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GNA/KS/785/08-09

22/07/2008

20

To,
The Controller of Patents
The Patent Office,
Boudhik Sampada Bhavan
Near Antop Hill Post Office
S.M.Road, Antop Hill,
Mumbai – 400 037.

Dear Sir,

Sub: Pre-grant Representation/Opposition to the patent u/s 25(1) of the Patents Act, 1970 (as amended upto 2005) and rule 55(1) of the Patents (Amendment) Rules, 2006

Patent Application No. IN/PCT/2001/00018/MUM A dated 03rd January, 2001

We are filing this pre-grant representation/Opposition U/s 25 (1) of the Patents (Amendment) Act 1970 (39 of 1970) (as amended upto 2005) & Rule 55(1) of the Patent amended Rule, 2006. The relevant statement and accompanying evidence are forwarded herewith.

As per provision of the Patent Act, 1970 (as amended upto 2005) [u/s 25(1) and the Patent (Amendment) Rules 2006 (Rule 55(1))], we are entitled to file this pre-grant opposition any time before grant.

भारत सरकार पेटेन्ट कार्यालय शाखा
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23 JUL 2008
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Contd....2

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This pre-grant opposition is filed by us on behalf of our client M/s CIPLA LIMITED, Mumbai. We further request you to grant us a personal hearing as per provision u/s 25(1) of the Patents Act, 1970 (as amended upto 2005) and Rule 55(1) of the Patent (Amendment) Rules, 2006.

Form 26 (Power of Attorney) will be submitted at the earliest.

Thanking you,

With best regards,

Dr. Gopakumar G. Nair
Gopakumar Nair Associates
Representing
M/s. Cipla Limited, Mumbai
Encl: As Above

Pregrant Opposition (Cipla) (3)

BEFORE THE CONTROLLER OF PATENTS,

MUMBAI

IN THE MATTER of Section 25(1) of The Patents Act; 1970, *as amended up to* The Patents (Amendment) Act, 2005

And

IN THE MATTER of The Patents Rules, 2006

And

IN THE MATTER of Patent Application IN/PCT/2001/00018/MUM, dated 03rd January, 2001, filed by ABBOTT LABORATORIES

..... Applicant

And

IN THE MATTER of PRE-GRANT OPPOSITION by M/s. CIPLA LIMITED, an Indian company, incorporated at Mumbai, India, having Registered Office at 289, Bellasis Road, Mumbai Central, Mumbai– 400 008 ..... Opponent

PRE-GRANT OPPOSITION

Representation by way of Opposition

U/S 25(1) and Rule 55(1)

Of The Patents Act, 1970

And Rules thereunder

Patent Application No. IN/PCT/2001/00018/MUM

It is respectfully submitted on behalf of the Opponent, CIPLA LTD., an Indian Public Limited Company, incorporated in Mumbai, India, having their registered office at 289, Bellasis Road, Mumbai Central, Mumbai – 400 008, (hereinafter referred to as "The Opponent"), that a pre-grant opposition under section 25(1) of The Patents Act, 1970 and Rule 55(1) of The Patent Rules, 2003, is hereby presented by the Opponent above named, to oppose the application for grant of Patent filed by the Applicant, as indicated in the cause title "POLYMORPH OF A PHARMACEUTICAL".

It is submitted by the Opponent as follows:

1. That the Opponent is in the pharmaceutical business, *inter alia*, manufacturing distributing and exporting pharmaceutical active ingredients and dosage forms.

2. The Patent Application under Opposition relates to the field of Polymorph/Crystalline forms and Salts of antiretroviral generally, and composition of known substances in particular.

3. That a representation of opposition can be made by any person under Section 25 (1) of The Patents Act, 1970, however the Opponent submits that they are interested in the field and have *locus standi* to initiate the present pre-grant opposition proceedings.

4. The Patent application has been filed in the Patent Office, Mumbai. The jurisdiction for this pre-grant opposition is, therefore, in the Patent Office, Mumbai, where this Opposition is being filed.

5. The Opposition is being filed as a pre-grant opposition under Sec. 25(1), any submissions made or evidence adduced with specific reference to any Sub-sections of Sec. 25(1) may be treated as being made without prejudice to other submissions made elsewhere in this pre-grant opposition

6. It is submitted by the Opponent that the Indian National Phase Patent Application No. IN/PCT/2001/00018/MUM titled "POLYMORPH OF A PHARMACEUTICAL" has been

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filed on 03rd January, 2001. The above Indian application was published in the Official Journal of The Indian Patent Office on 04th March, 2005. The said Indian National Phase Patent Application is attached as **Annexure I.** The above Indian National Phase Patent Application is claiming priority from US 09/119,345 and US 09/326,093 dated 20th July, 1998 and 4th June, 1999 respectively. The said priority document is attached herewith as **Annexure II (a) and Annexure II (b)** respectively.

7. It is further submitted by the Opponent that the Indian National Phase Patent Application No. IN/PCT/2001/00018/MUM has a corresponding PCT International Application No PCT/US99/16334, having Publication No. WO 00/04016 with International filing date of 19th July, 1999. The said PCT International application is attached herewith as **Annexure III.**

8. **The brief discussion of the scope of the claims of the impugned invention are:**

In one aspect, the alleged Patent Application relates to a novel crystalline Polymorph of (2S, 3S, 5S) -5- (N- (N- ((N-methyl-N- ((2-isopropyl-4-thiazolyl) methyl) amino) carbonyl) -L- valinyl) amino) -2- (N- ((5-thiazolyl) methoxycarbonyl) amino) -1,6-diphenyl-3- hydroxyhexane, methods for its preparation, methods for its use as a pharmaceutical agent and pharmaceutical compositions comprising the novel crystalline polymorph.

In another aspect, the alleged invention relates to an Amorphous form of (2S, 3S, 5S) -5- (N- (N- ((N-methyl-N- ((2-isopropyl-4-thiazolyl) methyl) amino) -carbonyl) -L-valinyl) amino) -2- (N- ((5-thiazolyl) methoxycarbonyl) amino) -1,6-diphenyl-3-hydroxyhexane and methods for its preparation.

9. **First Patent:**

Ritonavir was first disclosed before 1995 i.e. before the introduction of product patent regime in India. Product Patent regime was established in India on 01.01.1995 as India became a signatory to the TRIPs Agreement and member of WTO. Prior to 1995, only process patent were granted in India for drugs, food and chemicals. Hence, Ritonavir was non-patentable in India as the same is published and disclosed as such before 1995 in PCT International Application No. PCT/US1993/012326 having WO International Publication No. WO94/14436 filed on 16th December, 1993 by Abbot Laboratories and published on 7th July, 1994 titled "RETROVIRAL PROTEASE INHIBITING COMPOUNDS" which claims priority from US Application No. 07/998,114 dated 29th December, 1992. The said *WO International Application is attached herewith as* ***Annexure IV.***

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The corresponding US Patent No. 5541206 for Ritonavir is also granted to Abbott Laboratories dated 30th July, 1996 titled "Retroviral Protease Inhibiting Compounds" was filed on 25th April, 1995. The said US Patent is attached herewith as **Annexure V.**

10. *Grounds of Opposition:*

The Opponent is relying on Sec. 3(d) and Sec. 25(1)(f) of The Patents Act, 1970. Evidence in support of the opposition is submitted by the Opponent as follows:

The Opponent further opposes the grant of the alleged Indian National Phase Patent Application No. IN/PCT/2001/00018/MUM on following specific grounds provided in Section 25 (1) of The Patents Act, 1970.

10(a) U/s25(1)(e) of The Patents Act, 1970(Lack of inventive step and obviousness):

The Opponent respectfully submits that the invention as claimed in the impugned Application is obvious and clearly does not involve any inventive step under Sec 25(1)(e) of The Patents Act, 1970.

Sec 25(1)(e) relies on the definition in section 2(j) and 2(ja) of The Patents Act, 1970 for allowing an opposition when "an invention which is obvious and clearly does not involve any inventive step having regards to matter published as mentioned in sec 25(1)(b) of The Patents Act, 1970 or having regard to what was used in India before priority date of the Applicant's claim.

The Applicant has acknowledged that Ritonavir is a known substance from US Patent No. US5541206. The opponent believes that the claimed invention of the impugned application i.e. the crystalline or amorphous form, from this known form of Ritonavir would have been obvious to a person skilled in the art. It is widely known in the pharmaceutical industry that a solid form of a drug may exist in either amorphous or crystalline forms. Obtaining either the amorphous or crystalline forms, therefore, would certainly have been obvious to a person skilled in the art.

