyl, phenylbutyl and isomers thereof.

In the present specification, diphenyl(C1–4)alkyl is methyl, ethyl, propyl, butyl substituted with 2 of phenyl and isomers thereof.

In the present specification, C2–5 acyl is acetyl, propionyl, butyryl, valeryl and isomers thereof.

In the present specification, C1–2 alkylene is, methylene, ethylene and isomers thereof.

In the present specification, C1–3 alkylene is, methylene, ethylene, trimethylene and isomers thereof.

In the present specification, C1–4 alkylene is methylene, ethylene, trimethylene, tetramethylene and isomers thereof.

In the present specification, C1–5 alkylene is methylene, ethylene, trimethylene, tetramethylene, pentamethylene and isomers thereof.

In the present specification, C1–6 alkylene is methylene, ethylene, trimethylene, tetramethylene, pentamethylene, hexamethylene and isomers thereof.

In the present specification, C2–4 alkylene is ethylene, trimethylene, tetramethylene and isomers thereof.

In the present specification, C2–6 alkylene is ethylene, trimethylene, tetramethylene, pentamethylene, hexamethylene and isomers thereof.

In the present specification, C2–8 alkylene is ethylene, trimethylene, tetramethylene, pentamethylene, hexamethylene, heptamethylene, octamethylene and isomers thereof.

In the present specification, C2–3 alkenylene is vinylene, propenylene and isomers thereof.

In the present specification, C2–6 alkenylene is vinylene, propenylene, butenylene, pentenylene, hexenylene and isomers thereof.

In the present specification, C2–6 alkynylene is ethynylene, propynylene, butynylene, pentynylene, hexynylene and isomers thereof.

In the present specification, C2–8 alkylene is ethylene, trimethylene, tetramethylene, pentamethylene, hexamethylene, heptamethylene, octamethylene and isomers thereof.

In the present specification, C2–6 alkylene whose one carbon atom may be replaced by oxygen, sulfur, $—NR^{20}—$, $—NR^{40}—$ or $—NR^{60}—$ is ethylene, trimethylene, tetramethylene, pentamethylene, hexamethylene and isomers thereof, wherein one carbon atom thereof may be replaced by oxygen, sulfur, $—NR^{20}—$, $—NR^{40}—$, or $—NR^{60}—$, for example, such groups are $—CH_2—O—CH_2—$, $—CH_2—CH_2—O—CH_2—$, $—CH_2—CH_2—S—CH_2—$, $—CH_2—CH_2—NH—CH_2—$, $—CH_2—CH_2—O—CH_2—CH_2—$, $—CH_2—CH_2—S—CH_2—CH_2—$, $—CH_2—CH_2—NH—CH_2—CH_2—$, $—CH_2—CH_2—N(CH_3)—CH_2—CH_2—$, etc.

In the present specification, C2–8 alkylene whose one carbon atom may be replaced by oxygen, sulfur, $—NR^{20}—$, $—NR^{40}—$ or $—NR^{60}—$ is ethylene, trimethylene, tetramethylene, pentamethylene, hexamethylene, heptamethylene, octamethylene and isomers thereof, wherein one carbon atom may be replaced by oxygen, sulfur, $—NR^{20}—$, $—NR^{40}—$ or $—NR^{60}—$, for example, such groups are $—CH_2—O—CH_2—$, $—CH_2—CH_2—O—CH_2—$, $—CH_2—CH_2—S—CH_2—$, $—CH_2—CH_2—NH—CH_2$, $—CH_2—CH_2—O—CH_2—CH_2—$, $—CH_2—CH_2—S—CH_2—CH_2—$, $—CH_2—CH_2—NH—CH_2—CH_2—$, $—CH_2—CH_2—N(CH_3)—CH_2—CH_2—$, etc.

In the present specification, C1–4 alkoxy is methoxy, ethoxy, propoxy, butoxy and isomers thereof.

In the present specification, halogen atom means chlorine, fluorine, bromine and iodine atom.

In the present specification, C1–4 alkyl substituted with 1 to 3 of halogen atom(s) means methyl, ethyl, propyl, butyl which is substituted with 1 to 3 of atom(s) selected from chlorine, fluorine, bromine or iodine.

In the present specification, mono- or bi-cyclic C5–10 carboring is mono- or bi-cyclic C5–10 carboaryl or partially or completely saturated one thereof. For example, cyclopentane, cyclohexane, cycloheptane, cyclopentene, cyclohexene, cyclopentadiene, cyclohexadiene, benzene, pentalene, indene, naphthalene, azulene, perhydropentalene, perhydroindene, perhydronaphthalene, perhydroazulene, adamantyl ring, etc. are included.

In the present specification, mono-, bi- or tri-cyclic C3–15 carboring is mono-, bi- or tri-cyclic carboaryl or partially or completely saturated one thereof. For example, cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane, cyclopentene, cyclohexene, cyclopentadiene, cyclohexadiene, benzene, pentalene, indene, naphthalene, azulene, fluorene, phenanthrene, anthracene, acenaphthylene, biphenylene, perhydropentalene,

perhydroindene, perhydronaphthalene, perhydroazulene, perhydrofluorene, perhydrophenanthrene, perhydroanthracene, perhydroacenaphthylene, perhydrobiphenylene, adamantyl ring etc. are included.

In the present specification, mono- or bi-cyclic 5–10 membered heteroring containing 1–4 of nitrogen, 1 of oxygen and/or sulfur is mono- or bi-cyclic 5–10 membered heteroaryl containing 1–4 of nitrogen, 1 of oxygen and/or sulfur or partially or completely saturated one thereof.

Above 5–10 membered mono- or bi-cyclic heteroaryl containing 1–4 of nitrogen, 1 of oxygen and/or 1 of sulfur is, for example, pyrrole, imidazole, triazole, tetrazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, azepine, diazepine, furan, pyrane, oxepine, thiophene, thiaine (thiopyrane), thiepine, oxazole, isooxazole, thiazole, isothiazole, oxadiazole, oxazine, oxadiazine, oxazepine, oxadiazepine, thiadiazole, thiazine, thiadiazine, thiazepine, thiadiazepine, indole, isoindole, benzofuran, isobenzofuran, benzothiophene, isobenzothiophene, indazole, quinoline, isoquinoline, phthalazine, naphthyridine, quinoxaline, quinazoline, cinnoline, benzoxazole, benzothiazole, benzoimidazole, etc.

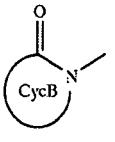
Above partially or completely saturated mono- or bi-cyclic 5–10 membered heteroaryl containing 1–4 of nitrogen, 1 of oxygen and/or 1 of sulfur is, for example, pyrroline, pyrrolidine, imidazoline, imidazolidine, triazoline, triazolidine, tetrazoline, tetrazolidine, pyrazoline, pyrazolidine, piperidine, piperazine, tetrahydropyridine, tetrahydropyrimidine, tetrahydropyridazine, dihydrofuran, tetrahydrofuran, dihydropyrane, tetrahydropyrane, dihydrothiophene, tetrahydrothiophene, dihydrothiaine (dihydrothiopyrane), tetrahydrothiaine (tetrahydrothiopyrane), oxazoline (dihydrooxazole), oxazolidine (tetrahydroxazole), dihydroisoxazole, tetrahydroisoxazole, oxadiazoline (dihydroxadiazole), oxadiazolidine (tetrahydroxadiazole), thiazoline (dihydrothiazole), thiazolidine (tetrahydrothiazole), dihydroisothiazole, tetrahydroisothiazole, morpholine, thiomorpholine, indoline, isoindoline, dihydrobenzofuran, perhydrobenzofuran, dihydroisobenzofuran, perhydroisobenzofuran, dihydrobenzothiophene, perhydrobenzothiophene, dihydroisobenzothiophene, perhydroisobenzothiophene, dihydroindazole, perhydroindazole, dihydroquinoline, tetrahydroquinoline, perhydroquinoline, dihydroisoquinoline, tetrahydroisoquinoline, perhydroisoquinoline, dihydrophthalazine, tetrahydrophthalazine, perhydrophthalazine, dihydronaphthyridine, tetrahydronaphthyridine, perhydronaphthyridine, dihydroquinoxaline, tetrahydroquinoxaline, perhydroquinoxaline, dihydroquinazoline, tetrahydroquinazoline, perhydroquinazoline, dihydrocinnoline, tetrahydrocinnoline, perhydrocinnoline, dihydrobenzoxazole, perhydrobenzoxazole, dihydrobenzothiazole, perhydrobenzothiazole, dihydrobenzoimidazole, perhydrobenzoimidazole, etc.

In the present specification, a 3–15 membered mono-, bi- or tri-cyclic heteroring containing 1–4 of nitrogen, 1–2 of oxygen and/or 1 of sulfur is 3–15 membered mono-, bi- or tri-cyclic heteroaryl containing 1–4 of nitrogen, 1–2 of oxygen and/or 1 of sulfur or partially or completely saturated one thereof.

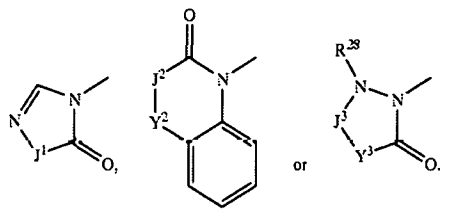
Above 3–15 membered mono-, bi- or tri-cyclic heteroring containing 1–4 of nitrogen, 1–2 of oxygen and/or 1 of sulfur is, for example, pyrrole, imidazole, triazole, tetrazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, azepine, diazepine, furan, pyrane, oxepine, oxazepine, thiophene, thiaine (thiopyrane), thiepine, oxazole, isoxazole, thiazole, isothiazole, oxadiazole, oxazine, oxadiazine, oxazepine, oxadiazepine, thiadiazole, thiazine, thiadiazine, thiazepine, thiadiazepine, indole, isoindole, benzofuran, isobenzofuran, benzothiophene, isobenzothiophene, indazole, quinoline, isoquinoline, phthalazine, naphthyridine, quinoxaline, quinazoline, cinnoline, benzoxazole, benzothiazole, benzoimidazole, carbazole, acridine ring, etc.

Above partially or completely saturated mono-, bi- or tri-cyclic 3–15 membered heteroring containing 1–4 of nitrogen, 1–2 of oxygen and/or 1 of sulfur is, aziridine, oxirane, azetidine, oxetane, thiirane, thietane, pyrroline, pyrrolidine, imidazoline, imidazolidine, triazoline, triazolidine, tetrazoline, tetrazolidine, pyrazoline, pyrazolidine, piperidine, piperazine, tetrahydropyridine, tetrahydropyrimidine, tetrahydropyridazine, dihydrofuran, tetrahydrofuran, dihydropyrane, tetrahydropyrane, dihydrothiophene, tetrahydrothiophene, dihydrothiaine (dihydrothiopyrane), tetrahydrothiaine (tetrahydrothiopyrane), oxazoline (dihydroxazole), oxazolidine (tetrahydroxazole), dihydroisoxazole, tetrahydroisoxazole, oxadiazoline (dihydroxadiazole), oxadiazolidine (tetrahydroxadiazole), thiazoline (dihydrothiazole), thiazolidine (tetrahydrothiazole), dihydroisothiazole, tetrahydroisothiazole, morpholine, thiomorpholine, indoline, isoindoline, dihydrobenzofuran, perhydrobenzofuran, dihydroisobenzofuran, perhydroisobenzoturan, dihydrobenzothiophene, perhydrobenzothiophene, dihydroisobenzothiophene, perhydroisobenzothiophene, dihydroindazole, perhydroindazole, dihydroguinoline, tetrahydroquinoline, perhydroquinoline, dihydroisoquinoline, tetrahydroisoquinoline, perhydroisoquinoline, dihydrophthalazine, tetrahydrophthalazine, perhydrophthalazine, dihydronaphthyridine, tetrahydronaphthyridine, perhydronaphthyridine, dihydroquinoxaline, tetrahydroquinoxaline, perhydroquinoxaline, dihydroquinazoline, tetrahydroquinazoline, perhydroquinazoline, dihydrocirinoline, tetrahydrocinnoline, perhydrocinnoline, dihydrobenzoxazole, perhydrobenzoxazole, dihydrobenzothiazole, perhydrobenzothiazole, dihydrobenzoimidazole, perhydrobenzoimidazole, benzoxazepine, benzoxadiazepine, benzothiazepine, benzothiadiazepine, benzazepine, benzodiazepine, indoloxazepine, indolotetrahydroxazepine, indoloxadiazepine, indolotetrahydroxadiazepine, indolothiazepine, indolotetrahydrothiazepine, indolothiadiazepine, indolotetrahydrothiadiazepine, indolazepine, indolotetrahydroazepine, indolodiazepine, indolotetrahydrodiazepine, benzofurazane, benzothiadiazole, benzotriazole, camphor, imidazothiazole, dihydrocarbazole, tetrahydrocarbazole, perhydrocarbazole, dihydroacridine, tetrahydroacridirie, perhydroacridine, dioxolane, dioxane, dioxazine ring etc.

In the present specification, a 5–12 membered heteroring containing 1–3 of nitrogen, 1 of oxygen and/or 1 of sulfur atom, i.e.

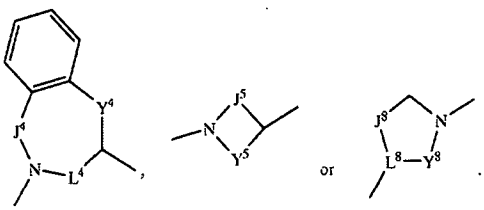


is, for example, a ring represented by



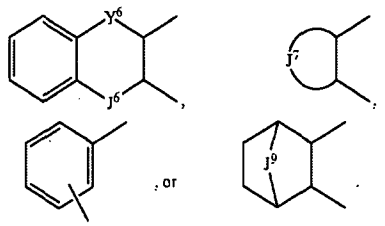
Specifically, 2-oxo-1,3,4-triazoline, 5-oxo-1,2,4-oxadiazoline, 5-oxo-1,2,4-thiadiazoline, 4-oxoimidazoline, 3,4-dihydro-4-oxopyrimidine, 3,4,5,6-tetrahydro-4-oxopyrimidine, 2-oxoindoline, 2-oxo-tetrahydroquinoline, 1,2-dihydro-2-oxoquinazoline, 1,2-dihydro-2-oxoquinoxaline, 3-oxopyrazolidine, perhydro-3-oxopyridazine, 2-oxo-1,3,4-oxadiazolidine, perhydro-2-oxo-1,3,4-oxadiazine, etc. are included.

In the specification, 3–17 membered heteroring containing 1–2 of nitrogen, 1 of oxygen and/or 1 of sulfur represented by CycC is, for example, a ring represented by



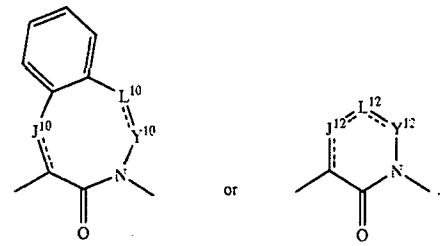
Specifically, pyrrolidine, imidazolidine, pyrazolidine, piperidine, piperazine, perhydropyrimidine, perhydropyridazine, thiazolidine, indoline, isoindoline, tetrahydroquinoline, tetrahydroisoquinoline, etc. are included.

In the specification, a C3–14 mono- or bi-cyclic carboring or 3–14 membered heteroring containing 1–2 of nitrogen, 1 of oxygen, and/or 1 of sulfur represented by CycD is, for example, a ring represented by



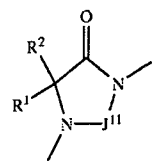
Specifically, cyclopentane, cyclohexane, cycloheptane, benzene, indan, tetrahydronaphthalene, oxorane, oxane, thiorane, thian, pyrrolidine, piperidine, bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane, 7-azabicyclo[2.2.1]heptane, 7-oxobicyclo[2.2.1]heptane, 7-thiabicyclo[2.2.1]heptane, etc. are included.

In the specification, 4–18 membered heteroring containing 1–2 of nitrogen, 1 of oxygen and/or 1 of $—S(O)_p—$, i.e. CycE is, for example, a ring represented by



Specifically, 2-oxopyrrolidine, 2-oxopiperidine, 2-oxoperhydroazepine, 3-oxopiperazine, 3-oxomorpholine, 1,1,-dioxo-3-isothiazolidine, 1,1-dioxo-3-isothiazine, 4-oxodiazepine, 2-oxoindoline, 2-oxo-tetrahydroquinoline, 1,1-dioxo-3-benzisothiazolidine, 1,1-dioxo-3-benzisothiazine, etc. are included.