The Opponent further submits that it is well known in the pharmaceutical industry that drugs may exist in various crystal states and the particular state and this depends on the solvent used. It is also well known in the art that crystalline forms of a given compound can be achieved using routine experiments. Generally the process of recrystallisation involves purification and crystallization of a compound

which comprises dissolving in solvents filtration and cooling the solution. When cooled, the solubility limit of the compound exceeds, so the dissolved substance crystallizes out, thus separating the crystals from the solution. Alternate method of carrying out recrystallization is the addition of an anti-solvent. Recrystallization is also commonly carried out by first dissolving the compound to a saturation level in a particular solvent and then adding the seed crystal to initiate the process of recrystallization.

The impugned application obtains Ritonavir crystalline formula II using these conventional techniques that are commonly known to a person skilled in the art, this clearly and convincingly demonstrates lack of inventive step.

Further, for an ordinary person skilled in the art it is obvious to use solvent mixtures such as ethanol, ethyl acetate or ethyl acetate hexane in the recrystallization process. These solvents are mentioned in the impugned application and are commonly used in recrystallization process. There is no inventive step in claiming the recrystallization process.

10 (b) U/s 25 (1) (f) of The Patents Act, 1970 (Not an Invention):

It is respectfully submitted by the Opponent that the alleged specification claims Polymorph form of Ritonavir, the subject matter of the alleged specification is not an invention within the meaning of The Patents Act, 1970. The alleged invention is thus not patentable under Sec 25 (1)(f) of The Patents Act, 1970, for being not an invention, being not eligible for a patent, and being devoid of inventive step.

The alleged invention does not qualify for grant of a patent under Sec 2 (1)(j) and Sec 2(1)(ja) of The Patents Act, 1970.

As stated earlier, the product claimed in Claims (1) to (6) is non-patentable, being not novel, having been a pre-1995 molecule, already disclosed, claimed and patented prior to the priority date of the alleged Application. The process claimed in Claims (7) to (30) is already non-patentable as these claims lack in inventive steps. The Claims are obvious to a person skilled in the art.

10 (c) U/s 25 (1) (g) of The Patents Act, 1970 (Not an Invention):

It is respectfully submitted by the Opponent that the alleged patent application and specification herein does not fulfill the enablement requirements of written

description as the specification does not describe a the advantages of the use of (2S)-N-((1S)-1-Benzyl-2-((4S,5S)-4-benzyl-2-oxo-1,3-oxazolidin-5-yl)ethyl)-2-(2-isopropyl-1,3-thiazol-4-yl)methyl)amino)-carbonyl)amino)-3-methylbutanamide to produce pure form of Ritonavir is not disclosed in the specification. The patent application is also devoid of embodiment to substantiate the claim in the specification. No patent can be granted when the patent application does not include a proper written description in the specification.

We submit that the written description and the enablement falls u/s 25(1) (g) and is liable to be rejected, in totality, on the complete specification does not sufficiently and clearly describe the invention or method by which it is to be performed.

10 (d) Section 3(d) No significant enhancements in efficacy:

The Opponent also submits that the alleged invention clearly falls within the scope of Section 3(d) of The Patents Act, 1970, due to which the alleged invention of the Applicant cannot be granted the Patent.

Quote:

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

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

Unquote:

Section 3(d) of The Indian Patents Act, 1970 unequivocally states that a mere discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of a substance is not patentable. The explanation of Section 3(d) also states that the isomers, salts, polymorphs, combinations and other derivatives of known substances shall be considered as the

same substance, unless they differ significantly in properties with regard to efficacy. The validity of Sec 3(d) of The Patents Act, 1970 has been upheld by the Chennai High Court in Glivec case (W. P. Nos. 24759 and 24760 of 2006, dated 06/08/2007).

11. The Opponent now responds to the Specification filed by the Applicant, in detail as follows:

11(a) Specification:

The specification specifically acknowledges that Ritonavir is a known compound marketed as NORVIR. This statement is a direct indication for prior existence of the molecule prior to the priority date of the alleged invention.

It is further stated that the Pharmaceutical Compositions comprising Ritonavir or a Pharmaceutical acceptable salts thereof are disclosed in various granted Patents. However, this specification further states as follows "*It has now been unexpectedly discovered that Ritonavir can be prepared as a new crystalline polymorph which is termed crystalline Form II*". The opponent respectfully draws the attention of the Ld. Examiner/Controller to the statement "*unexpectedly discovered*", it is submitted that as per the state of knowledge of Chemistry as on the priority date, the formation of crystalline forms are not unexpected by adopting different forms of crystallization, it is well known that different forms in Crystalline/Polymorphic forms can be obtained. However, it is nature which decides which crystal should be formed in which processes since the molecule is already known in all its chemical and structural description. The formation of the Polymorphic form by subjection to the known and obvious form of crystallization, which results in discovery of new physical form that does not meet the requirements of Patentability such as novelty, inventiveness and industrial application. The statement "*unexpectedly*" is made to confuse and mislead the Ld. Examiner/Controller into believing that there is an invention in the alleged Application.

The Opponent is relying on the US case laws:

1) *Purdue Pharma L.P., et al. v. Endo Pharmaceuticals, Inc., et al.,*
2) *Smithkline Beecham Corporation & Beecham Group v. Apotex Corp & Torpharm, Inc. and*
3) *Pfizer v. Apotex.*

The Judgment in *Pfizer v. Apotex* (**Annexure-IX**) examines the underlying factual determination for review as follows:

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"(1) the scope and content of the prior art,
(2) the level of ordinary skill in the art,
(3) the differences between the claimed invention and the prior art, and
(4) objective indicia of non-obviousness".

It further states that "*By statute, a claimed invention is unpatentable if the differences between it and the prior art 'are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art'*".

The Opponent respectfully states from page 20, para 2 line 7, that *"Motivation to Combine Prior Art References to Achieve the Claimed Invention"*, is a ground for invalidating the invention or denying the patent. Without prejudice to our contention that crystalline form of known substance is not patentable, the opponent submits that, extensively in the description of the process, there is reference to preparation of Form II crystals of Ritonavir by seeding the solution with Form II crystals of Ritonavir. When an alleged invention is obtained by using the alleged invention itself by the input in the process, the alleged invention fails and becomes prior art.

The various examples 1 to 8 are obvious and not patentable. The protocol described in the specification for the polymorphic forms of Ritonavir as well as process for preparation of the same is not patentable. The standard processes as described in the specification are widely used and well known in the prior art.

11(b) Claims:

The Opponent will now deal with specific Claims in the alleged invention:

11(b)(i) The Opponent opposes Claims 1 and 2 on following grounds:

The Opponent respectfully submits that Claims 1 and 2 deals with Crystalline Polymorphic form of Ritonavir which is not-patentable under Section 25 (1) (f) and Section 3 (d) of The Patents Act, 1970.

As stated earlier, the product claimed in Claims (1) and (2) is non-patentable, being not novel, having been a Pre-1995 molecule, already disclosed, claimed and patented prior to the priority date of the alleged Application.

The Opponent vehemently submits that the increased efficacy for the polymorphic form claimed in claims 1-2 is not disclosed in the impugned Application.

11(b)(ii) The Opponent opposes Claims 3 and 4 on following grounds:

Claims 3 to 4 deals with Crystalline Polymorphic form of Ritonavir which is not-patentable under Section 25 (1) (f) and Section 3 (d) of The Patents Act, 1970.

As stated earlier, the product claimed in Claims (3) to (4) is non-patentable, being not novel, having been a pre-1995 molecule, already disclosed, claimed and patented prior to the priority date of the alleged Application.

The Opponent further submits that the increased efficacy for the substantially pure crystalline polymorphic form claimed in claims 3-4 is not disclosed in the impugned Application.

11(b)(iii) The Opponent opposes Claims 5 and 6 on following grounds:

Claims 5 to 6 deals with Amorphous form of Ritonavir which is not-patentable under Section 25 (1) (f) and Section 3 (d) of The Patents Act, 1970.

The Opponent respectfully states that the increased efficacy of the substantially pure amorphous form of Ritonavir as claimed in claim 5-6 over the original form of (2S,3S,5S)-5-(N-(N-((N-methyl-N-2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane (Ritonavir) is not disclosed in the impugned Application.