In the present invention, 5–8 membered heteroring which contains 2 of nitrogen. i.e. CycF is, for example, a ring represented by



Specifically, 2,4-dioxoimidazolidine, 2-oxopiperazine, 2-oxoperhydrodiazepine substituted by R^1 and R^2 are included.

In the present invention, as may be easily understood by those skilled in the art, the symbol:

indicates that the substituent attached thereto is in front of the sheet (β-position) unless specified,

indicates that the substituent attached thereto is behind the sheet (α-position) unless specified, and

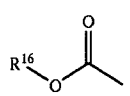
indicates that the substituent attached thereto is in β-position or α-position or a mixture thereof.

In the formula (I), all groups represented by R are preferable, but preferably, R is

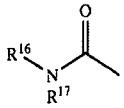
(i) hydrogen,
(ii) C1–8 alkyl,
(iii) CycA,
(iv) C1–8 alkyl substituted with a group selected from CycA and nitro,

(v)

(vi)



(vii)



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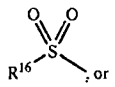
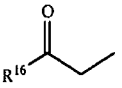
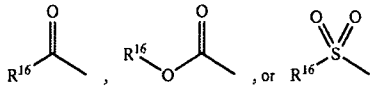
(viii)



(ix)



more preferably, C1–8 alkyl or C1–8 alkyl substituted with CycA or nitro, or



Any group represented by R^{16} is preferable, but more preferably, R^{16} is

[I] (1) C1–8 alkyl,
(2) C2–8 alkenyl,
(3) C2–8 alkynyl,
(4) CycA, or
(5) C1–8 alkyl substituted with a group selected from CycA or —NHC (O)-CycA,
(6) C2–8 alkenyl substituted with CycA or
(7) C2–8 alkynyl substituted with CycA,
wherein CycA may be substituted with 1–5 of R^{27a}, and R^{27a} is (1) C1–8 alkyl,
(2) halogen,
(3) $—NR^{11}R^{12}$,
(4) $—OR^{13}$,
(5) phenyl,
(6) nitro,
(7) CF_3,
(8) cyano,
(9) tetrazole,
(10) $—SR^{14}$,
(11) $—COR^{15}$,
(12) oxo or
(13) C1–8 alkyl substituted with 1–5 of group selected from the following (a) to (k):
(a) halogen, (b) $—NR^{11}R^{12}$, (c) $—OR^3$, (d) phenyl, (e) nitro, (f) CF_3, (g) cyano, (h) tetrazole, (j) $—SR^{14}$, (k) $—COR^{15}$, or
[II] (a) C1–8 alkyl, C2–8 alkenyl or C2–8 alkynyl substituted with a group selected from halogen, CF_3, nitro, cyano or $NR^{18}R^{19}$ or
(b) (1) CycA containing 1–5 of substituent R^{27} or
(2) C1–8 alkyl, C2–8 alkenyl or C2–8 alkynyl substituted with CycA, which contains 1–5 of substituent R^{27},

wherein at least one of R27 described in (1) and (2) is selected from

(i) a C5–10 mono- or bi-cyclic carboring,
(ii) a 5–10 membered mono- or bi-cyclic heteroring,
(iii) $—SO_2R^{15}$, (iv) $—OCF_3$ or
(v) C1–8 alkyl substituted with 1–5 of the group selected from (a) halogen, (b) $—NR^{11}R^{12}$, (c) $—OR^{13}$, (d) a C5–10 mono- or bi-cyclic carboring, (e) nitro, (f) CF_3, (g) cyano, (h) a 5–10 membered mono- or bi-cyclic heteroring, (j) $—SR^{14}$, (k) $—COR^{15}$, (l) $—SO_2R^{15}$ and (m) $—OCF_3$ (at least one is a C5–10 mono- or bi-cyclic carboring, a 5–10 mono- or bi-cyclic heteroring, $—SO_2R^{15}$ or $—OCF_3$))

Particularly preferably,

[I] (1) C1–8 alkyl,
(2) C2–8 alkenyl,
(3) C2–8 alkynyl,
(4) CycA or
(5) C1–8 alkyl substituted with a group selected from CycA or —NHC(O)-CycA,
(6) C2–8 alkenyl substituted with CycA or
(7) C2–8 alkynyl substituted with CycA,
wherein CycA is a mono- or bi-cyclic C5–10 carboaryl which may be substituted with 1–5 of R^{27} or partially or completely saturated one thereof, or mono- or bi-cyclic 5–10 membered heteroaryl containing 1–2 of nitrogen, 1–2 of oxygen and/or 1 of sulfur atom, or partially or completely saturated one thereof or
[II] (a) C1–8 alkyl, C2–8 alkenyl or C2–8 alkynyl substituted with a group selected from halogen atom, CF_3, nitro, cyano and $NR^{18}R^{19}$ or
(b) CycA containing 1–5 of substituent R^{27} or
(2) C1–8 alkyl, C2–8 alkenyl or C2–8 alkynyl substituted with CycA, which contains 1–5 of substituent R^{27},
wherein at least one of R^{27} described in (1) and (2) is selected from

(i) a C5–10 mono- or bi-cyclic carboring,
(ii) a 5–10 membered mono- or bi-cyclic heteroring,
(iii) $—SO_2R^{15}$, (iv) $—OCF_3$ or
(v) C1–8 alkyl substituted with 1–5 of group selected from (a) halogen, (b) $—NR^{11}R^{12}$, (c) $—OR^{13}$, (d) a C5–10 mono- or bi-cyclic carboring, (e) nitro, (f) CF_3, (g) cyano, (h) a 5–10 membered mono- or bi-cyclic heteroring, (j) $—SR^{14}$, (k) $—COR^{15}$, (l) $—SO_2R^{15}$ and (m) OCF_3, wherein at least one group is selected from a C5–10 mono- or bi-cyclic carboring or a 5–10 membered mono- or bi-cyclic heteroring, $—SO_2R^{15}$ or OCF_3,

above CycA is C5–10 mono- or bi-cyclic carboaryl or partially or completely saturated one, or 5–10 membered mono- or bi-cyclic heteroaryl containing 1–2 of nitrogen, 1–2 of oxygen and/or 1 of sulfur, or partially or completely saturated one thereof.

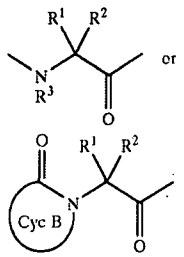
Particularly preferably, [I] (1) C1–4 alkyl, (2) C2–4 alkenyl, (3) C2–4 alkynyl, (4) CycA or (5) C1–4 alkyl, C2–4 alkenyl or C2–4 alkynyl substituted with CycA which is preferably cyclopentane, cyclohexane, benzene, naphthalene, pyrrolidine, piperidine, piperazine, morpholine, pyrrole, furan, thiophene, pyridine, pyrimidine, pyrazine, pyridazine, indole, isoindole, quinoline, isoquinoline, quinazoline, quinoxaline, phthalazine, benzothiophene, benzofuran, benzoxazole, tetrahydroquinoline, tetrahydroquinazoline, tetrahydroquinoxaline, optionally substituted with 1–5 of R^{27a} or
[II] (a) C1–8 alkyl, C2–8 alkenyl or C2–8 alkynyl substituted with a group selected from halogen, CF_3, nitro, cyano or $NR^{18}R^{19}$ or
(b) (1) CycA which contains 1–5 of substituent R^{27}, or
(2) C1–8 alkyl, C2–8 alkenyl or C2–8 alkynyl substituted with CycA which contains 1–5 of substituent R^{27},

wherein at least one of R^{27} described in (1) and (2) is selected from

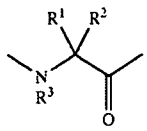
(i) a C5–10 mono- or bi-cyclic carboring,
(ii) a 5–10 membered mono- or bi-cyclic heteroring,
(iii) $—SO_2R^{15}$, (iv) $—OCF_3$, or
(v) C1–8 alkyl substituted with 1–5 of group selected from (a) halogen atom, (b) $—NR^{11}R^{12}$, (c) $—OR^{13}$, (d) a C5–10 mono- or bi-cyclic carboring, (e) nitro, (f) CF_3, (g) cyano, (h) a 5–10 membered mono- or bi-cyclic heteroring, (j) $—SR^{14}$, (k) $—COR^{15}$, (l) $—SO_2R^{15}$ or (m) $—OCF_3$, wherein at least one group is selected from a C5–10 mono- or bi-cyclic carboring, a 5–10 membered mono- or bi-cyclic heteroring, $—SO_2R^{15}$ or $—OCF_3$, and

CycA is preferably cyclopentane, cyclohexane, benzene, naphthalene, pyrrolidine, piperidine, piperazine, morpholine, pyrrole, furan, thiophene, pyridine, pyrimidine, pyrazine, pyridazine, indole, isoindole, quinoline, isoquinoline, quinazoline, quinoxaline, phthalazine, benzothiophene, benzofuran, benzoxadiazole, tetrahydroquinoline, tetrahydroquinazoline, or tetrahydroquinoxaline.

In the formula (I), AA^1 is preferably a single bond,



which is formed with R, but more preferably, AA^1 is a single bond or



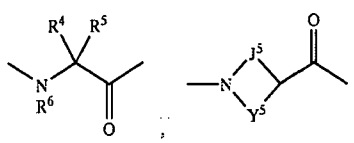
Any group represented by R^1 is preferable, but more preferably, R^1 is hydrogen, C1–8 alkyl, phenyl or C1–8 alkyl substituted with NH_2, C1–4 alkoxy, SH, SCH_3, phenyl, hydroxyphenyl, COOH, $CONH_2$, guanidino, imidazole or indole. Particularly preferably, R^1 is hydrogen, C1–8 alkyl, phenyl or C1–8 alkyl substituted with C1–4 alkoxy or phenyl. Then, any group represented by R^2 is preferable, but hydrogen is particularly preferable.

And C3–6 alkylene which R^1 and R^2 together form is also preferable.

Any group represented by R^3 is preferable, but more preferably R^3 is hydrogen or C1–4 alkyl.

And C2–4 alkylene which R^3 and R^1 together form is also preferable.

In the formula (I), Any group represented AA^2 is preferable, but more preferably, AA^2 is a single bond,



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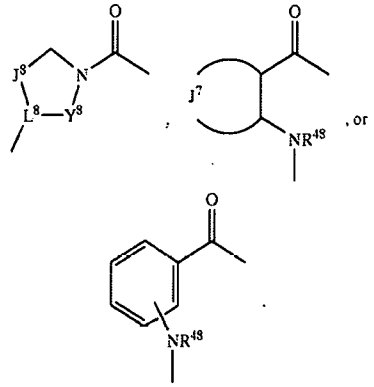
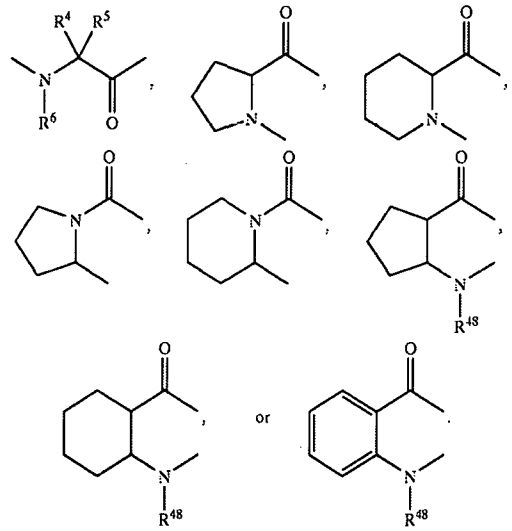


Particularly preferably, AA^2 is a single bond,



Any group represented by R^4 is preferable, but more preferably, R^4 is hydrogen, C1–8 alkyl, phenyl or C1–8 alkyl substituted with NH_2, C1–4 alkoxy, SH, SCH_3, phenyl, hydroxyphenyl, COOH, $CONH_2$, guanidino, imidazole or indole. Particularly preferably, R^4 is hydrogen, C1–8 alkyl, phenyl or C1–8 alkyl substituted with C1–4 alkoxy or phenyl. Then, any group represented by R^5 is preferable, and hydrogen is particularly preferable.

And C3–6 alkylene which R^4 and R^5 together form is also preferable.

Any group represented by R^6 is preferable, but more preferably R^6 is hydrogen or C1–4 alkyl.

And C2–4 alkylene which R^6 and R^4 together form is also preferable.

Any group represented by R^{48} is all preferable, but more preferably, R^{48} is

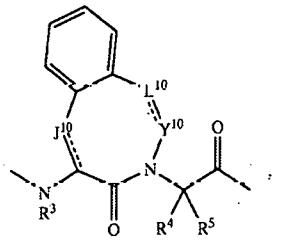
[I] hydrogen, C1–4 alkyl, phenyl or C1–4 alkyl substituted with phenyl, or

[II] C2–6 alkylene, wherein one carbon atom may be replaced by oxygen, sulfur or $—NR^{47}—$, wherein R^{47} is hydrogen or C1–4 alkyl to be formed together with R^4, when AA^1 is a single bond. Particularly preferably, R^{48} is [I] hydrogen atom or C1–4 alkyl, or

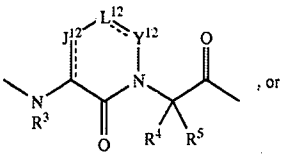
[II] when AA^1 is a single bond, taken together with R to form tetramethylene, pentamethylene, $—CH_2—CH_2—O—CH_2—CH_2—$, $—CH_2—CH_2—NH—CH_2—CH_2—$ or $—CH_2—CH_2—N(CH_3)—CH_2—CH_2—$.

In the formula (I), any group which AA^1 and AA^2 together form is preferable, but preferably, it is

(i)

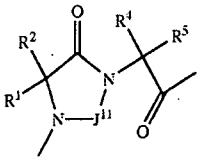


(ii)

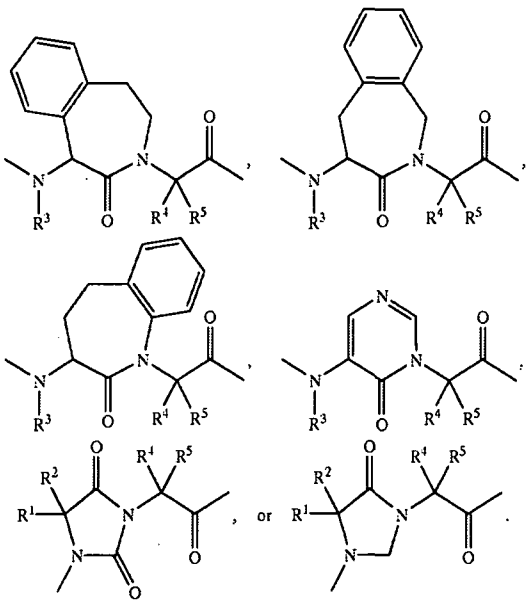


, or

(iii)



particularly preferably, it is



Any group represented by R^7 is preferable. More preferably, R^7 is hydrogen atom, C1–8 alkyl, phenyl, or C1–8 alkyl substituted with NH_2, C1–4 alkoxy, SH, SCH_3, phenyl, hydroxyphenyl, COOH, $CONH_2$, guanidino, imidazole or indole.

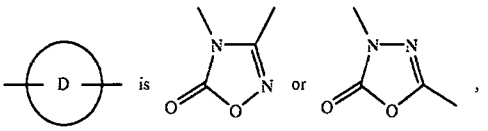
Particularly preferably, R^7 is hydrogen, C1–8 alkyl, phenyl, or C1–8 alkyl substituted with C1–4 alkoxy or phenyl. Then, any group represented by R^8 is preferable, but hydrogen is most preferable.

And C3–6 alkylene which R^7 and R^8 together form is also preferable.

Any group represented by R^9 is preferable, but more preferably R^9 is hydrogen or C1–4 alkyl.

And C2–4 alkylene which R^9 and R^7 together form is also preferable.

And when D ring is



R^7 and R^8 are preferably C1–8 alkyl substituted with $—COR^{65}$, in addition to the groups described above. More preferably, carboxymethyl, 2-carboxyethyl, carbamoylmethyl, 2-carbamoylethyl, etc. are included in addition to the above groups.

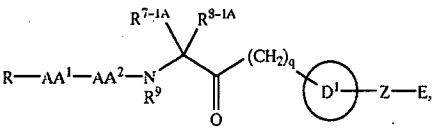
Any of q, which represents an integer of 1 to 4, is preferable, but particularly preferably q is 1.

Any group represented by Z is preferable, but more preferably, Z is a single bond, C1-6alkylene, oxygen atom, sulfur atom, or C1–6 alkylene whose one carbon atom is replaced by —O—, —S— or $—NR^{10}—$.

Any group represented by E described above is preferable, but more preferably E is hydrogen atom, C1–4 alkyl, $—COOR^{18}$, $—G—(R^{35})_r$, wherein G is preferably C5–10 mono- or bi-cyclic carboring or 5–10 membered mono- or bi-cyclic heteroring containing 1 to 3 of nitrogen atom(s), 1 of oxygen and/or 1 of sulfur atom.

Preferable compounds in the present invention are the compounds of formula (I-1A)

(I-1A)

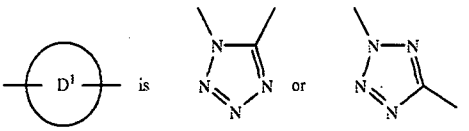


wherein $R^{7\text{-}1A}$ and $R^{8\text{-}1A}$ are each independently,

(1) hydrogen atom,
(2) C1–8 alkyl,
(3) Cyc, or
(4) C1–8 alkyl substituted with 1 to 5 of group(s) selected from the following (a) to (h):

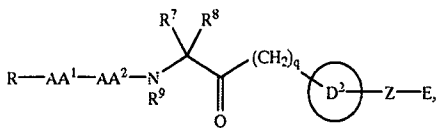
(a) $—NR^{61}R^{62}$ (b) $—OR^{63}$, (c) $—SR^{64}$, (d) $—NR^{66}CONR^{61}R^{62}$, (e) guanidino, (f) Cyc, (g) $—NR^{66}SO_2R^{64}$ or (h) $—CONR^{61}SO_2R^{64}$, or

$R^{7\text{-}1A}$ and $R^{8\text{-}1A}$ are taken together to form C2–8 alkylene, wherein one carbon atom may be replaced by oxygen atom, sulfur atom or $—NR^{60}—$ and the alkylene may be substituted with $—NR^{61}R^{62}$ or $—OR^{63}$,

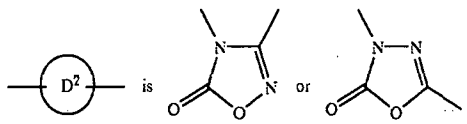


and the other symbols have the same meanings as above, and the compound of formula (I-1B)

(I-1B)



wherein

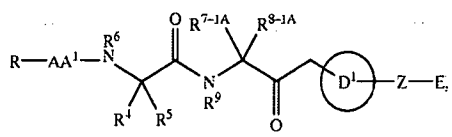


and the other symbols have the same meanings as above, a non-toxic salt thereof and a hydrate thereof.

In the compounds of the present invention, the following compounds, non-toxic salts thereof and hydrates thereof are preferred;

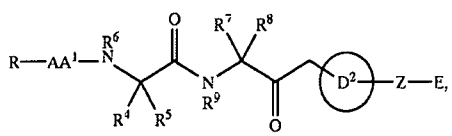
the compound of formula (I-2A)

(I-2A)



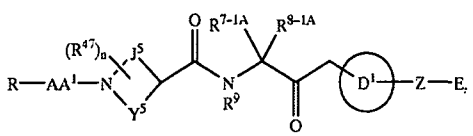
wherein all symbols have the same meanings as above, the compound of formula (I-2B)

(I-2B)



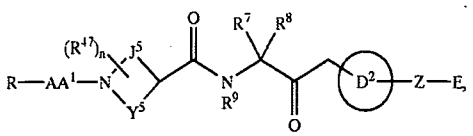
wherein all symbols have the same meanings as above, the compound of formula (I-3A)

(I-3A)



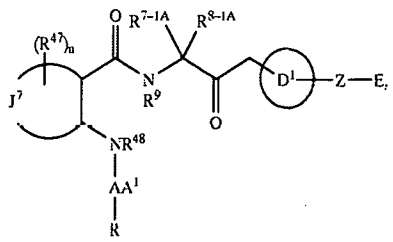
wherein all symbols have the same meanings as above, the compound of formula (I-3B)

(I-3B)



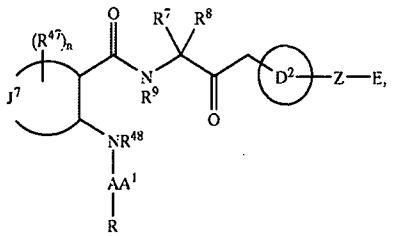
wherein all symbols have the same meanings as above, the compound of formula (I-4A)

(I-4A)



wherein all symbols have the same meanings as above, the compound of formula (I-4B)

(I-4B)

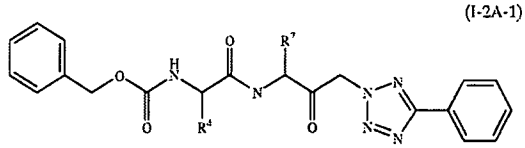


wherein all symbols have the same meanings as above.

Concretely, the compounds described in the following tables 1 to 30, non-toxic salts thereof, hydrates thereof and the compounds described in the examples are preferable.

TABLE 1

(I-2A-1)



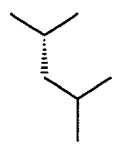
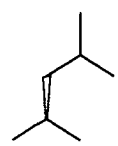
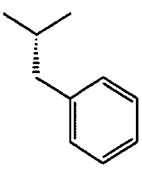
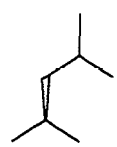
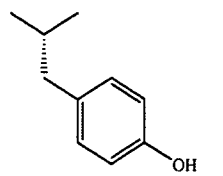
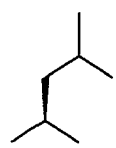
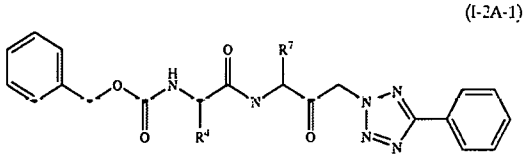
No.		
1		
2		
3		

TABLE 1-continued

(I-2A-1)



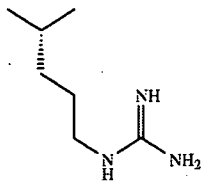
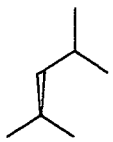
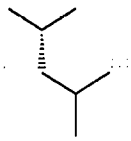
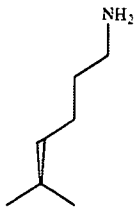
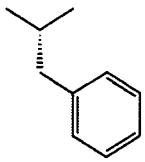
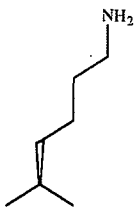
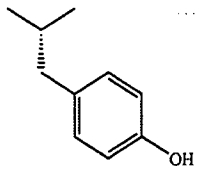
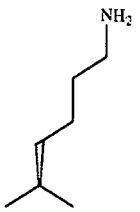
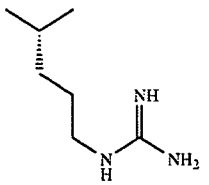
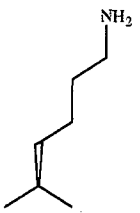
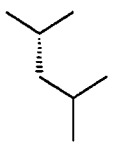
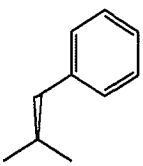
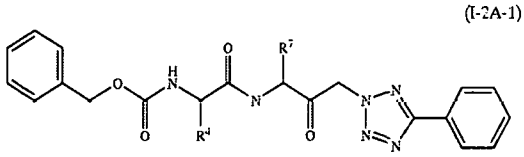
No.	R^4	R^7
4		
5		
6		
7		
8		
9		

TABLE 1-continued

(I-2A-1)



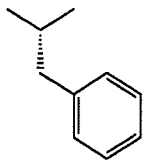
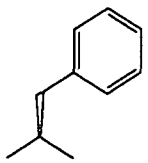
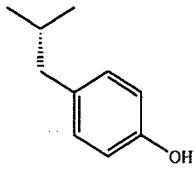
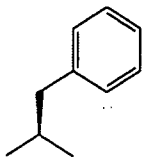
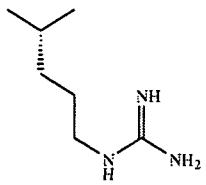
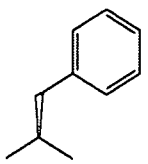
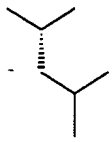
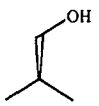
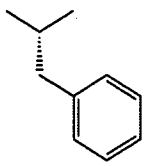
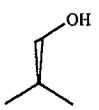
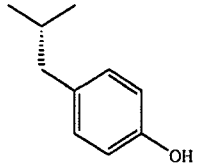
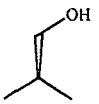
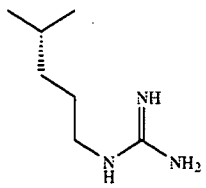
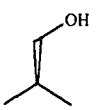
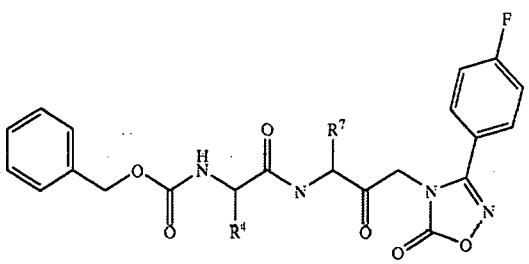
No.	R^4	R^7
10		
11		
12		
13		
14		
15		
16		

TABLE 2

(I-2B-1)



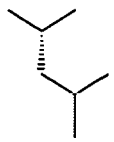
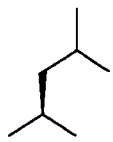
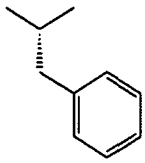
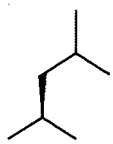
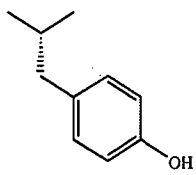
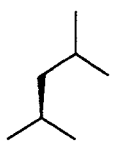
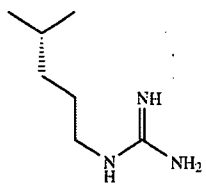
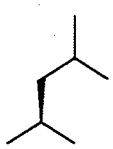
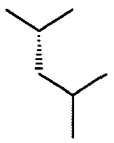
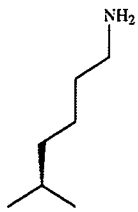
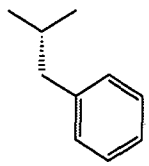
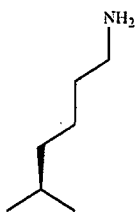
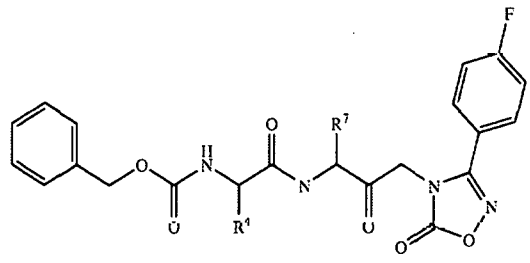
No.	R^4	R^7
1		
2		
3		
4		
5		
6		

TABLE 2-continued

(I-2B-1)



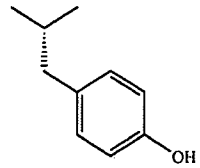
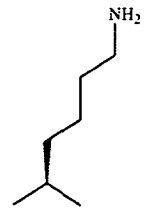
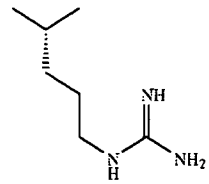
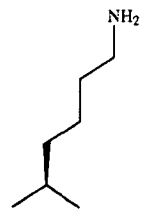
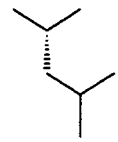
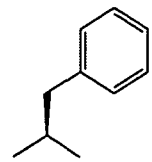
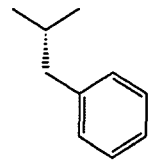
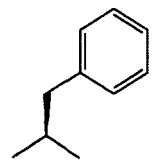
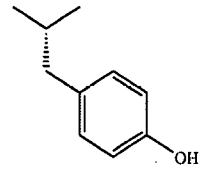
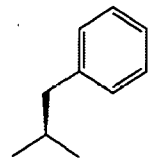
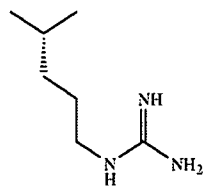
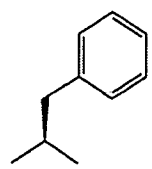
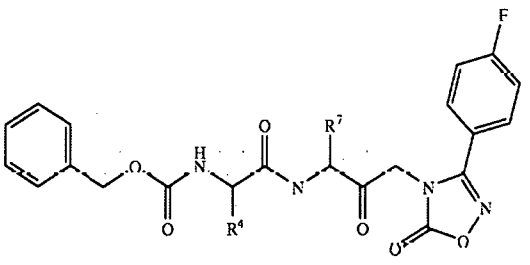
No.	R^4	R^7
7		
8		
9		
10		
11		
12		

TABLE 2-continued

(I-2B-1)



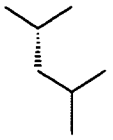
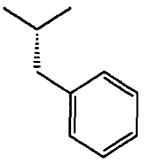
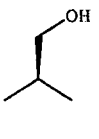
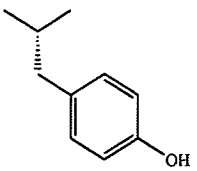
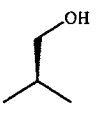
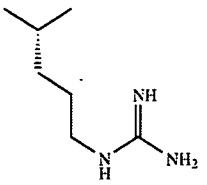
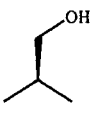
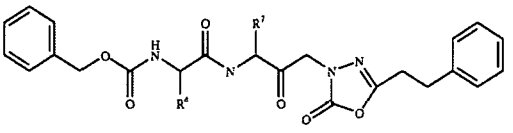
No.	R^4	R^7
13		
14		
15		
16		

TABLE 3

(I-2B0-2)



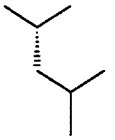
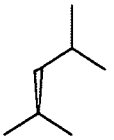
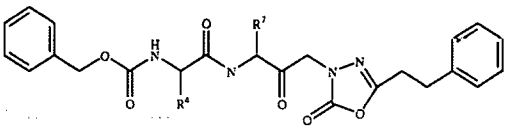
No.	R^4	R^7
1		

TABLE 3-continued

(I-2B0-2)



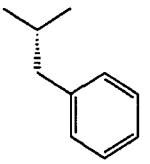
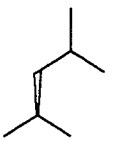
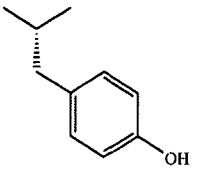
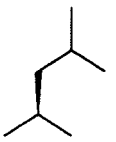
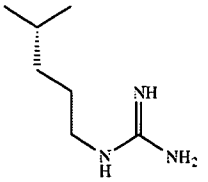
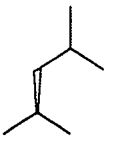
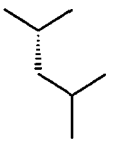
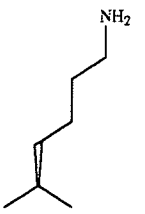
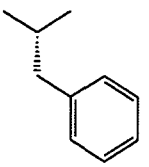
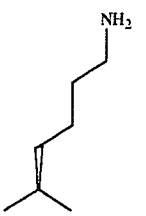
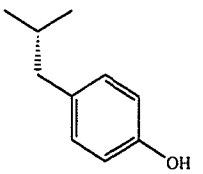
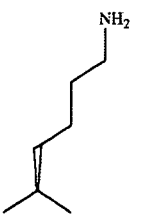
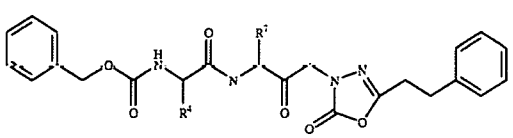
No.	R^4	R^7
2		
3		
4		
5		
6		
7		

TABLE 3-continued

(I-2B0-2)