Therefore, the present claims are, mere discoveries that are not inventions and are not patentable. The intent of section 3(d) of the Patents Act, 1970, is clearly to show, within the ambit of pharmaceutical inventions and the effect in the human body, what does not constitute an invention. In the present case, both the crystalline and amorphous forms of (2S,3S,5S)-5-(N-(N-((N-methyl-N-2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valinyl)amino)-2-(N-((5-thiazolyl)methoxy carbonyl)amino)-1, 6-diphenyl -3- hydroxyhexane do not demonstrate any increase in efficacy and should be promptly rejected by the Ld Controller/Examiner.

11(b)(iv) The Opponent opposes Claims 7-18 on following grounds:

Claims 7 to 16 deals with the preparation process of Amorphous form of Ritonavir by adding a solution of Ritonavir/ Ritonavir Form I, to an antisolvent such as methylene chloride to hexane and methanol to methyl t-butyl ether.

The Opponent respectfully submits that claim 7-16 describes a process of adding a solution of Ritonavir to an antisolvent, which is routinely used in pharmaceutical industry to obtain Crystalline/Amorphous forms of the compound and as such claim 7-16 is opposed under section 25(1)(e), under section 25(1)(f), section 2(1)(j) and 2(1)(ja) of The Patents Act, 1970.

The Opponent further strongly states that for a person ordinarily skilled in the art it is obvious to use solvent mixtures such as ethanol, ethyl acetate or ethyl acetate/ hexane (claimed in the impugned application) for the recrystallization process, as are also commonly used in recrystallization process. Thus the claims 7-16 of the alleged invention is not patentable under The Patents Act, 1970 for being not an invention, being not eligible for a patent, and being devoid of novelty and inventive step.

Claims 17 and 18 discloses process of lyophilization of a solution of Ritonavir in isobutanol to produce amorphous Ritonavir. The process of lyophilization for obtaining amorphous form of a drug is long known in the pharmaceutical art and hence is obvious to a person ordinary skilled in the art.

The Opponent further states that GB Patent No.761163 having title "Process for preparing a substance having anti-tuberculous activity", published on 24.04.1957, which discloses the anti-tuberculous substance, recovered by evaporation of the final liquid or by lyophilization, is white, amorphous solid, soluble and stable in aqueous solution. The Opponent respectfully quotes from the description of the said GB Patent, Page No. 4, Col 1, Line No.59 to Page No.4, Col 2, Line 2,

"*The depyrogenized liquid gives, by evaporation on a water bath, or by lyophilization, the product in the shape of a white, amorphous residue soluble in water, thermostable Lyophilization can be effected at a temperature 65°C in the condenser, prefreezing temperature 45° C and subsequent sizing up to the room temperature for 3 hours.*" The evidence in support to the above explanation is attached herewith as **Annexure VIII** and is having a priority date of 07.04.1953.

Thus the process for preparation of Amorphous forms of Ritonavir by lyophilization of a solution of Ritonavir in isobutanol are not patentable as these claims lack patentability requirement of inventive step and are obvious to a person skilled in the art.

11(b)(v) The Opponent opposes Claims 19-21 on following grounds:

Claims 19-21 describes the process for preparation of substantially pure crystalline form of Ritonavir by seeding a solution of Ritonavir with the seed crystals of (2S)-N-((1S)-1-Benzyl-2-((4S,5S)-4-benzyl-2-oxo-1,3-oxazolidin-5-yl)ethyl)-2-((((2-isopropyl-1,3-thiazol-4-yl) methyl)amino)-carbonyl)amino)-3-methylbutanamide in ethanol (solvent). The said process of recrystallization is commonly carried out by first dissolving the compound to a saturation level in a particular solvent and then adding the seed crystal to initiate the process of recrystallization. The advantages of using the above mentioned chemical as a seed crystals for obtaining the substantially pure crystalline form of Ritonavir is not supported by the written description and enablement requirement. As such the claims 19-21 are liable to be rejected under section 25(1)(g) of The Patents Act,1970.

The substantially pure crystalline form of Ritonavir obtained by seeding the solution of Ritonavir with seed crystals of (2S) -N- ((1 S) -1 -Benzyl-2- ((4S, 5S) -4-benzyl-2-oxo-1,3-oxazolidin-5-yl) ethyl) -2- ((((2-isopropyl-1,3-thiazol-4-yl) methyl) amino) -carbonyl) amino) -3- methylbutanamide is also not supported by any data which demonstrates the enhancement in the efficacy of the resultant pure crystalline form of Ritonavir. As such Claims 19-21 are not patentable under section 25(1)(e)(lack of inventive step) and section 25(1)(f) (Not an invention) of the Patents Act, 1970.

11(b)(vi) The Opponent opposes Claims 22-24 on following grounds:

The Opponent respectfully submits that the known general process of recrystallization involves purification and crystallization of a compound which comprises dissolving in solvents filtration and cooling the solution. When cooled, the solubility limit of the compound exceeds, so the dissolved substance crystallizes out, thus separating the crystals from the solution. Alternate method of carrying out recrystallization is the addition of an anti-solvent. Recrystallization is also commonly carried out by first dissolving the compound to a saturation level in a particular solvent and then adding the seed crystal to initiate the process of recrystallization

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The Opponent further vehemently states that it is obvious to use solvent mixtures such as ethanol, ethyl acetate or ethyl acetate hexane (claimed in the impugned application for the recrystallization process) as are also routinely practiced in recrystallization process. Thus the claims 22-24 of the alleged invention is not patentable under The Patents Act, 1970 for being not an invention, being not eligible for a patent, and being devoid of novelty and inventive step.

11(b)(vii) The Opponent opposes Claims 25-30 on following grounds:

The Opponent respectfully submits that for obtaining a pure form I Ritonavir by adding a solution of Ritonavir to slurry of seed crystals of Ritonavir crystalline polymorph form–I in an anti-solvent, is obvious to a person skilled in the art.

The claims 25-30 are very obvious to a person skilled in the art to obtain crystalline form I by seeding crystalline form I. Hence, the claims are not patentable as being not novel and lack of inventive step. As such the Opponent vehemently opposes claims 25-30 under section 25(1)(e) and section 25(1)(f) of the Patents Act,1970.

12. The Opponent relies on the Glivec Case (Imatinib Mesylate Patent Application) relating to Patent Application No. 1602/MAS/1998, which has been decided by Chennai Patent Office. A copy of the decision is attached herewith as **Annexure VI**.

The Opponent further submits as evidence a copy of Judgment of the Chennai High Court upholding the constitutional validity of Sec 3 (d) (Glivec Case)(W.P.Nos.24759 and 24760 of 2006 dated 06/08/2007), of The Patents Act, 1970. The Judgment is attached herewith as **Annexure VII**.

13. The opponent further submits that the alleged invention deserves to be rejected outright on following grounds as opposed under Sec 25 (1) of The Patents Act, 1970:

1. Fails to meet patentability criteria under Sec 2(1)(j) and 2(1)(ja),
2. Alleged Invention in the present Application is not patentable under Sec 3 (d) of The Patent Act, 1970,
3. No significant enhancement of efficacy has been demonstrated for the Form II or crystalline form of the known form of Ritonavir,
4. The Indian Patent Law provisions for the criteria for patentability and invention not patentable (Sec 3) (being different from the patents laws of the other countries), the alleged invention is not patentable in India.

5. The obviousness criteria as exemplified in Judgments of Appeal Courts in USA.

14. Reliefs Sought:

The Opponent prays for the following reliefs:

(1) That the Indian National Phase Patent Application No. IN/PCT/2001/0018/MUM filed by the Applicant be rejected and the request for grant of Patent by the Applicant be dismissed.

(2) That the Opponent be granted leave to file further evidence in support of the pre-grant Opposition for which a request is pending with the Mumbai Patent Office.

(3) That the Opponent be granted hearing in this case.

(4) Such other and further relief/s be granted to the Opponent, as the Learned Controller may deem fit in the facts and circumstances of this case.

Dated this 22nd day of July, 2008

DR. GOPAKUMAR G. NAIR
(Agent for the Opponent)
GOPAKUMAR NAIR ASSOCIATES
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Kandivli (East), Mumbai-400 101
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To,
The Controller of Patents,
The Patent Office,
Mumbai.