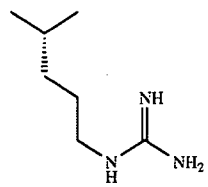
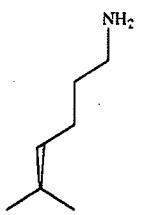
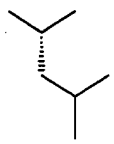
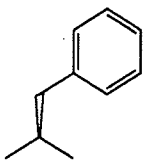
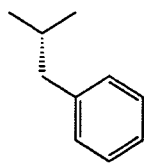
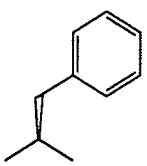
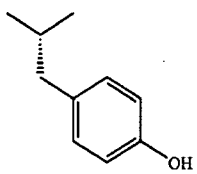
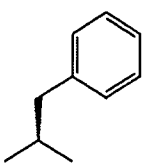
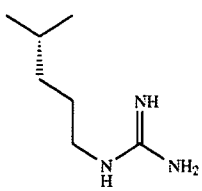
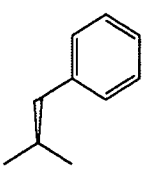
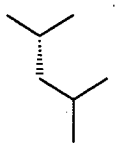
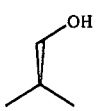
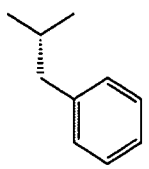
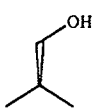
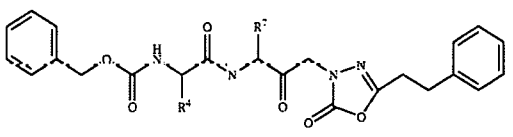
No.	R^4	R^7
8		
9		
10		
11		
12		
13		
14		

TABLE 3-continued

(I-2B0-2)



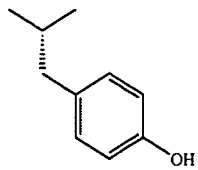
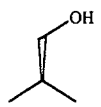
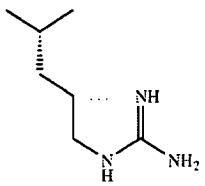
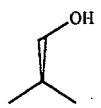
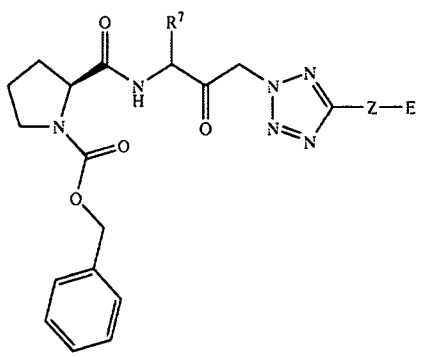
No.	R^4	R^7
15		
16		

TABLE 4

(I-3A-1)



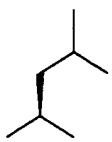
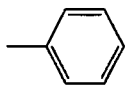
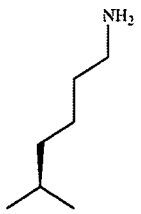
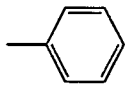
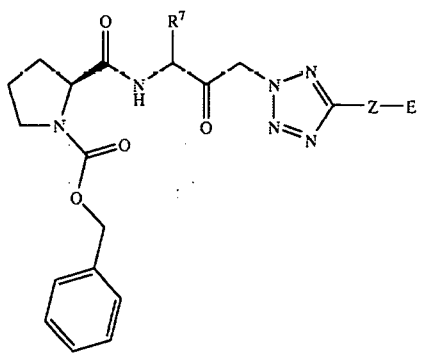
No.	R^7	—Z—E
1		
2		

TABLE 4-continued

(I-3A-1)



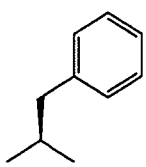
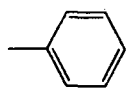
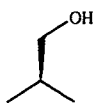
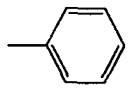
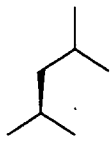
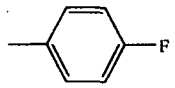
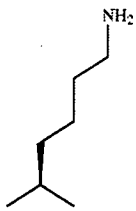
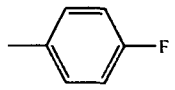
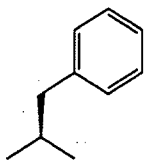
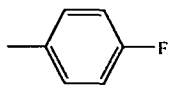
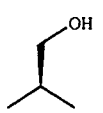
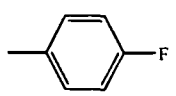
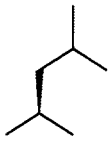
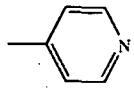
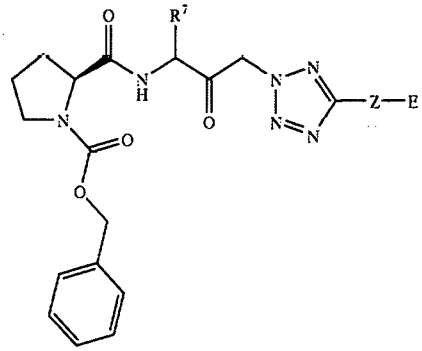
No.	R^7	—Z—E
3		
4		
5		
6		
7		
8		
9		

TABLE 4-continued

(I-3A-1)



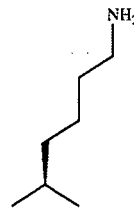
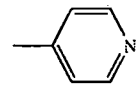
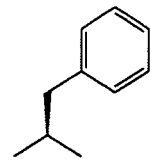
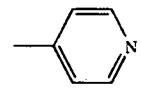
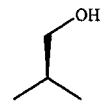
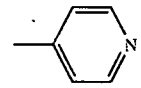
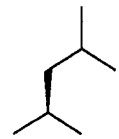
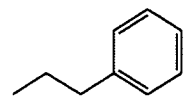
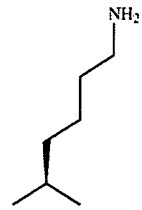
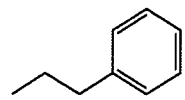
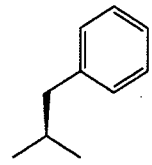
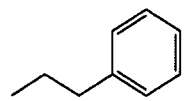
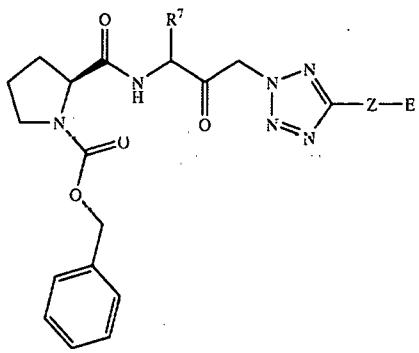
No.	R^7	—Z—E
10		
11		
12		
13		
14		
15		

TABLE 4-continued

(I-3A-1)



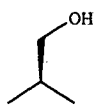
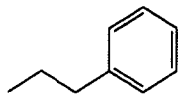
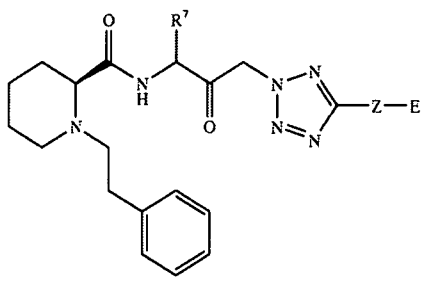
No.	R^7	—Z—E
16		

TABLE 5

(I-3A-2)



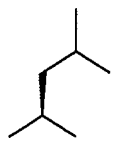
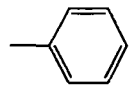
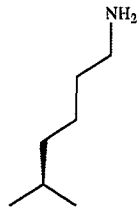
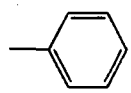
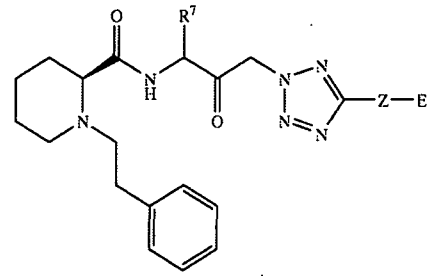
No.	R^7	—Z—E
1		
2		

TABLE 5-continued

(I-3A-2)



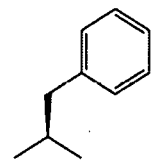
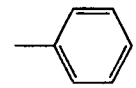
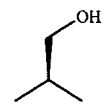
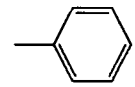
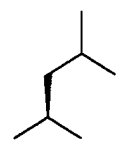
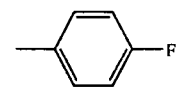
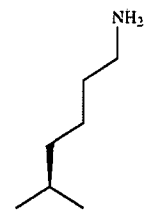
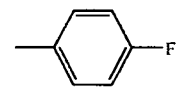
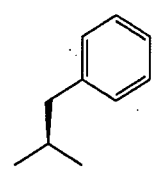
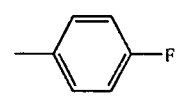
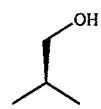
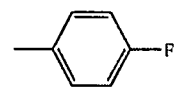
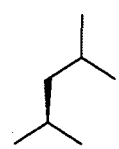
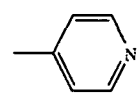
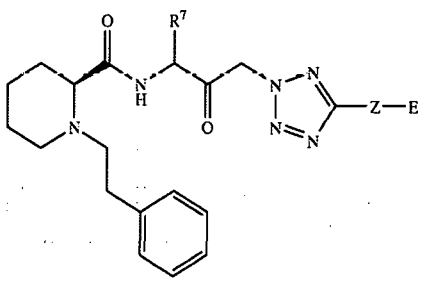
No.	R^7	—Z—E
3		
4		
5		
6		
7		
8		
9		

TABLE 5-continued

(I-3A-2)



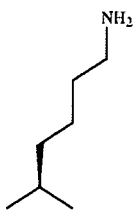
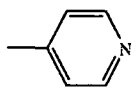
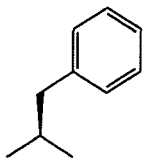
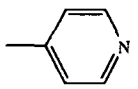
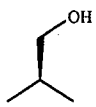
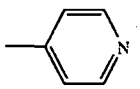
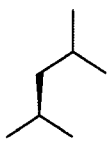
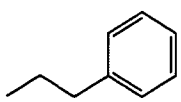
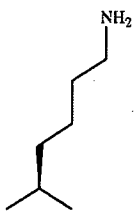
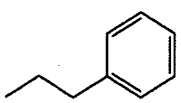
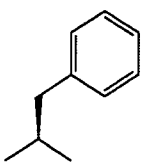
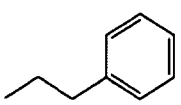
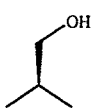
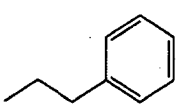
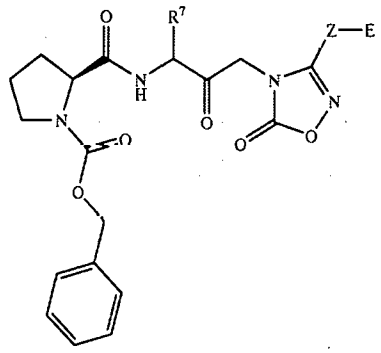
No.	R^7	—Z—E
10		
11		
12		
13		
14		
15		
16		

TABLE 6

(I-3B-1)



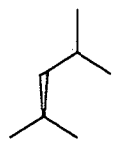
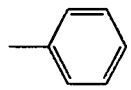
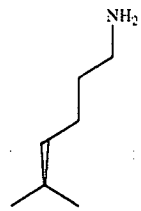
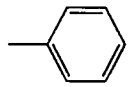
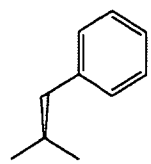
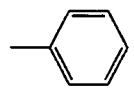
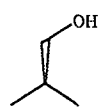
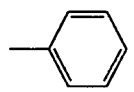
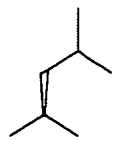
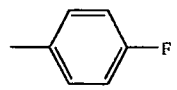
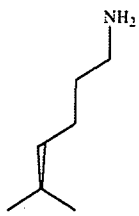
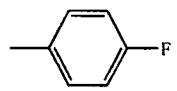
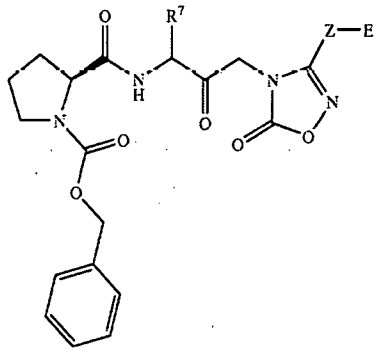
No.	R^7	—Z—E
1		
2		
3		
4		
5		
6		

TABLE 6-continued

(I-3B-1)



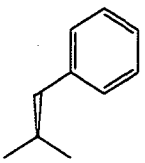
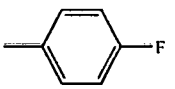
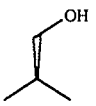
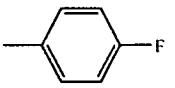
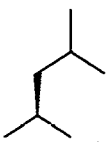
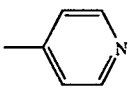
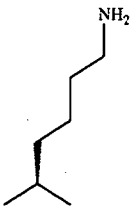
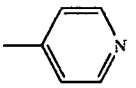
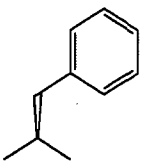
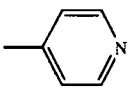
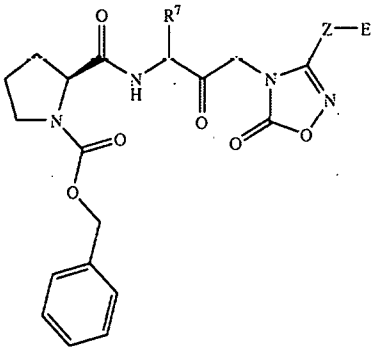
No.	R^7	—Z—E
7		
8		
9		
10		
11		

TABLE 6-continued

(I-3B-1)



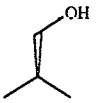
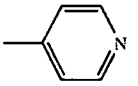
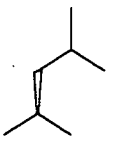
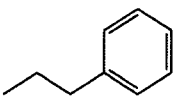
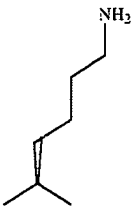
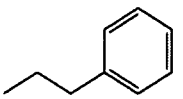
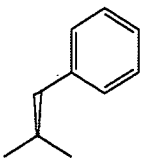
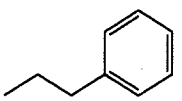
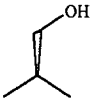
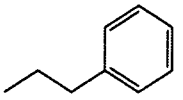
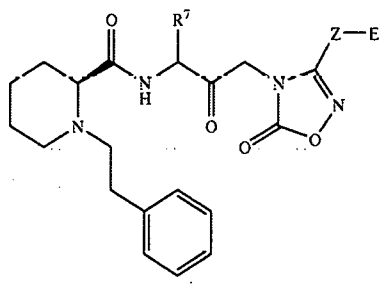
No.	R^7	—Z—E
12		
13		
14		
15		
16		

TABLE 7

(I-3B-2)



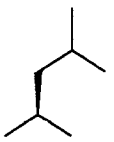
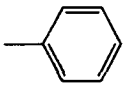
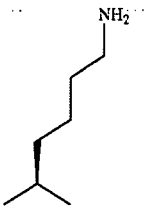
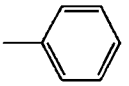
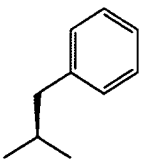
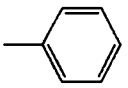
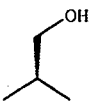
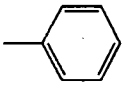
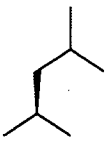
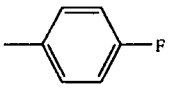
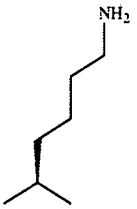
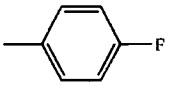
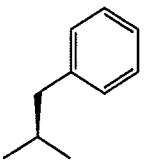
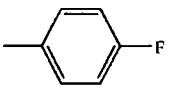
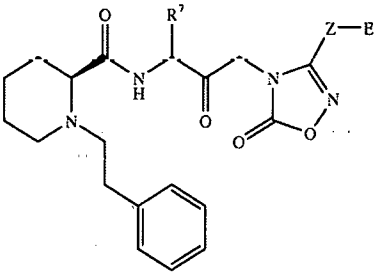
No.	R^7	—Z—E
1		
2		
3		
4		
5		
6		
7		

TABLE 7-continued

(I-3B-2)



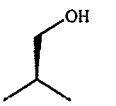
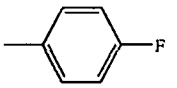
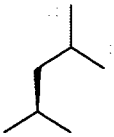
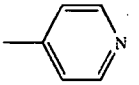
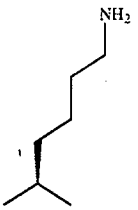
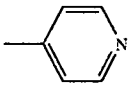
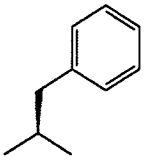
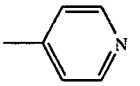
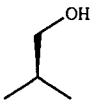
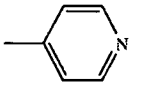
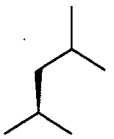
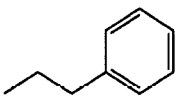
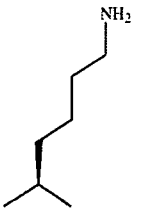
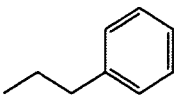
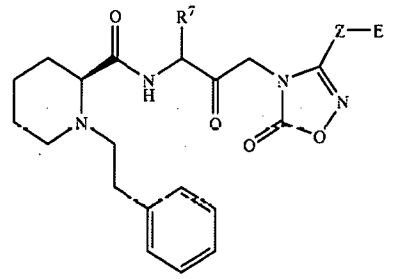
No.	R^7	—Z—E
8		
9		
10		
11		
12		
13		
14		

TABLE 7-continued

(I-3B-2)



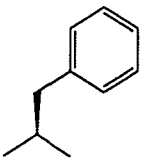
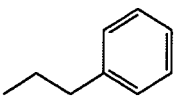
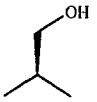
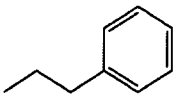
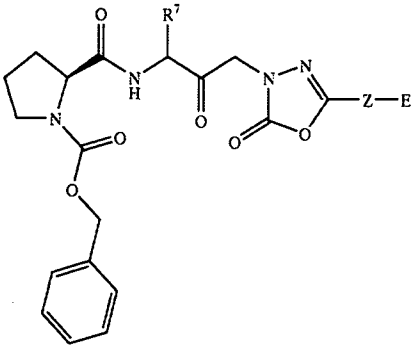
No.	R^7	—Z—E
15		
16		

TABLE 8

(I-3B-3)



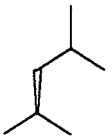
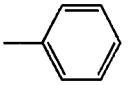
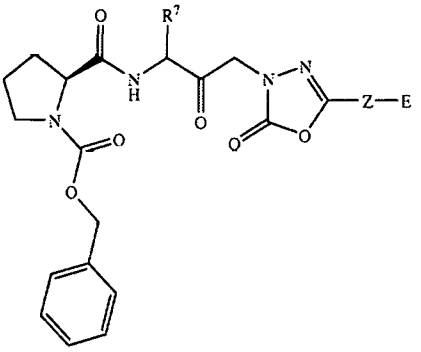
No.	R^7	—Z—E
1		

TABLE 8-continued

(I-3B-3)



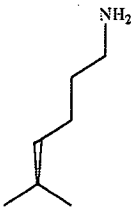
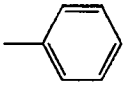
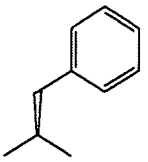
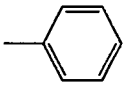
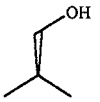
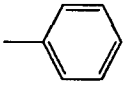
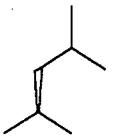
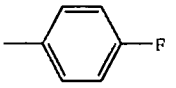
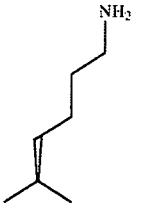
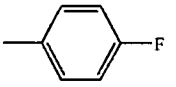
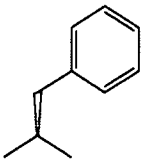
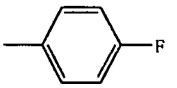
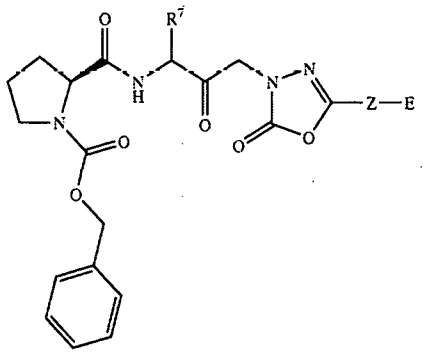
No.	R^7	—Z—E
2		
3		
4		
5		
6		
7		

TABLE 8-continued

(I-3B-3)



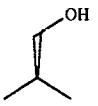
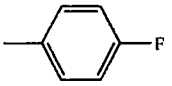
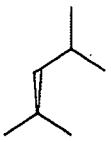
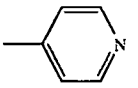
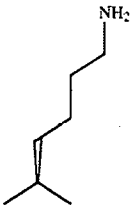
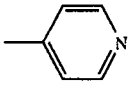
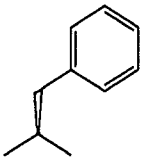
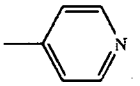
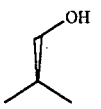
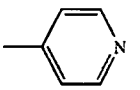
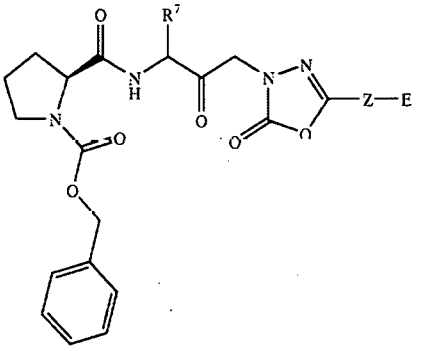
No.	R^7	—Z—E
8		
9		
10		
11		
12		

TABLE 8-continued

(I-3B-3)



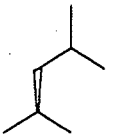
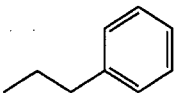
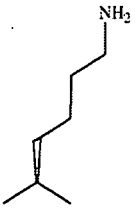
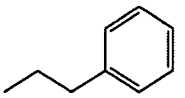
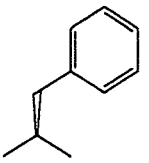
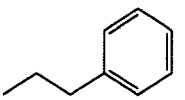
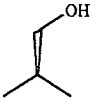
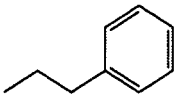
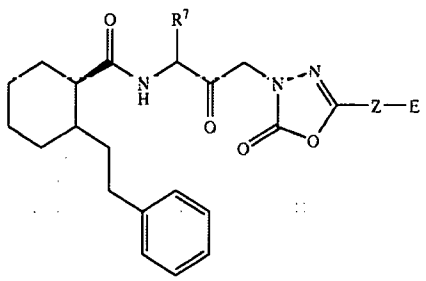
No.	R^7	—Z—E
13		
14		
15		
16		

TABLE 9

(I-3B-4)



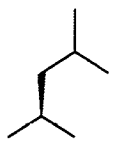
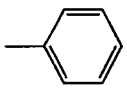
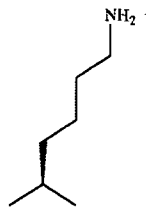
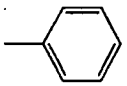
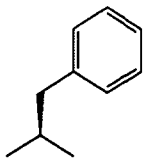
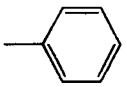
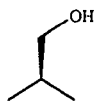
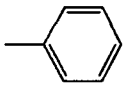
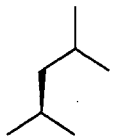
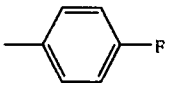
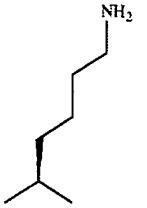
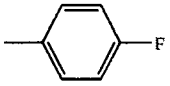
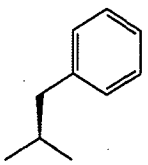
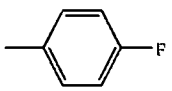
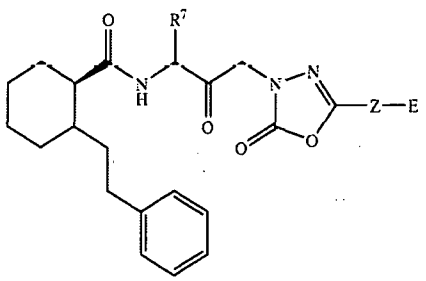
No.	R^7	—Z—E
1		
2		
3		
4		
5		
6		
7		

TABLE 9-continued

(I-3B-4)



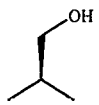
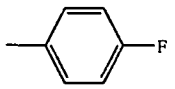
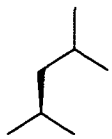
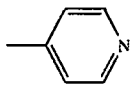
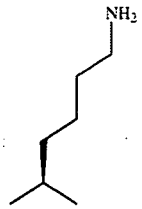
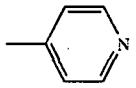
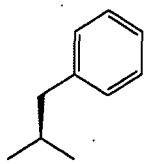
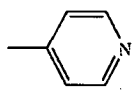
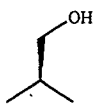
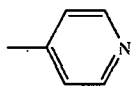
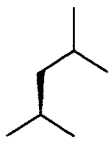
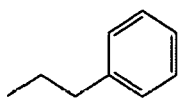
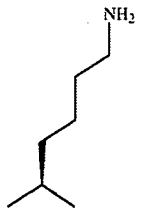
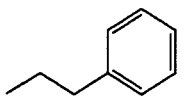
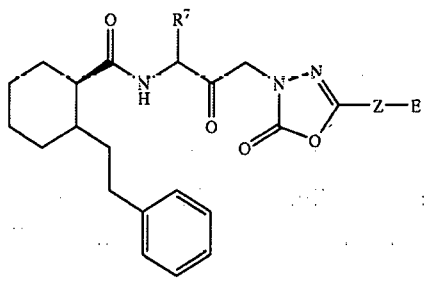
No.	R^7	—Z—E
8		
9		
10		
11		
12		
13		
14		

TABLE 9-continued

(I-3B-4)



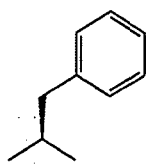
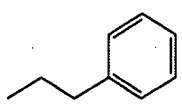
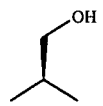
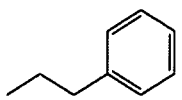
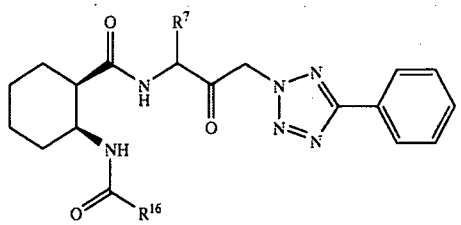
No.	R^7	—Z—E
15		
16		

TABLE 10

(I-4A-1)



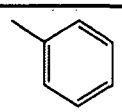
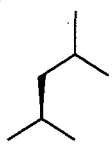
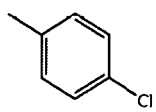
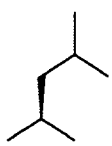
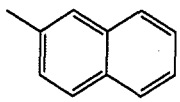
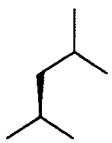
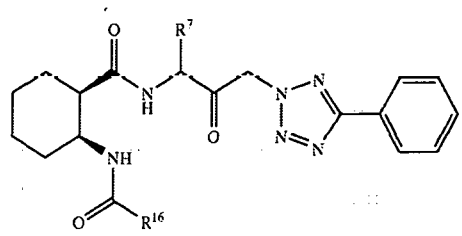
No.	R^{16}	R^7
1		
2		
3		

TABLE 10-continued

(I-4A-1)



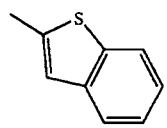
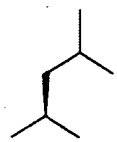
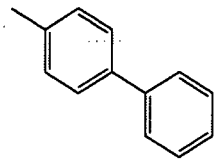
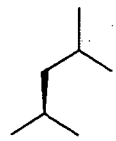
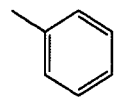
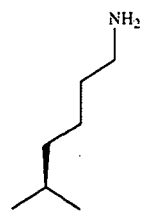
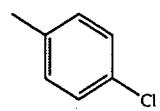
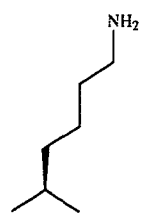
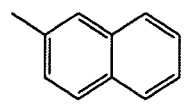
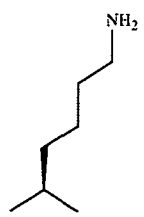
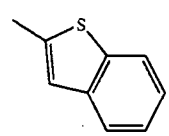
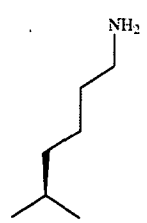
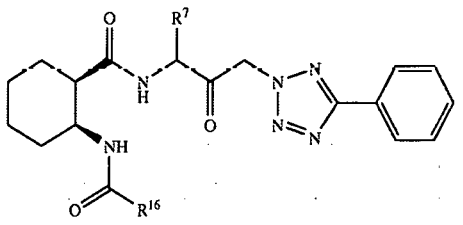
No.	R^{16}	R^7
4		
5		
6		
7		
8		
9		

TABLE 10-continued

(I-4A-1)



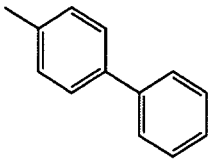
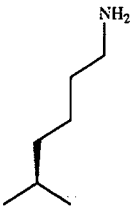
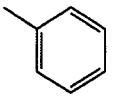
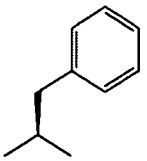
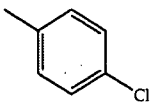
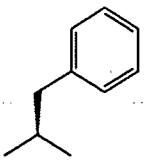
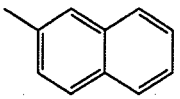
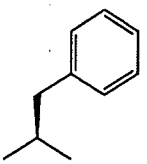
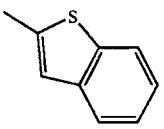
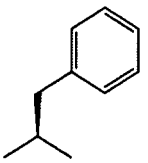
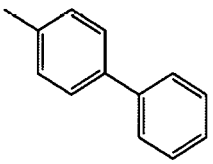
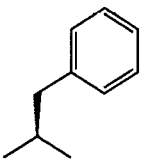
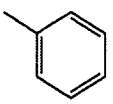
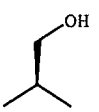
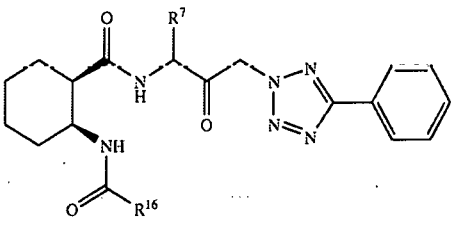
No.	R^{16}	
10		
11		
12		
13		
14		
15		
16		

TABLE 10-continued

(I-4A-1)



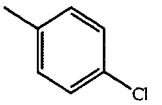
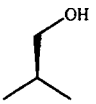
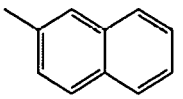
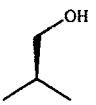
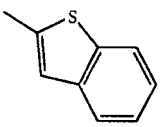
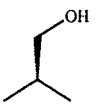
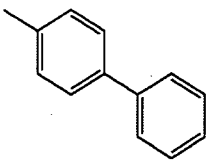
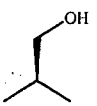
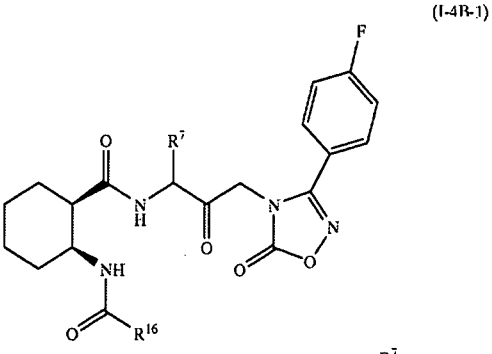
No.	R^{16}	
17		
18		
19		
20		

TABLE 11

(I-4B-1)



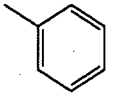
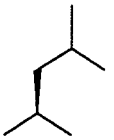
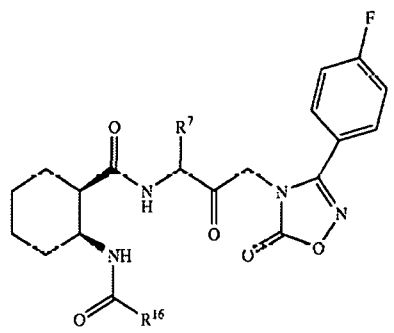
No.	R^{16}	
1		

TABLE 11-continued

(I-4B-1)