INDEX OF IN/PCT/2001/00018/MUM A

SR. NO.	ANNEXURE	TITLE
1.	**Annexure I**	Indian Patent Application No. IN/PCT/2001/00018/MUM
2.	**Annexure II (a)**	Priority document – US Patent Application No. 09/119,345
3.	**Annexure II (b)**	Priority document – US Patent Application No. 09/326,093
4.	**Annexure III**	Corresponding PCT International Application No. PCT/US99/16334 (WO 00/04016)
5.	**Annexure IV**	**First Patent Ritonavir:** PCT International Application No. PCT/US1993/012326 (WO94/14436)
6.	**Annexure V**	**First Patent Ritonavir:** US Patent No. 5541206
7.	**Annexure VI**	Gleevec Case relating to Patent Application No. 1602/MAS/1998 decided by Chennai Patent Office
8.	**Annexure VII**	Judgment of the Chennai High Court upholding the constitutional validity of 3 (d) f The Patents Act, 1970, (W. P. Nos. 24759 and 24760 of 2006 dated 06/08/2007)
9.	**Annexure VIII**	GB Patent No.761163
10.	**Annexure IX**	*Pfizer v. Apotex (Amlodipine case)*

Dr. Gopakumar G Nair

ANNEXURE-I

Annexure - I

(1)

CRAWFORD BAYLEY & Co.
(Registered)

C. H. PARDIWALA*
S. Y. REGE*
R. A. SHAH
A. R. WADIA
D. E. ENGINEER
H. C. ASHER
C. M. MANIAR
S. N. TALWAR
D. C. SHROFF

SOLICITORS & ADVOCATES
*NOTARIES

Hale Bank Buildings,
N. G. N. Vaidya Marg,
Mumbai 400 023

Ritewair Polymers

CMM/RB/ 008657 26th December, 2000

11324

The Deputy Controller of Patents & Designs,
The Patent Office Branch,
Todi Estate, 3rd Floor,
Lower Parel West,
Mumbai - 400 013.

Received Rs. 5000/- by Cash
Challan/M.O./P.O. No. 3/2001
Vide Form (Cr.) 1903 in the Register of Valuables, Bombay.

PCT/2001/00018/MUM

Dear Sir,

Patent Act, 1970
National Phase Entry for PCT Application
PCT Application No. PCT/US99/16334 Chapter II
in the name of Abbott Laboratories, U.S.A.

We are concerned for our clients, Abbott Laboratories, U.S.A.

We have to inform you that our clients have filed a Patent Application No. PCT/US99/16334 in the United States on the 19th July, 1999 under the Patent Co-operation Treaty Chapter II and the National Phase Application was published on the 27th January, 2000 and it is due for National Phase Entry in India on or before the 20th January, 2001 under PCT Chapter II, the particulars of which are furnished hereunder:-

1. This is a Patent Co-operation Treaty Application.

2. Name of Applicant: Abbott Laboratories, U.S.A.

3. International Application No.: PCT/US99/16334, Chapter II.

4. International Filing Date: 19th July, 1999.

5. Priority Date : 09/119, 345 20th July, 1998
09/326,093 4th June, 1999

6. This is a Product Application as provided under Section 5(2) of the Patents Act, 1970.

7. Address for service in India:

TELEPHONE : 2663713, 2660639, 2660277, 2660910, 2660488, 2665443 CABLE : "LEX BOMBAY"

JUL 2000

C/o. CRAWFORD BAYLEY & CO.
Solicitors & Advocates
State Bank Buildings,
N.G.N. Vaidya Marg,
Fort, Mumbai - 400 023.

We hold a General Power of Attorney from our clients duly executed by them in our favour authorising us to act on their behalf in all patent matters which has been filed in connection with the Patent Application No. 518/BOM/97 in your office.

In this connection, we enclose copies of the following documents with a request that this Application be entered into the National Phase before the 20th January, 2001.

1. The published PCT Application.
2. The Request.
3. The Demand.
4. International Search Report.
5. International Preliminary Examination Report.

We send herewith the prescribed fee of Rs.5000/- payable in respect of the above Application.

We request you to take all the documents on record and process the Application according to the Patent Co-operation Treaty.

Yours faithfully,
CRAWFORD BAYLEY & CO.

Partner

Encl: a/a.

Received Rs. 5000/- in cash
Obsvn/M.O. No. 31/2001
Vide Entry No. 1903 in the Register of Application Number,
0301-01 NCR

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TN/PCT/2001/00018/Mum

Polymorph of a Pharmaceutical

Technical Field

This invention relates to a novel crystalline polymorph of (2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane, methods for its preparation, methods for its use as a pharmaceutical agent and pharmaceutical compositions comprising the novel crystalline polymorph. This invention also relates to an amorphous form of (2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)-carbonyl)-L-valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane and methods for its preparation

Background of the Invention

Inhibitors of human immunodeficiency virus (HIV) protease have been approved for use in the treatment of HIV infection for several years. A particularly effective HIV protease inhibitor is (2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valinyl)amino)-2-(N-((5-thiazolyl)-methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane (ritonavir), which is marketed as NORVIR®.. Ritonavir is known to have utility for the inhibition of HIV protease, the inhibition of HIV infection, the inhibition of cytochrome P450 monooxygenase and the enhancement of the pharmacokinetics of compounds

which are metabolized by cytochrome P450 monooxygenase. Ritonavir is particularly effective for the inhibition of HIV infection when used alone or in combination with one or more reverse transcriptase inhibitors and/or one or more other HIV protease inhibitors.

Ritonavir and processes for its preparation are disclosed in U.S. Patent No. 5,541,206, issued July 30, 1996. This patent discloses processes for preparing ritonavir which produce a crystalline polymorph of ritonavir which is termed crystalline Form I. Substantially pure Form I has the powder X-ray diffraction pattern, ^{13}C solid state nuclear magnetic resonance spectrum, the FT near infrared spectrum and the FT mid infrared spectrum which appear in FIGS. 1, 4, 6 and 8, respectively. The angular positions (two theta) of the characteristic peaks in the powder X-ray diffraction pattern of substantially pure Form I shown in FIG. 1 are 3.33° ± 0.1°, 5.76° ± 0.1°, 8.33° ± 0.1°, 14.61° ± 0.1°, 16.33° ± 0.1°, 16.76° ± 0.1°, 17.03° ± 0.1°, 18.02° ± 0.1°, 18.62° ± 0.1°, 19.47° ± 0.1°, 19.86° ± 0.1°, 20.25° ± 0.1°, 21.46° ± 0.1°, 23.46° ± 0.1° and 24.36° ± 0.1°.

Another process for the preparation of ritonavir is disclosed in U.S. Patent No. 5,567,823, issued October 22, 1996. The process disclosed in this patent also produces ritonavir as crystalline Form I.

Pharmaceutical compositions comprising ritonavir or a pharmaceutically acceptable salt thereof are disclosed in U.S. Patent Nos. 5,541,206, issued July 30, 1996; 5,484,801, issued January 16, 1996; 5,725,878, issued March 10, 1998; and 5,559,158, issued September 24, 1996 and in International Application No. WO98/22106, published May 28, 1998 (corresponding to U.S. Serial No. 08/966,495, filed November 7, 1997).

The use of ritonavir to inhibit an HIV infection is disclosed in U.S. Patent No. 5,541,206, issued July 30, 1996. The use of ritonavir in combination with one or more reverse transcriptase inhibitors to inhibit an HIV infection is disclosed in U.S. Patent No. 5,635,523, issued June 3, 1997. The use of ritonavir in

FIG. 9 is the FT mid infrared spectrum of the substantially pure Form II crystalline polymorph of ritonavir.

FIG. 10 is the differential scanning calorimetric thermogram for substantially pure amorphous ritonavir.

Disclosure of the Invention

In accordance with the present invention, there is a novel substantially pure crystalline polymorph of (2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valinyl)amino)-2-(N-((5-thiazolyl)-methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane (ritonavir). For the sake of identification, this crystalline polymorph is designated as the Form II crystalline polymorph of ritonavir.

Substantially pure Form II has the powder X-ray diffraction pattern, ^{13}C solid state nuclear magnetic resonance spectrum, the FT near infrared spectrum and the FT mid infrared spectrum which appear in FIGS. 2, 5, 7 and 9, respectively. The two-theta angle positions of characteristic peaks in the powder X-ray diffraction pattern of substantially pure Form II as shown in FIG. 2 are: 8.67° ± 0.1°, 9.88° ± 0.1°, 16.11° ± 0.1°, 16.70° ± 0.1°, 17.36° ± 0.1°, 17.78° ± 0.1°, 18.40° ± 0.1°, 18.93° ± 0.1°, 20.07° ± 0.1°, 20.65° ± 0.1°, 21.71° ± 0.1°and 25.38° ± 0.1°.