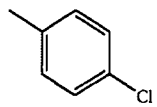
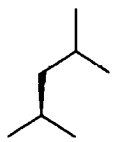
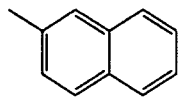
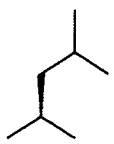
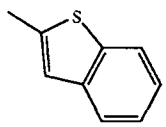
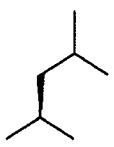
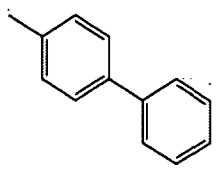
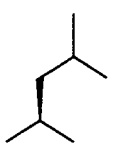
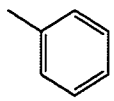
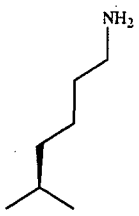
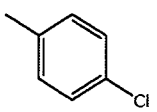
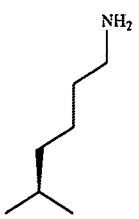
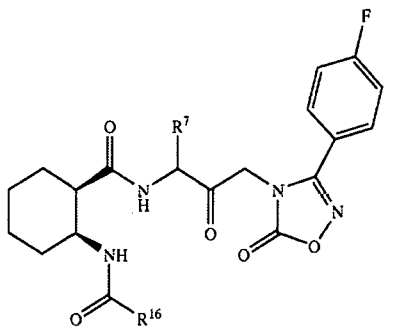
No.	R^{16}	R^7
2		
3		
4		
5		
6		
7		

TABLE 11-continued

(I-4B-1)



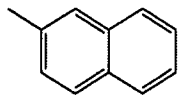
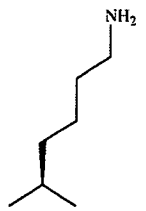
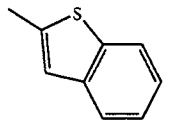
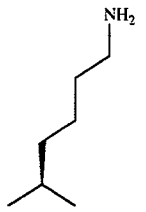
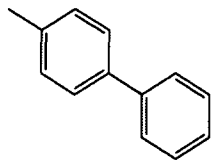
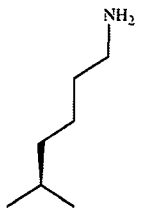
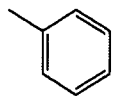
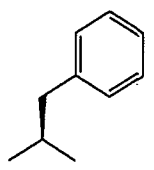
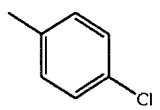
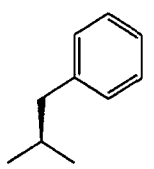
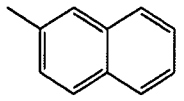
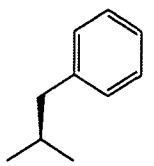
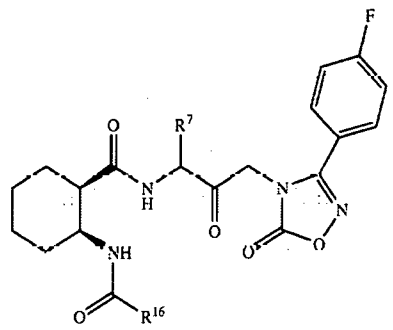
No.	R^{16}	R^7
8		
9		
10		
11		
12		
13		

TABLE 11-continued

(I-4B-1)



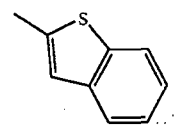
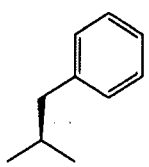
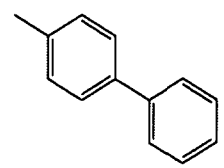
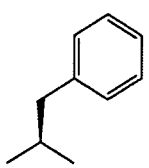
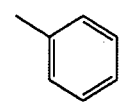
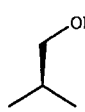
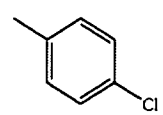
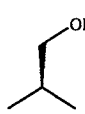
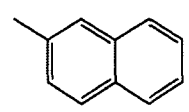
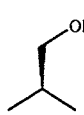
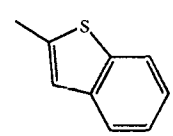
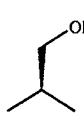
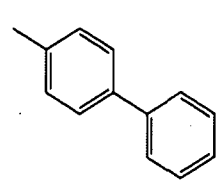
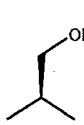
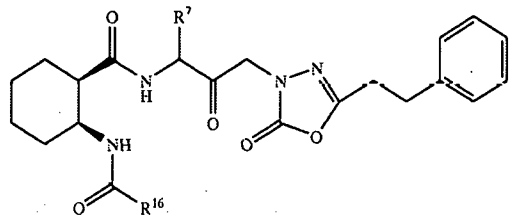
No.	R^{16}	R^7
14		
15		
16		
17		
18		
19		
20		

TABLE 12

(I-4B-2)



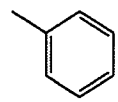
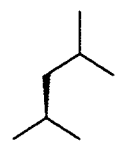
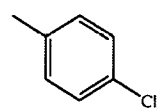
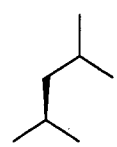
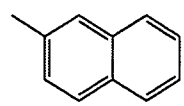
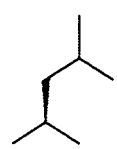
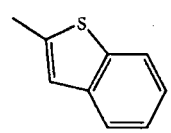
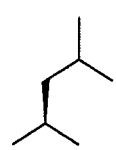
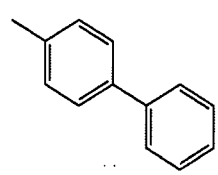
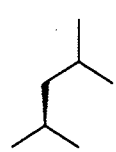
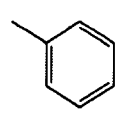
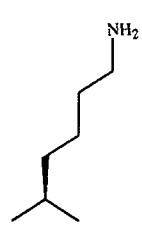
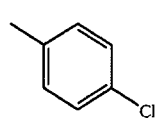
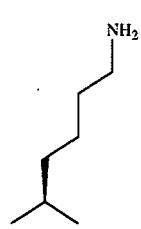
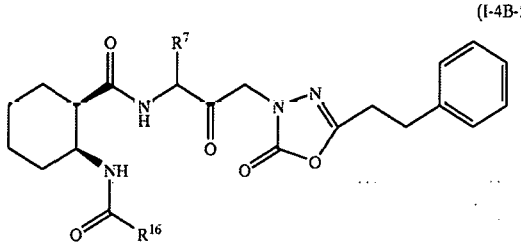
No.	R^{16}	R^7
1		
2		
3		
4		
5		
6		
7		

TABLE 12-continued

(I-4B-2)



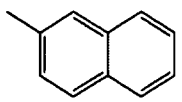
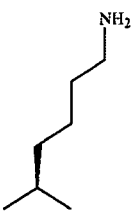
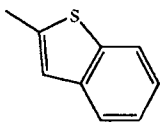
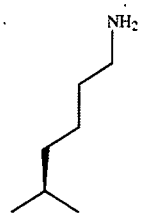
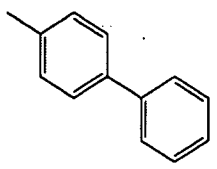
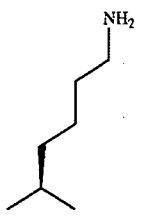
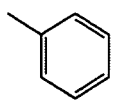
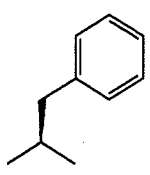
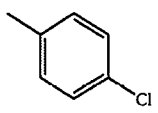
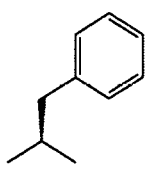
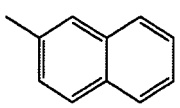
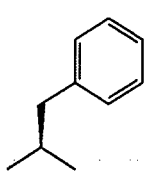
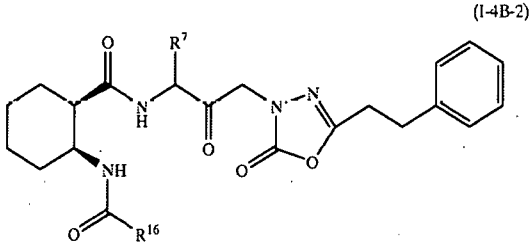
No.	R^{16}	R^7
8		
9		
10		
11		
12		
13		

TABLE 12-continued

(I-4B-2)



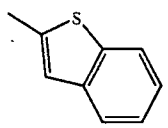
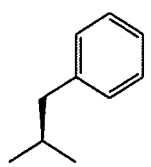
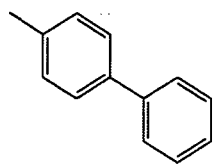
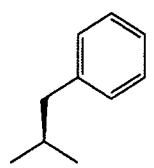
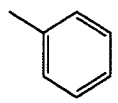
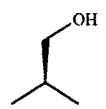
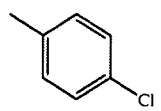
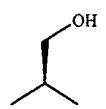
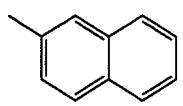
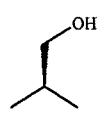
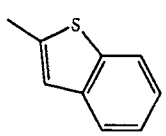
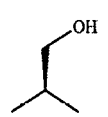
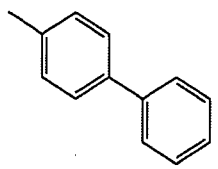
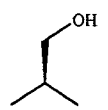
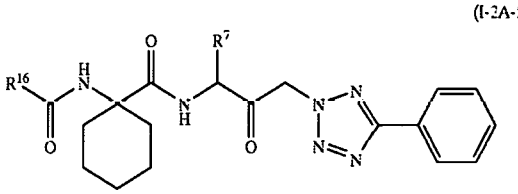
No.	R^{16}	R^7
14		
15		
16		
17		
18		
19		
20		

TABLE 13

(I-2A-2)



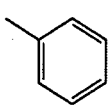
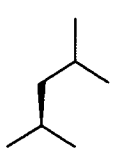
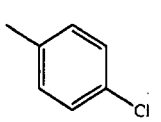
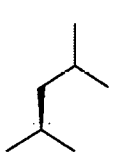
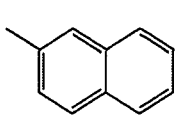
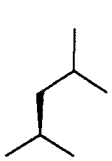
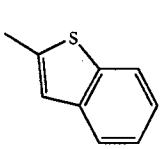
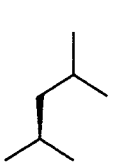
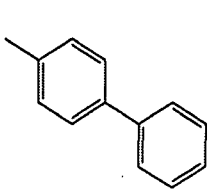
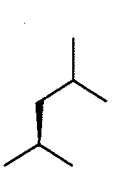
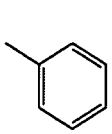
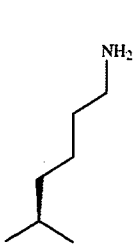
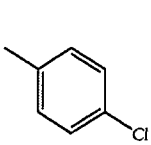
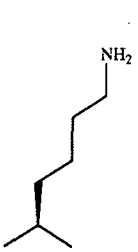
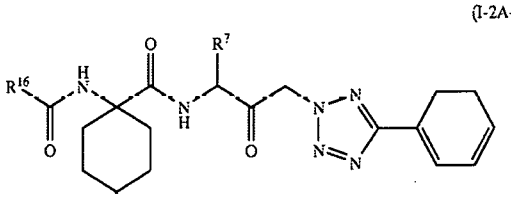
No.	R^{16}	R^7
1		
2		
3		
4		
5		
6		
7		

TABLE 13-continued

(I-2A-2)



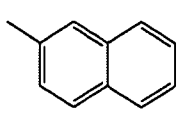
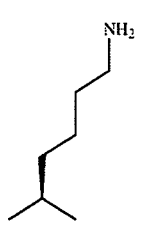
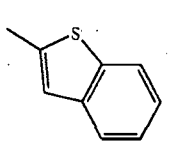
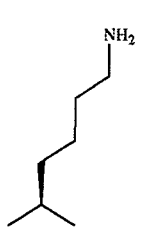
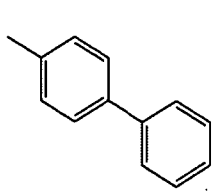
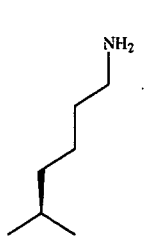
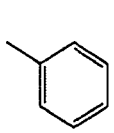
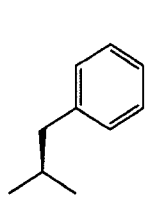
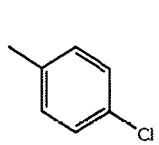
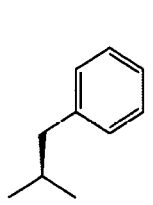
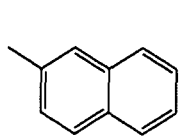
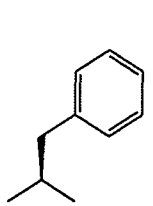
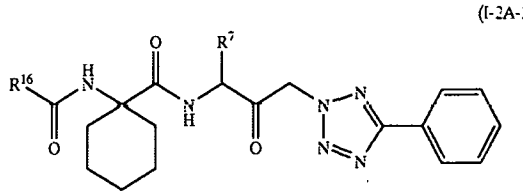
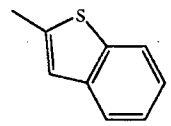
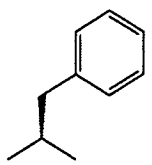
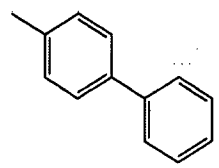
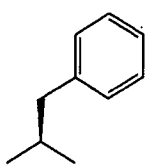
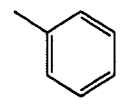
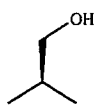
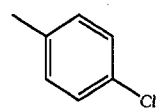
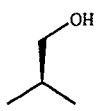
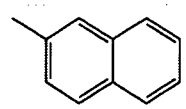
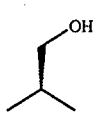
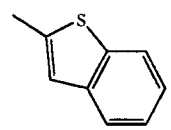
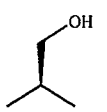
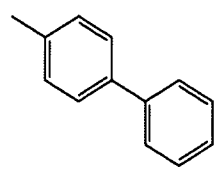
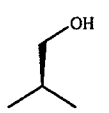
No.	R^{16}	R^7
8		
9		
10		
11		
12		
13		

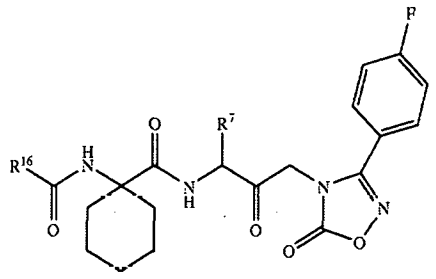
TABLE 13-continued

(I-2A-2)



No.	R^{16}	R^7
14		
15		
16		
17		
18		
19		
20		

(I-2B-3)



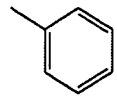
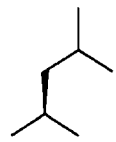
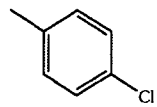
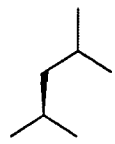
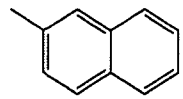
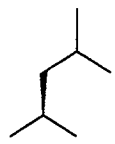
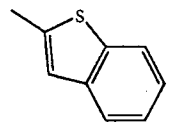
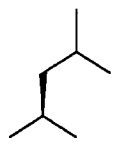
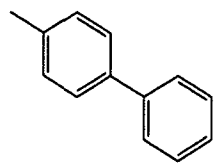
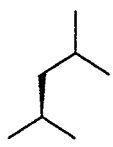
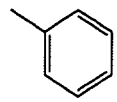
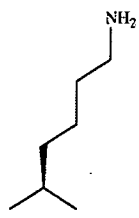
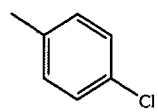
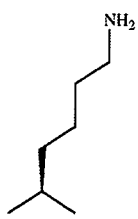
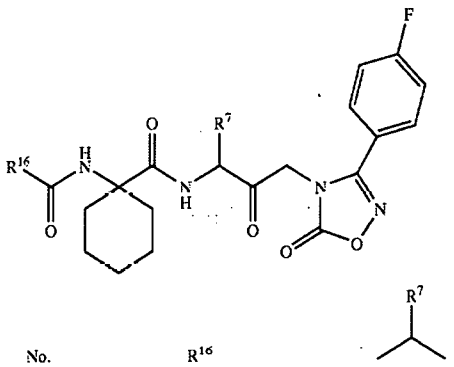
No.	R^{16}	R^7
1		
2		
3		
4		
5		
6		
7		

TABLE 14-continued

(I-2B-3)