More preferably, substantially pure Form II is characterized by peaks in the powder X-ray diffraction pattern having two-theta angle positions as shown in FIG. 2 of:
8.67° ± 0.1°, 9.51° ± 0.1°, 9.88° ± 0.1°, 10.97° ± 0.1°, 13.74° ± 0.1°, 16.11° ± 0.1°, 16.70° ± 0.1°, 17.36° ± 0.1°, 17.78° ± 0.1°, 18.40° ± 0.1°, 18.93° ± 0.1°, 19.52° ± 0.1°, 19.80° ± 0.1°, 20.07° ± 0.1°, 20.65° ± 0.1°, 21.49° ± 0.1°, 21.71° ± 0.1°, 22.23° ± 0.1°, 25.38° ± 0.1°, 26.15° ± 0.1° and 28.62° ± 0.1°.

combination with one or more HIV protease inhibitors to inhibit an HIV infection is disclosed in U.S. Patent No. 5,674,882, issued October 7, 1997. The use of ritonavir to inhibit cytochrome P450 monooxygenase and to enhance the pharmacokinetics of compounds metabolized by cytochrome P450 monooxygenase is disclosed in WO97/01349, published January 16, 1997 (corresponding to U.S. Serial No. 08/687,774; filed June 26, 1996).

It has now been unexpectedly discovered that ritonavir can be prepared as a new crystalline polymorph which is termed crystalline Form II.

All publications, issued patents and patent applications cited herein are hereby incorporated by reference.

Brief Description of the Drawings

FIG. 1 is the powder X-ray diffraction pattern of the substantially pure Form I crystalline polymorph of ritonavir.

FIG. 2 is the powder X-ray diffraction pattern of the substantially pure Form II crystalline polymorph of ritonavir.

FIG. 3 is the powder X-ray diffraction pattern of substantially pure amorphous ritonavir.

FIG. 4 is the 400 MHz solid state ^{13}C nuclear magnetic resonance spectrum of the substantially pure Form I crystalline polymorph of ritonavir.

FIG. 5 is the 400 MHz solid state ^{13}C nuclear magnetic resonance spectrum of the substantially pure Form II crystalline polymorph of ritonavir.

FIG. 6 is the FT near infrared spectrum of the substantially pure Form I crystalline polymorph of ritonavir.

FIG. 7 is the FT near infrared spectrum of the substantially pure Form II crystalline polymorph of ritonavir.

FIG. 8 is the FT mid infrared spectrum of the substantially pure Form I crystalline polymorph of ritonavir.

The substantially pure Form II crystalline polymorph of ritonavir can be prepared from amorphous ritonavir by contacting amorphous ritonavir with a C1-C3 alcohol. The method of contacting may be either by saturating the amorphous compound in the solvent at ambient temperature and then allowing the mixture to stand for an extended period of time (for example, overnight) or by dissolving the amorphous compound in the solvent at elevated temperature, preferably, at reflux, followed by cooling the solution to room temperature and isolating Form II.

In one embodiment of the process, the substantially pure Form II crystalline polymorph of ritonavir can be prepared from amorphous ritonavir by preparing a saturated solution of amorphous ritonavir in a C1-C3 alcohol at room temperature and isolating Form II which results. In practice this can be accomplished by dissolving a sufficient amount of amorphous ritonavir in the C1-C3 alcohol at elevated temperature (up to reflux) such that when the solution is allowed to cool to room temperature a saturated solution is obtained, from which Form II precipitates and can be isolated. A preferred solvent for the preparation of Form II is anhydrous ethanol. Isolation of the resulting solid provides Form II.

Substantially pure amorphous ritonavir is prepared from the Form I crystalline polymorph of ritonavir by melting Form I ritonavir and rapidly cooling the melt. Isolation of the resulting solid provides amorphous ritonavir.

Substantially pure amorphous ritonavir can also be prepared by slowly adding a solution of ritonavir Form I in a suitable solvent (methylene chloride and the like; preferably, methylene chloride) at a concentration of, preferably, about 1 g of ritonavir per about 1.5-2.0 mL of solvent (preferably, about 1 g of ritonavir/ about 1.5 mL of methylene chloride) to an anti-solvent (for example, hexane or heptane and the like; preferably, hexane) at a concentration of about 60-110 mL

of antisolvent/ g of ritonavir; preferably, about 85-90 mL of hexane/ g of ritonavir, followed by isolation (for example, by filtration) of the resulting solid.

Similarly, substantially pure amorphous ritonavir can also be prepared by slowly adding a solution of ritonavir Form I in a suitable solvent such as methanol or the like at a concentration of, preferably, about 1 g of ritonavir per about 1.5-2.0 mL of solvent (preferably, about 1 g of ritonavir/ about 1.5 mL of methanol) to an anti-solvent such as methyl t-butyl ether (MTBE) or the like at a concentration of about 60-150 mL of antisolvent/ g of ritonavir, preferably, about 90-110 mL of MTBE/ g of ritonavir and, most preferably, about 100 mL of MTBE/ g of ritonavir, followed by isolation (for example, by filtration) of the resulting solid.

Substantially pure amorphous ritonavir can also be prepared by slowly adding a solution of ritonavir Form I in a suitable solvent (for example, methanol and the like; preferably, methanol) at a concentration of about 1 g of ritonavir per about 1.5-2.0 mL of solvent (preferably, about 1 g of ritonavir/ about 1.6 mL of methanol) to water at about 0°C at a concentration of about 400-500 mL of water/ g of ritonavir (preferably, about 400 mL of water/ g of ritonavir), followed by isolation (for example, by filtration) and drying of the resulting solid.

Substantially pure amorphous ritonavir can also be prepared by lyophilization of a solution of ritonavir Form I. Preferred solvents are C1-C6 alcohols. A more preferred solvent is isobutanol.

Alternatively, in a preferred process, substantially pure crystalline Form II can be prepared by seeding a solution of ritonavir Form I in a suitable solvent (preferably, a C1-C3 alcohol; most preferably, ethanol) with undissolved (2S)-N-((1S)-1-Benzyl-2-((4S,5S)-4-benzyl-2-oxo-1,3-oxazolidin-5-yl)ethyl)-2-((((2-isopropyl-1,3-thiazol-4-yl)methyl)amino)carbonyl)amino)-3-methylbutanamide. In a preferred method, ritonavir Form I is dissolved in ethanol (preferably, 200 proof ethanol) at a concentration of from about 150 g/ L to about 200 g/ L, preferably, about 160 g/ L. To the solution is added seed crystals of

(2S)-N-((1S)-1-Benzyl-2-((4S,5S)-4-benzyl-2-oxo-1,3-oxazolidin-5-yl)ethyl)-2-((((2-isopropyl-1,3-thiazol-4-yl)methyl)amino)carbonyl)-amino)-3-methylbutanamide in the amount of from about 0.02 g to about 0.10 g of seed crystals/ g of ritonavir. The amount of seed crystals added is such that it exceeds the saturation amount in the solvent being used so that there are undissolved seed crystals present in the ritonavir solution. The mixture is allowed to stand at a temperature of from about 0° C to about 15° C (preferably, about 5° C) for from about 12 hours to about 48 hours (preferably, about 24 hours). The resulting crystalline ritonavir Form II is isolated by filtration.

In yet another preferred alternative method, substantially pure Form II can be prepared by recrystallization of Form I or mixtures of Form I and Form II from a solution in a suitable solvent (for example, ethyl acetate or isopropyl acetate or chloroform and the like other solvents with like dielectric constant; preferably, ethyl acetate), with seeding with Form II crystals, followed by addition of an anti-solvent (for example, heptane, hexane, toluene, petroleum ether and the like other anti-solvents with like dielectric constant; preferably, heptane). The amount of seed crystals added is such that it exceeds the saturation amount in the solvent being used so that there are undissolved seed crystals present in the ritonavir solution. In a preferred method, ritonavir (Form I or a mixture of Form I and Form II) is dissolved in ethyl acetate (from about 4.0 L to about 6.0 L/kg of ritonavir) with heating (at from about 65 °C to about 70°C). The solution is slowly cooled to from about 55°C to about 50°C, preferably about 52°C. Seed crystals of ritonavir Form II (from about 0.5 g of Form II seed crystals/kg of ritonavir to about 10.0 g of Form II seed crystals/kg of ritonavir, preferably about 1.25 g of Form II seed crystals/kg of ritonavir) are added and the mixture is stirred for about 1 hour at a temperature of from about 55°C to about 50°C, preferably about 52°C. The amount of seed crystals added is such that it exceeds the saturation amount in the solvent being used so that there are undissolved seed crystals

present in the ritonavir solution. Heptane (from about 1.0 L/kg of ritonavir to about 4.0 L/kg of ritonavir; preferably, about 2.8 L/kg of ritonavir) is added with mixing and the mixture is allowed to slowly cool to about 25°C and is then stirred for at least 12 hours at about 25°C. The product is isolated by filtration/centrifugation and is dried under vacuum with heating. On a manufacturing scale (300-400 kg batches), it has been observed that isolation by filtration/centrifugation is considerably faster for Form II than for the corresponding amount of Form I (16 hours versus 24-30 hours).

It has also been found that Form II or mixtures of Form II and Form I can be converted to substantially pure Form I by dissolving the Form II or mixture of Form II and Form I in a suitable solvent (for example, ethyl acetate or isopropyl acetate and the like; preferably, ethyl acetate) at a concentration of about 1 kg of ritonavir/4 L of solvent (preferably, ethyl acetate) with heating. The hot solution of ritonavir is slowly added (preferably, through a filter) to a slurry of seed crystals of ritonavir Form I (from about 0.5% to about 10% by weight relative to amount of ritonavir Form II or mixture of Form II and Form I; preferably, from about 0.5% to about 5% by weight and, most preferably, from about 0.5% to about 1% by weight) in an anti-solvent (for example, heptane or hexane and the like; preferably, heptane) at a concentration of about 1 kg of ritonavir (Form II or mixture of Form II and Form I) per about 4-8 L of antisolvent (preferably, about 1 kg of ritonavir (Form II or mixture of Form II and Form I)/ about 4 L of heptane). The mixture is cooled to about 20°C and stirred for at least 3 hours. Isolation (for example, by filtration) and drying of the resulting solid provides ritonavir Form I.

The following examples will serve to further illustrate the preparation of the novel forms of ritonavir of the invention and the conversion of Form II to Form I.

Example 1

Preparation of Amorphous Ritonavir

Form I crystalline polymorph of ritonavir (100 g) was melted at 125°C by heating Form I. The melt was maintained at a temperature of 125°C for 3 hours. The melt was rapidly cooled by placing the container holding the melt into a Dewar flask containing liquid nitrogen. The resulting glass was ground with a mortar and pestle to provide amorphous ritonavir (100 g). Powder X-ray diffraction analysis confirmed that the product was amorphous. Differential scanning calorimetric analysis determined that the glass transition point was from about 45°C to about 49°C. (Measured onset at 45.4°C and which ends at 49.08°C, with a midpoint of 48.99°C).

Example 2

Preparation of Crystalline Ritonavir (Form II)

Amorphous ritonavir (40.0 g) was dissolved in boiling anhydrous ethanol (100 mL). Upon allowing this solution to cool to room temperature, a saturated solution was obtained. After standing overnight at room temperature, the resulting solid was isolated from the mixture by filtration and was air dried to provide Form II (approximately 24.0 g).

Example 3

Preparation of (2S)-N-((1S)-1-Benzyl-2-((4S,5S)-4-benzyl-2-oxo-1,3-oxazolidin-5-yl)ethyl)-2-(((((2-isopropyl-1,3-thiazol-4-yl)methyl)amino)carbonyl)amino)-3-methylbutanamide

Example 3a

Preparation of (4S,5S)-5-((2S)-2-t-butyloxycarbonylamino-3-phenylpropyl)-4-benzyl-1,3-oxazolidin-2-one

(2S,3S,5S)-2-Amino-3-hydroxy-5-t-butyloxycarbonylamino-1,6-diphenylhexane succinate salt (30 g, 63 mmol; U.S. Patent No. 5,654,466), ((5-thiazolyl)methyl)-(4-nitrophenyl)carbonate hydrochloride (22.2 g; U.S. Patent No. 5,597,926) and sodium bicarbonate (16.2 g) were mixed with 300mL of water and 300 mL of ethyl acetate and the mixture was stirred at room temperature for about 30 minutes. The organic layer was then separated and heated at about 60°C for 12 hours, and then stirred at 20-25°C for 6 hours. 3 mL of ammonium hydroxide (29% ammonia in water) was added and the mixture stirred for 1.5 hours. The resulting mixture was washed with 4 x 200 mL of 10% aqueous potassium carbonate and the organic layer was separated and evaporated under vacuum to provide an oil. The oil was suspended in about 250 mL of heptane. The heptane was evaporated under vacuum to provide a yellow solid. The yellow solid was dissolved in 300 mL of THF and 25 mL of 10% aqueous sodium hydroxide was added. After stirring for about 3 hours, the mixture was adjusted to pH 7 by addition of 4N HCl (about 16 mL). The THF was evaporated under vacuum to leave an aqueous residue, to which was added 300 mL of distilled water. After stirring this mixture, a fine suspension of solids resulted. The solid was collected by filtration and the filtered solid was washed with water (1400 mL) in several portions, resulting in the desired product.

Example 3b

Preparation of (4S,5S)-5-((2S)-2-amino-3-phenylpropyl)-4-benzyl-1,3-oxazolidin-2-one

The crude, wet product of Example 3a was slurried in 1N HCl (192 mL) and the slurry was heated to 70°C with stirring. After 1 hour, THF (100 mL) was

added and stirring at 65°C was continued for 4 hours. The mixture was then allowed to cool to 20-25°C and was stirred overnight at 20-25°C. The THF was removed by evaporation under vacuum and the resulting aqueous solution was cooled to about 5°C, causing some precipitation to occur. The aqueous mixture was adjusted to pH 7 by addition of 50% aqueous sodium hydroxide (about 18.3 g). The resulting mixture was extracted with ethyl acetate (2 x 100 mL) at about 15°C. The combined organic extracts were washed with 100 mL of brine and the organic layer was separated and stirred with sodium sulfate (5 g) and Darco G-60 (3 g). This mixture was warmed on a hot plate for 1 hour at 45°C. The hot mixture was then filtered through a bed of diatomaceous earth and the filter pad was washed with ethyl acetate (100 mL). The filtrate was evaporated under vacuum to provide an oil. The oil was redissolved in methylene chloride (300 mL) and the solvent was evaporated under vacuum. The resulting oil was dried at room temperature under vacuum to provide the desired product (18.4 g) as a glassy syrup.

Example 3c

Preparation of (2S)-N-((1S)-1-Benzyl-2-((4S,5S)-4-benzyl-2-oxo-1,3-oxazolidin-5-yl)ethyl)-2-((((2-isopropyl-1,3-thiazol-4-yl)methyl)amino)carbonyl)amino)-3-methylbutanamide

N-((N-Methyl-N((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine (10.6 g, 33.9 mmol; U.S. Patent No. 5,539,122 and International Patent Application No. WO98/00410), the product of Example 3b (10.0 g, 32.2 mmol) and 1-hydroxybenzotriazole (5.2 g, 34 mmol) were dissolved in THF (200 mL). 1,3-dicylcohexylcarbodiimide (DCC, 7.0 g, 34 mmol) was then added to the THF mixture and the mixture was stirred at 22°C for 4 hours. Citric acid (25 mL of 10% aqueous solution) was added and stirring continued for 30 minutes. The

THF was then evaporated under vacuum. The residue was dissolved in ethyl acetate (250 mL) and washed with 10% citric acid solution (175 mL). NaCl (5 g) was added to accelerate the separation of the layers. The organic layer was sequentially washed with 10% aq. sodium carbonate (2 x 200 mL) and water (200 mL). The organic layer was then dried over sodium sulfate (20 g), filtered and evaporated under vacuum. The resulting product (20.7 g of a foam) was dissolved in hot ethyl acetate (150 mL) and then heptane (75 mL) was added. Upon cooling, another 75 mL of heptane was added and the mixture was heated to reflux. Upon cooling to room temperature, no precipitate formed. The solvents were evaporated under vacuum and the residue was redissolved in a mixture of 200 mL ethyl acetate/100 mL heptane. The small amount of undissolved solid was removed by filtration. The filtrate was evaporated under vacuum and the residue was dissolved in a mixture of 100 mL ethyl acetate/ 50 mL heptane, giving a clear solution. The solution was cooled to –10°C and a white precipitate formed. The mixture was allowed to sit at –15°C for 24 hours. The resulting solid was collected by filtration, washed with 1:1 ethyl acetate/heptane (2 x 24 mL) and dried in a vacuum oven at 55°C to provide the desired product as a beige solid (16.4 g).