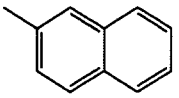
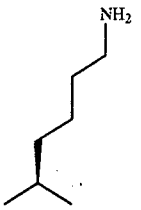
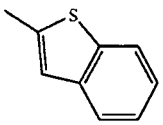
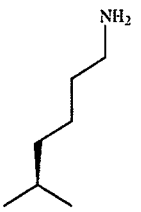
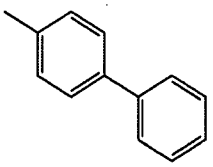
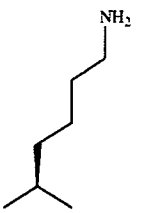
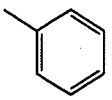
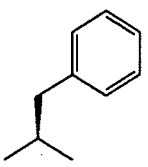
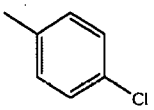
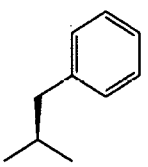
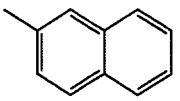
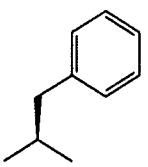
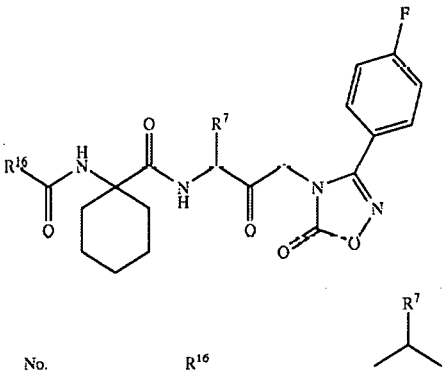
No.	R^{16}	R^7
8		
9		
10		
11		
12		
13		

TABLE 14-continued

(I-2B-3)



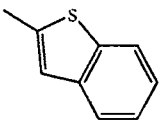
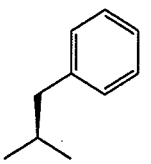
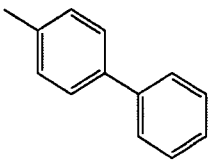
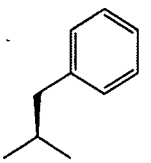
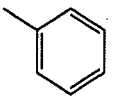
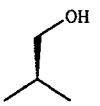
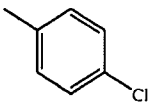
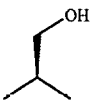
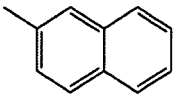
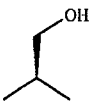
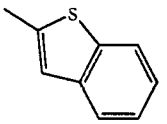
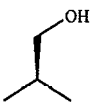
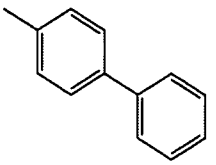
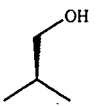
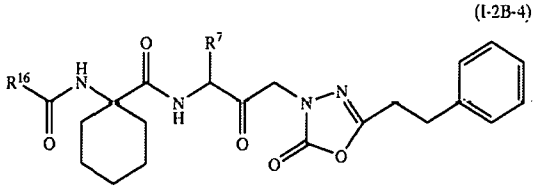
No.	R^{16}	R^7
14		
15		
16		
17		
18		
19		
20		

TABLE 15

(I-2B-4)



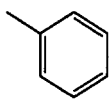
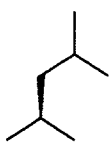
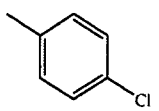
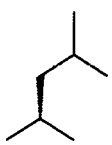
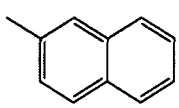
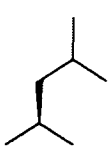
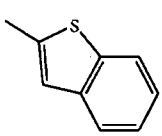
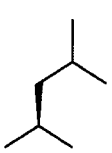
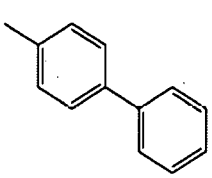
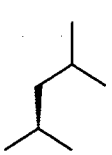
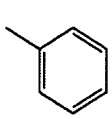
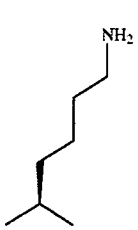
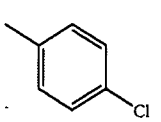
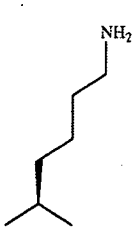
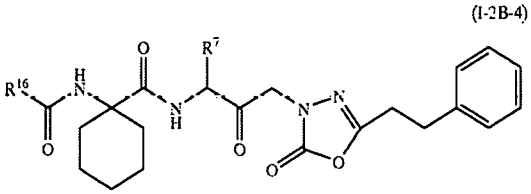
No.	R^{16}	R^7
1		
2		
3		
4		
5		
6		
7		

TABLE 15-continued

(I-2B-4)



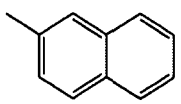
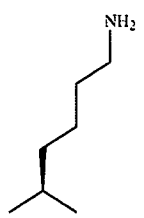
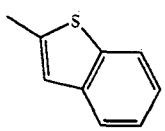
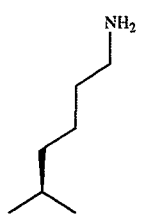
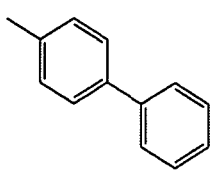
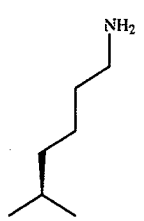
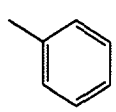
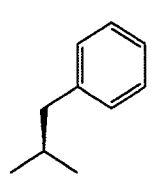
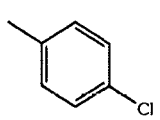
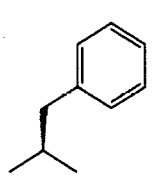
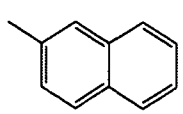
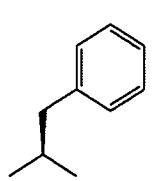
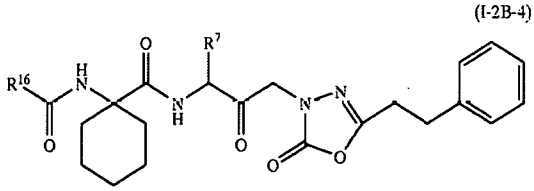
No.	R^{16}	R^7
8		
9		
10		
11		
12		
13		

TABLE 15-continued

(I-2B-4)



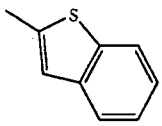
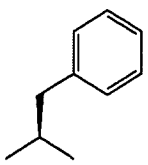
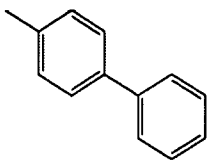
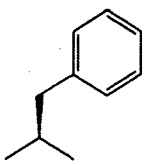
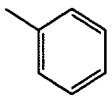
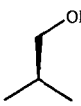
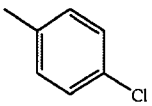
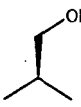
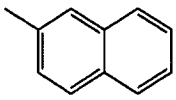
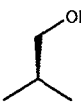
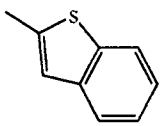
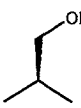
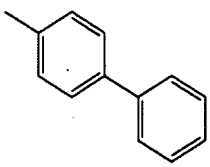
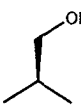
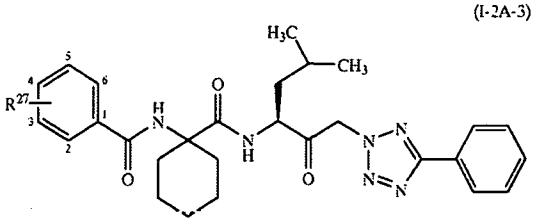
No.	R^{16}	R^7
14		
15		
16		
17		
18		
19		
20		

TABLE 16

(I-2A-3)



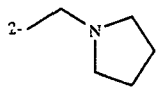
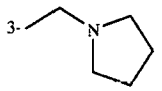
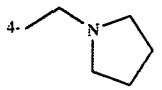
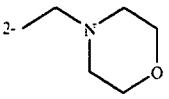
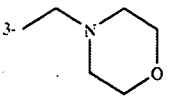
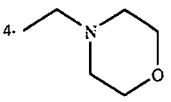
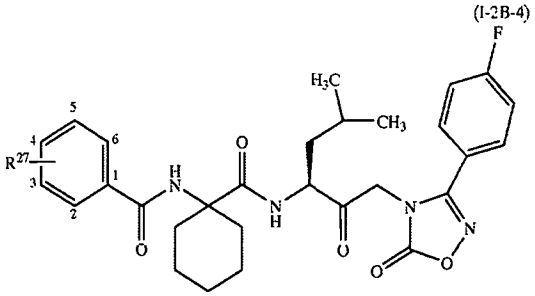
No.	R^{27}
1	2-$CH_2N(CH_3)_2$
2	3-$CH_2N(CH_3)_2$
3	4-$CH_2N(CH_3)_2$
4	
5	
6	
7	
8	
9	

TABLE 17

(I-2B-4)



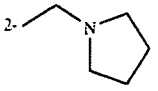
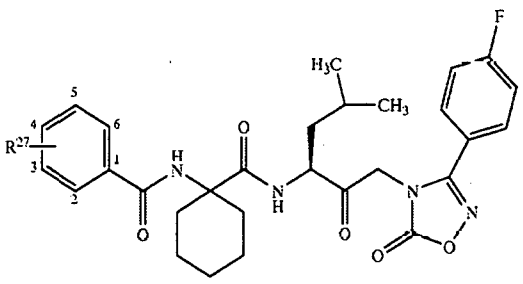
No.	R^{27}
1	2-$CH_2N(CH_3)_2$
2	3-$CH_2N(CH_3)_2$
3	4-$CH_2N(CH_3)_2$
4	

TABLE 17-continued

(I-2B-4)



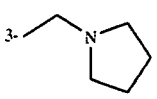
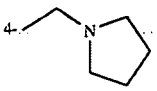
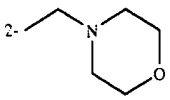
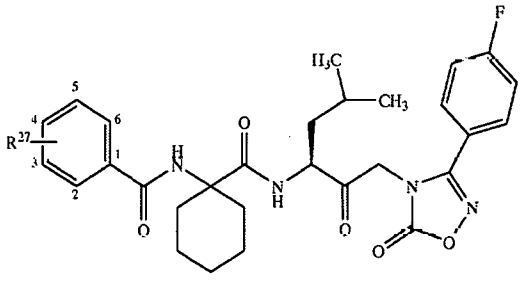
No.	R^{27}
5	
6	
7	

TABLE 17-continued

(I-2B-4)



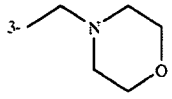
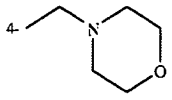
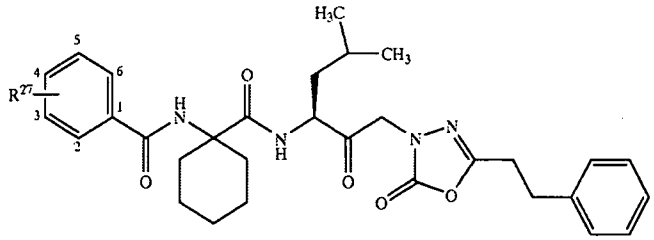
No.	R^{27}
8	
9	

TABLE 18

(I-2B-4)



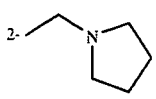
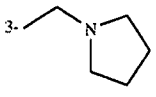
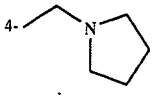
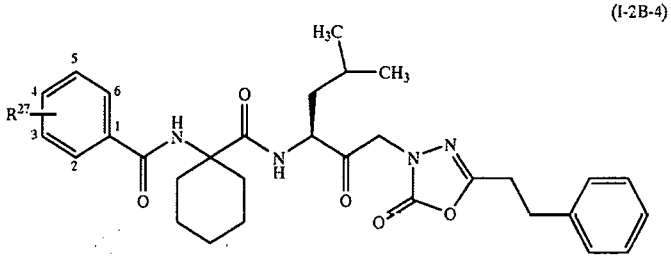
No.	R^{27}
1	2-$CH_2N(CH_3)_2$
2	3-$CH_2N(CH_3)_2$
3	4-$CH_2N(CH_3)_2$
4	
5	
6	

TABLE 18-continued

(I-2B-4)



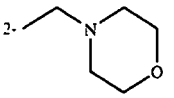
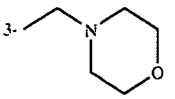
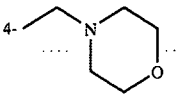
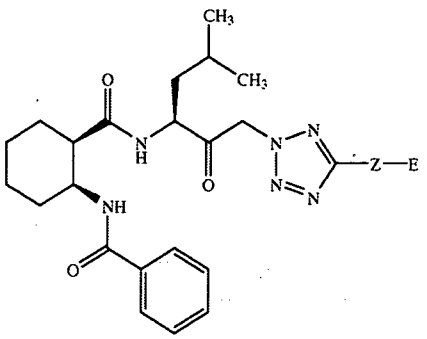
No.	R^{27}
7	
8	
9	

TABLE 19

(I-4A-2)



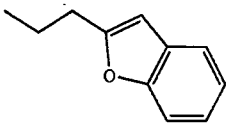
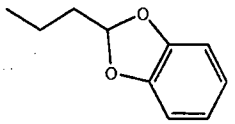
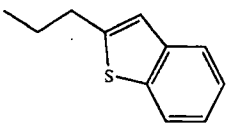
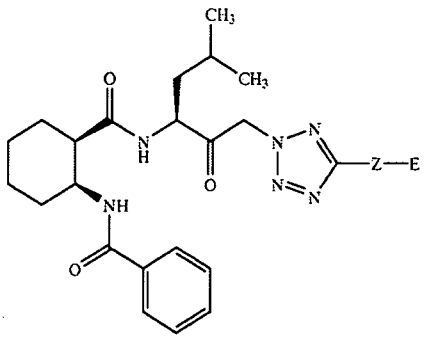
No.	-Z-E
1	
2	
3	

TABLE 19-continued

(I-4A-2)



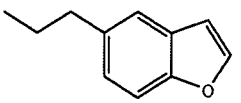
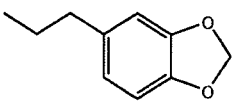
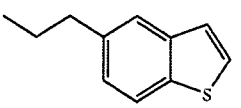
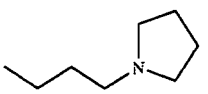
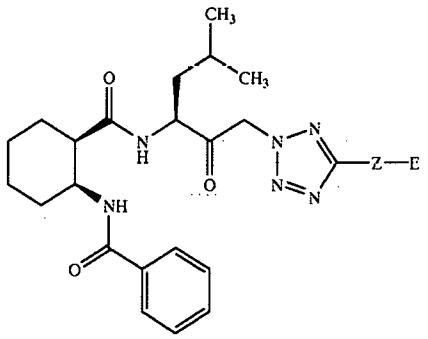
No.	-Z-E
4	
5	
6	
7	

TABLE 19-continued

(I-4A-2)



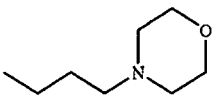
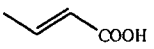
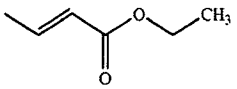
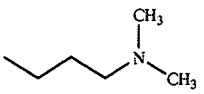
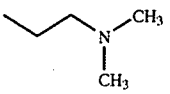
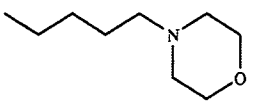
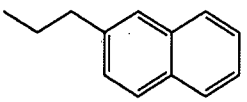
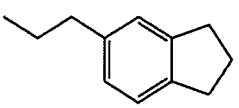
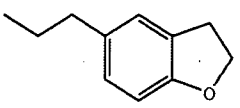
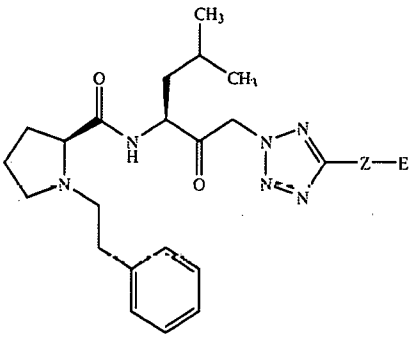
No.	-Z-E
8	
9	
10	
11	
12	
13	
14	
15	
16	

TABLE 20

(I-3A-3)