^{1}H NMR (DMSO-d_6) δ 7.84 (1H, doublet J=8.6), 7.71 (1H, singlet), 7.32-7.11 (11H, multiplet), 6.09 (1H, doublet J=8.5), 4.51 (1H AB J=16.2), 4.43 (1H AB J=16.2), 4.22 (1H, multiplet), 4.07 (1H, multiplet), 3.96 (1H, doublet of doublet J=7.3,7.4), 3.65 (1H, multiplet), 3.23 (1H, septuplet J=6.9), 2.89 (3H, singlet), 2.84-2.60 (4H, multiplet), 1.94 (1H, multiplet), 1.76-1.49 (2H, multiplet), 1.30 (6H, doublet J=6.9), 0.80 (3H, doublet J=5.8), 0.77 (3H, doublet J=5.8)

Example 5

Alternative Preparation of Crystalline Ritonavir (Form II)

Ethyl acetate (6.0 L/kg of ritonavir) was added to ritonavir (Form I or a mixture of Form I and Form II) in a reaction vessel. The mixture was stirred and heated to 70°C until all solids were dissolved. The solution was filtered (utilizing a centrifuge pump and 5X20 inch cartridge filters having a porosity of 1.2 microns) and the filtrate was allowed to cool to 52°C at a rate of 2-10°C/hour. To this solution was added ritonavir Form II seed crystals (about 1.25 g of Form II seed crystals/kg of ritonavir) and the mixture was stirred at 52°C for not less than 1 hour at an agitation rate of 15 RPM. The mixture was then allowed to cool to 40°C at a rate of 10°C/hour. Heptane (2.8 L/kg of ritonavir) was added at a rate of 7L/minute with mixing. The mixture was allowed to cool to 25°C at a rate of 10°C/hour with mixing. Then the mixture was stirred for not less than 12 hours at 25°C. The product was isolated by filtration using a Heinkel type centrifuge (run time approximately 16 hours). The product was dried at 55°C under vacuum (50 mm Hg) for 16-25 hours to provide ritonavir crystal Form II.

Example 6

Preparation of Amorphous Ritonavir

Ritonavir Form I (40 g) was dissolved in methylene chloride (60 mL). This solution was slowly added over 15 minutes to a round bottom flask equipped with an overhead stirrer and containing hexanes (3.5 L). The resulting slurry was allowed to stir for 10 minutes. The precipitate was filtered and dried at room temperature in a vacuum oven to provide amorphous ritonavir (40 g).

Example 7

Preparation of Amorphous Ritonavir

Ritonavir Form I (5 g) was dissolved in methanol (8 mL). This solution was slowly added to a round bottom flask equipped with an overhead stirrer and containing distilled water (2 L), while maintaining the internal temperature near 0°C. The resulting solid was filtered to give a sticky solid which was dried in a vacuum oven to give amorphous ritonavir (2.5 g).

Example 8

Preparation of Ritonavir Form I

Ritonavir Form II (1 kg) was added to a reactor (A), followed by the addition of ethyl acetate (4 L). This mixture was refluxed until all of the solids were dissolved.

To a separate reactor (B) was added seed crystals of ritonavir Form I (5 g), followed by the addition of heptane (4 L). This mixture was stirred at 23°C ±5°C.

The hot solution from reactor A was slowly filtered, using a 0.2 micron filter cartridge, into the mixture in reactor B over not less than 2 hours. The resulting slurry in reactor B was cooled to 20°C and stirred for not less than 3 hours. The resulting slurry was filtered, the filtered solid washed with heptane and then dried in a vacuum oven at 65°C to provide ritonavir Form I.

A preferred pharmaceutical composition comprising ritonavir, especially, ritonavir Form II, has the following composition, encapsulated in a soft elastic gelatin capsule.

^{13}C NMR (DMSO-d_6) δ 177.2, 171.5, 157.6, 157.5, 152.8, 138.3, 136.5, 129.5, 129.2, 128.2, 128.0, 126.4, 126.0, 114.0, 77.2, 59.9, 57.6, 48.2, 46.2, 40.4, 40.1, 39.1, 34.5, 32.4, 30.3, 22.8, 22.8, 19.4, 18.3.

Example 4

Preparation of Crystalline Ritonavir (Form II)

To a solution of 1.595 g of ritonavir Form I in 10 mL of 200 proof ethanol was added an amount of the product of Example 3c (approximately 50 micrograms) such that all of the added amount of the product of Example 3c did not dissolve. This mixture was allowed to stand at about 5°C for 24 hours. The resulting crystals were isolated by filtration through 0.45 micron nylon filter and air dried to provide ritonavir Form II.

Example 5

Alternative Preparation of Crystalline Ritonavir (Form II)

Ethyl acetate (6.0 L/kg of ritonavir) was added to ritonavir (Form I or a mixture of Form I and Form II) in a reaction vessel. The mixture was stirred and heated to 70°C until all solids were dissolved. The solution was filtered (utilizing a centrifuge pump and 5X20 inch cartridge filters having a porosity of 1.2 microns) and the filtrate was allowed to cool to 52°C at a rate of 2-10°C/hour. To this solution was added an amount of ritonavir Form II seed crystals (about 1.25 g of Form II seed crystals/kg of ritonavir) such that all of the seed crystals did not dissolve and the mixture was stirred at 52°C for not less than 1 hour at an agitation rate of 15 RPM. The mixture was then allowed to cool to 40°C at a rate of 10°C/hour. Heptane (2.8 L/kg of ritonavir) was added at a rate of 7L/minute with mixing. The mixture was allowed to cool to 25°C at a rate of 10°C/hour with mixing. Then the mixture was stirred for not less than 12 hours at 25°C. The

product was isolated by filtration using a Heinkel type centrifuge (run time approximately 16 hours). The product was dried at 55°C under vacuum (50 mm Hg) for 16-25 hours to provide ritonavir crystal Form II.

Example 6

Preparation of Amorphous Ritonavir

Ritonavir Form I (40 g) was dissolved in methylene chloride (60 mL). This solution was slowly added over 15 minutes to a round bottom flask equipped with an overhead stirrer and containing hexanes (3.5 L). The resulting slurry was allowed to stir for 10 minutes. The precipitate was filtered and dried at room temperature in a vacuum oven to provide amorphous ritonavir (40 g).

Example 7

Preparation of Amorphous Ritonavir

Ritonavir Form I (5 g) was dissolved in methanol (8 mL). This solution was slowly added to a round bottom flask equipped with an overhead stirrer and containing distilled water (2 L), while maintaining the internal temperature near 0°C. The resulting solid was filtered to give a sticky solid which was dried in a vacuum oven at 20-25°C for 12-18 hours to give amorphous ritonavir (2.5 g).

Example 8

Preparation of Ritonavir Form I

Ritonavir Form II (1 kg) was added to a reactor (A), followed by the addition of ethyl acetate (4 L). This mixture was refluxed until all of the solids were dissolved.

To a separate reactor (B) was added an amount of seed crystals of ritonavir Form I (5 g), followed by the addition of heptane (4 L), such that all of the seed crystals did not dissolve. This mixture (a slurry) was stirred at 22°C ±5°C.

The hot solution from reactor A was slowly filtered, using a 0.2 micron filter cartridge, into the mixture in reactor B over not less than 2 hours. The resulting slurry in reactor B was cooled to 20°C and stirred for not less than 3 hours. The resulting slurry was filtered, the filtered solid washed with heptane and then dried in a vacuum oven at 65°C to provide ritonavir Form I.

A preferred pharmaceutical composition comprising ritonavir, especially, ritonavir Form II, has the following composition, encapsulated in a soft elastic gelatin capsule.

Ritonavir Form II	100.0 mg
Ethanol, dehydrated	120.0 mg
Oleic acid	709.75 mg
Butylated hydroxytoluene	0.25 mg
Polyoxyl 35 castor oil (Cremophor EL®)	60.0 mg
Water	10.0 mg

The preferred composition can be prepared according to the following method.