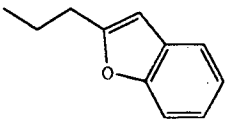
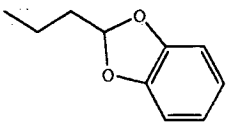
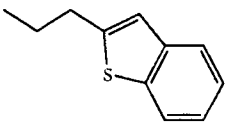
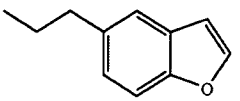
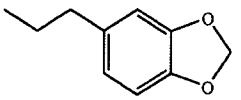
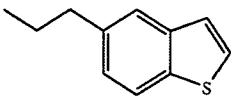
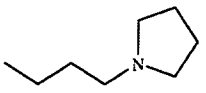
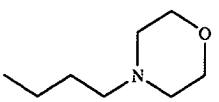
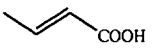
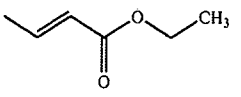
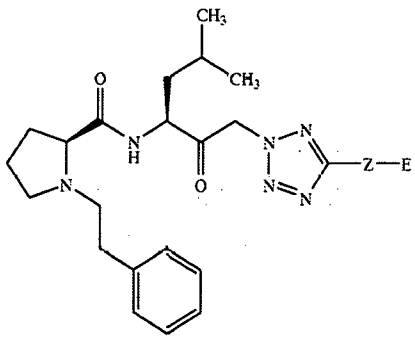
No.	-Z-E
1	
2	
3	
4	
5	
6	
7	
8	
9	
10	

TABLE 20-continued

(I-3A-3)



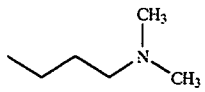
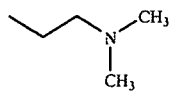
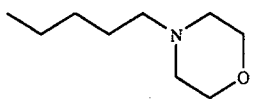
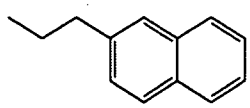
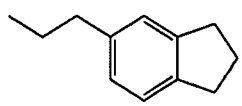
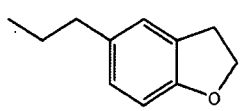
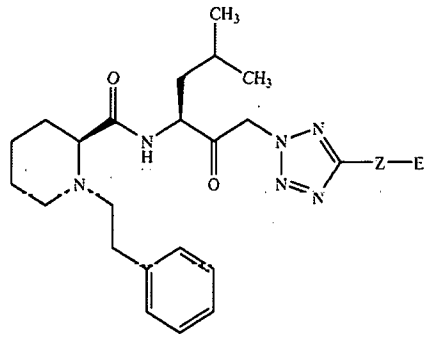
No.	-Z-E
11	
12	
13	
14	
15	
16	

TABLE 21

(I-3A-4)



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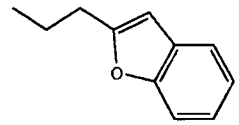
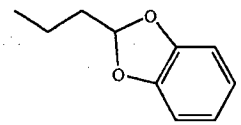
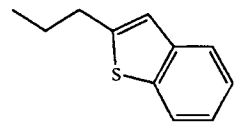
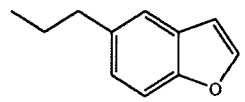
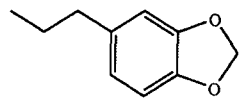
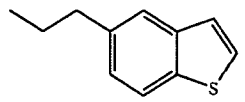
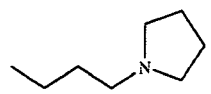
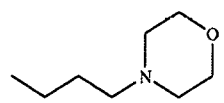
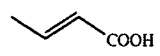
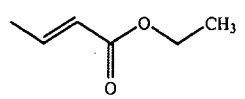
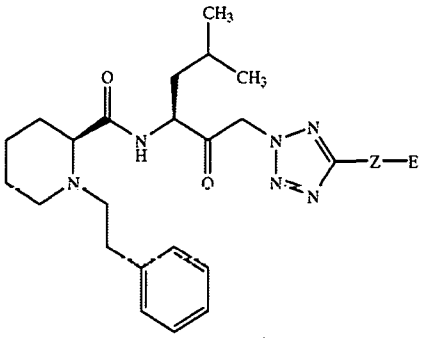
1	
2	
3	
4	
5	
6	
7	
8	
9	
10	

TABLE 21-continued

(I-3A-4)



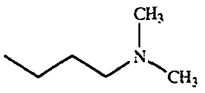
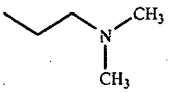
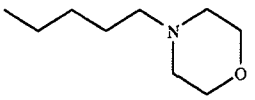
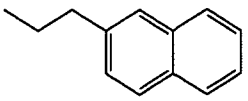
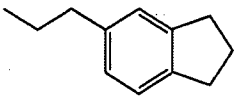
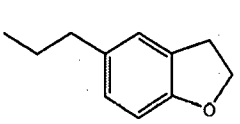
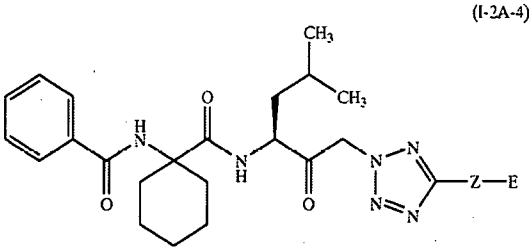
No.	—Z—E
11	
12	
13	
14	
15	
16	

TABLE 22

(I-2A-4)



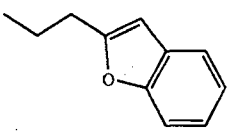
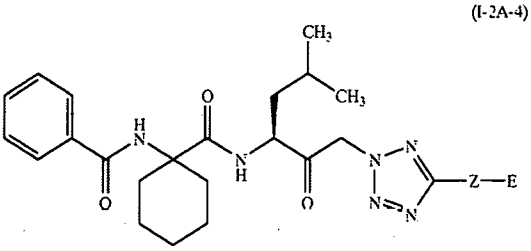
No.	—Z—E
1	

TABLE 22-continued

(I-2A-4)



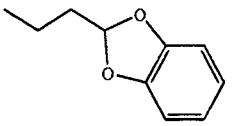
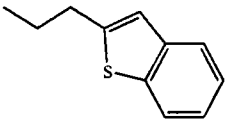
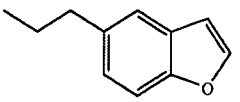
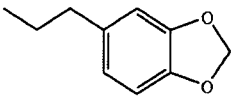
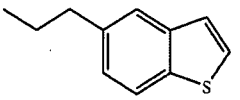
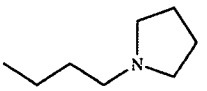
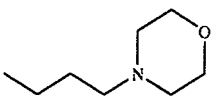
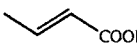
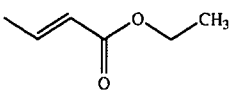
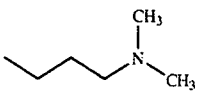
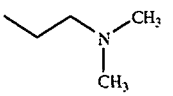
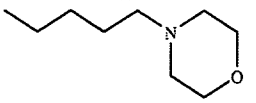
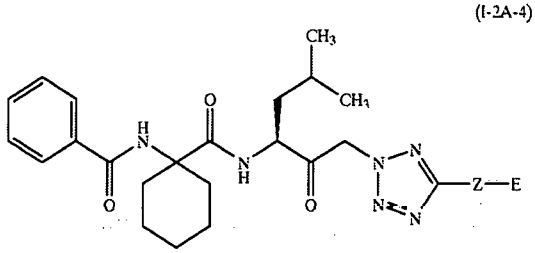
No.	Z—E
2	
3	
4	
5	
6	
7	
8	
9	
10	
11	
12	
13	

TABLE 22-continued

(I-2A-4)



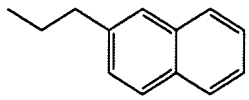
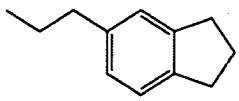
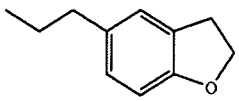
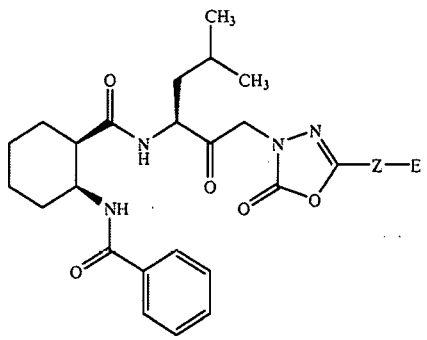
No.	—Z—E
14	
15	
16	

TABLE 23

(I-4B-3)



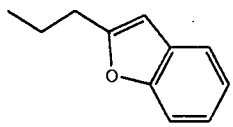
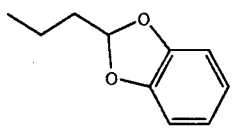
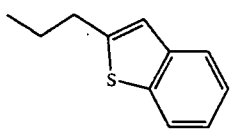
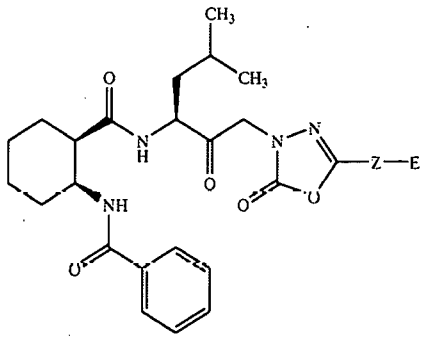
No.	—Z—E
1	
2	
3	

TABLE 23-continued

(I-4B-3)



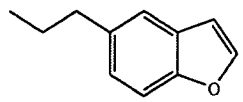
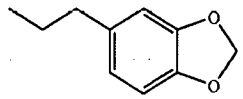
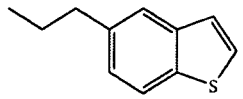
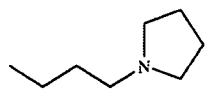
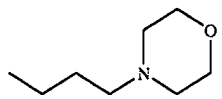
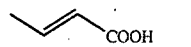
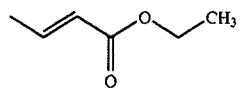
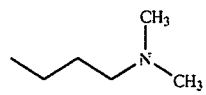
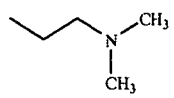
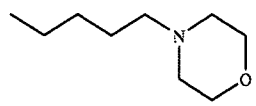
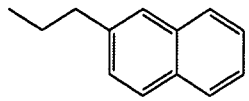
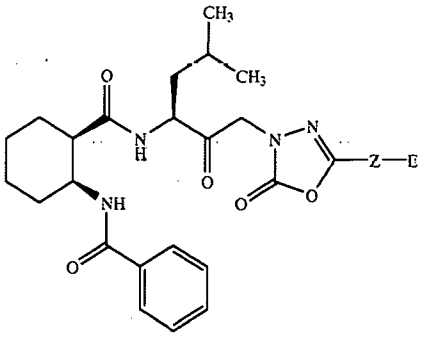
No.	—Z—E
4	
5	
6	
7	
8	
9	
10	
11	
12	
13	
14	

TABLE 23-continued

(I-4B-3)



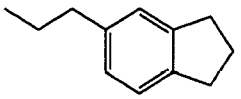
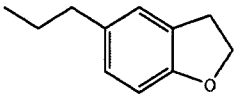
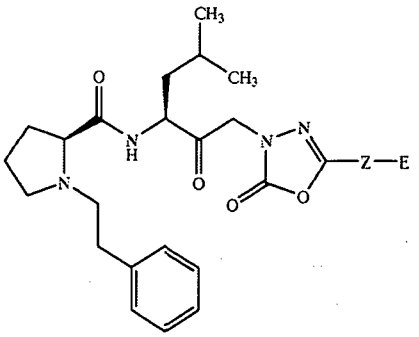
No.	—Z—E
15	
16	

TABLE 24

(I-3B-5)



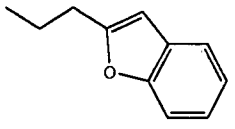
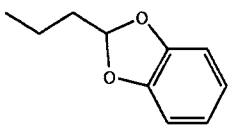
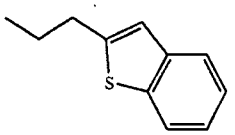
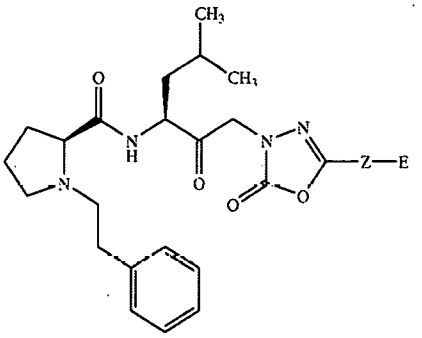
No.	—Z—E
1	
2	
3	

TABLE 24-continued

(I-3B-5)



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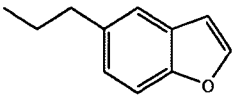
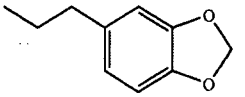
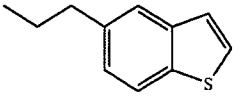
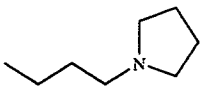
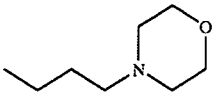
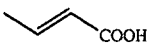
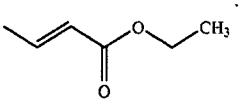
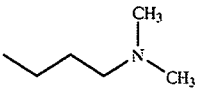
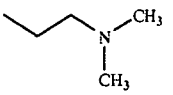
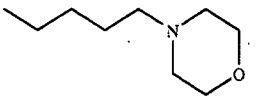
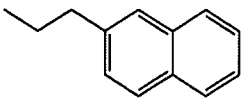
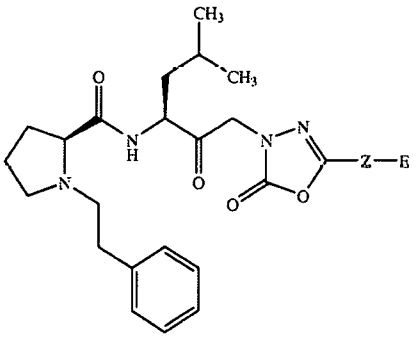
4	
5	
6	
7	
8	
9	
10	
11	
12	
13	
14	

TABLE 24-continued

(I-3B-5)



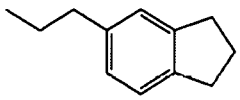
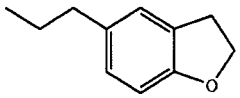
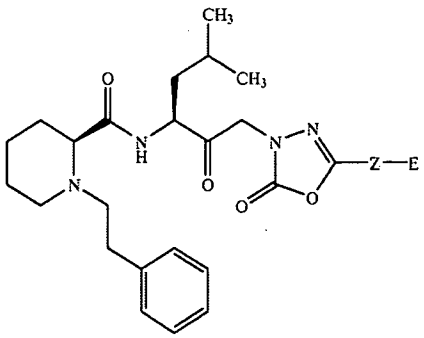
No.	—Z—E
15	
16	

TABLE 25

(I-3B-6)



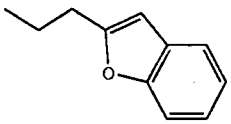
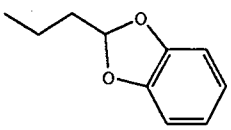
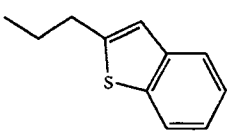
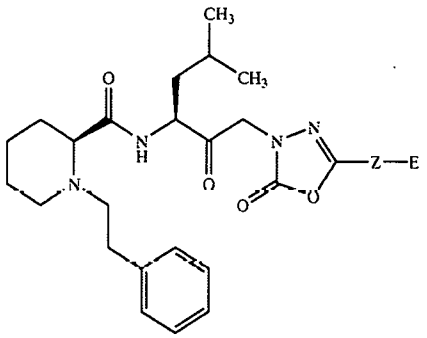
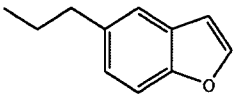
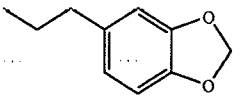
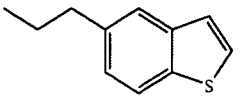
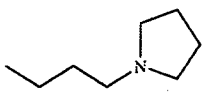
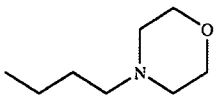
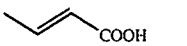
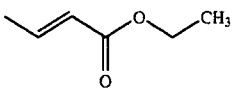
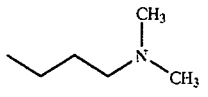
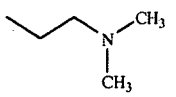
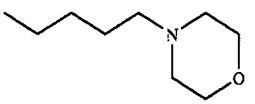
No.	—Z—E
1	
2	
3	

TABLE 25-continued

(I-3B-6)



No.	—Z—E
4	
5	
6	
7	
8	
9	
10	
11	
12	
13	
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