The following protocol is employed in the preparation of 1000 soft gelatin capsules:

Scale (mg/capsule)	Name	Amount (g)
Q.S.	Nitrogen, N.F.	Q.S.
118.0	Ethanol, dehydrated, USP, 200 Proof	118.0
2.0	Ethanol, dehydrated, USP, 200 Proof	2.0
0.25	Butylated Hydroxytoluene, NF	0.25
704.75	Oleic Acid, NF	704.75
100.0	Ritonavir Form II	100.0
10.0	Water, purified, USP (distilled)	10.0
60.0	Polyoxyl 35 Castor Oil, NF	60.0
5.000	Oleic Acid, NF	5.000

A mixing tank and suitable container are purged with nitrogen. 118.0 g of ethanol is weighed, blanketed with nitrogen, and held for later use. The second aliquot of ethanol (2 g) is then weighed, and mixed with 0.25 g of butylated hydroxytoluene until clear. The mixture is blanketed with nitrogen and held. The main mixing tank is heated to 28 °C (not to exceed 30 °C). 704.75 g of oleic acid is then charged into the mixing tank. 100.0 g of ritonavir Form II is then added to the oleic acid with mixing. The ethanol/butylated hydroxytoluene is then added to the mixing tank, followed by the 118.0 g of ethanol measured previously, and mixed for at least 10 minutes. 10 g of water is then charged into the tank and mixed until the solution is clear (for not less than 30 minutes). 60.0 g of Polyoxyl 35 castor oil is charged into the tank and mixed until uniform. The solution is stored at 2-8 °C until encapsulation. According to the procedures described in

International Patent Application WO98/22106, 1.0 g of the solution is filled into each soft gelatin capsule and the soft gelatin capsules are then dried, and stored at 2-8 °C.

As used herein, the term "substantially pure", when used in reference to a polymorph of ritonavir, refers to a polymorph of ritonavir, Form I or Form II, which is greater than about 90% pure. This means that the polymorph of ritonavir 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 ritonavir. More preferably, the term "substantially pure" refers to a polymorph of ritonavir, Form I or Form II, which is greater than about 95% pure. This means that the polymorph of ritonavir does not contain more than about 5% of any other compound and, in particular, does not contain more than about 5% of any other form of ritonavir. Even more preferably, the term "substantially pure" refers to a polymorph of ritonavir, Form I or Form II, which is greater than about 97% pure. This means that the polymorph of ritonavir does not contain more than about 3% of any other compound and, in particular, does not contain more than about 3% of any other form of ritonavir.

As used herein, the term "substantially pure", when used in reference to amorphous ritonavir, refers to amorphous ritonavir which is greater than about 90% pure. This means that the amorphous ritonavir 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 ritonavir. More preferably, the term "substantially pure", when used in reference to amorphous ritonavir, refers to amorphous ritonavir which is greater than about 95% pure. This means that the amorphous ritonavir does not contain more than about 5% of any other compound and, in particular, does not contain more than about 5% of any other form of ritonavir. Even more preferably, the term "substantially pure", when used in reference to

amorphous ritonavir, refers to amorphous ritonavir which is greater than about 97% pure. This means that the amorphous ritonavir does not contain more than about 3% of any other compound and, in particular, does not contain more than about 3% of any other form of ritonavir.

Powder X-ray diffraction analysis of samples was conducted in the following manner. Samples for X-ray diffraction analysis were prepared by spreading the sample powder (with no prior grinding required) in a thin layer on the sample holder and gently flattening the sample with a microscope slide. A Nicolet 12/V X-ray Diffraction System was used with the following parameters: X-ray source: Cu-Kα1; Range: 2.00-40.00° Two Theta; Scan Rate: 1.00 degree/minute; Step Size: 0.02 degrees; Wavelength: 1.540562 angstroms.

Characteristic powder X-ray diffraction pattern peak positions are reported for polymorphs in terms of the angular positions (two theta) with an allowable variability of ± 0.1°. This allowable variability is specified by the U.S. Pharmacopeia, pages 1843-1844 (1995). The variability of ± 0.1° is intended to be used when comparing two powder X-ray diffraction patterns. In practice, if a diffraction pattern peak from one pattern is assigned a range of angular positions (two theta) which is the measured peak position ± 0.1° and a diffraction pattern peak from the other pattern is assigned a range of angular positions (two theta) which is the measured peak position ± 0.1° and if those ranges of peak positions overlap, then the two peaks are considered to have the same angular position (two theta). For example, if a diffraction pattern peak from one pattern is determined to have a peak position of 5.20°, for comparison purposes the allowable variability allows the peak to be assigned a position in the range of 5.10° – 5.30°. If a comparison peak from the other diffraction pattern is determined to have a peak position of 5.35°, for comparison purposes the

allowable variability allows the peak to be assigned a position in the range of 5.25° – 5.45°. Because there is overlap between the two ranges of peak positions (i.e., 5.10° - 5.30° and 5.25° – 5.45°) the two peaks being compared are considered to have the same angular position (two theta).

Solid state nuclear magnetic resonance analysis of samples was conducted in the following manner. A Bruker AMX-400 MHz instrument was used with the following parameters: CP- MAS (cross-polarized magic angle spinning); spectrometer frequency for ^{13}C was 100.627952576 MHz; pulse sequence was cp2lev; contact time was 2.5 milliseconds; temperature was 27.0 °C; spin rate was 7000 Hz; relaxation delay was 6.000 sec; 1st pulse width was 3.8 microseconds; 2nd pulse width was 8.6 microseconds; acquisition time was 0.034 seconds; sweep width was 30303.0 Hz; 2000 scans.

FT near infrared analysis of samples was conducted in the following manner. Samples were analyzed as neat, undiluted powders contained in a clear glass 1 dram vial. A Nicolet Magna System 750 FT-IR spectrometer with a Nicolet SabIR near infrared fiber optic probe accessory was used with the following parameters: the source was white light; the detector was PbS; the beamsplitter was CaF2; sample spacing was 1.0000; digitizer bits was 20; mirror velocity was 0.3165; the aperture was 50.00; sample gain was 1.0; the high pass filter was 200.0000; the low pass filter was 11000.0000; the number of sample scans was 64; the collection length was 75.0 seconds; the resolution was 8.000; the number of scan points was 8480; the number of FFT points was 8192; the laser frequency was 15798.0 cm -1; the interferogram peak position was 4096; the apodization was Happ-Genzel; the number of background scans was 64 and the background gain was 1.0.

FT mid infrared analysis of samples was conducted in the following manner. Samples were analyzed as neat, undiluted powders. A Nicolet Magna System 750 FT-IP spectrometer with a Spectra-Tech InspectIR video

microanalysis accessory and a Germanium attenuated total reflectance (Ge ATR) crystal was used with the following parameters: the source was infrared; the detector was MCT/A; the beamsplitter was KBr; sample spacing was 2.0000; digitizer bits was 20; mirror velocity was 1.8988; the aperture was 100.00; sample gain was 1.0; the high pass filter was 200.0000; the low pass filter was 20000.0000; the number of sample scans was 128; the collection length was 79.9 seconds; the resolution was 4.000; the number of scan points was 8480; the number of FFT points was 8192; the laser frequency was 15798.0 cm -1; the interferogram peak position was 4096; the apodization was triangular; the number of background scans was 128 and the background gain was 1.0.

Differential scanning calorimetric analysis of samples was conducted in the following manner. A T.A. Instruments Thermal Analyzer 3100 with Differential Scanning Calorimetry module 2910 was used, along with Modulated DSC software version 1.1A. The analysis parameters were: Sample weight: 2.28 mg, placed in a covered, uncrimped aluminum pan; Heating rate: room temperature to 150°C at 5°C/minute under a nitrogen purge.

The foregoing is merely illustrative of the invention and is not intended to limit the invention to the disclosed embodiments. Variations and changes which are obvious to one skilled in the art are intended to be within the scope and nature of the invention which are defined in the appended claims.

CLAIMS

What is claimed is

1. The crystalline polymorph of (2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane with characteristic peaks in the powder X-ray diffraction pattern at values of two theta of 8.67° ± 0.1°, 9.88° ± 0.1°, 16.11° ± 0.1°, 16.70° ± 0.1°, 17.36° ± 0.1°, 17.78° ± 0.1°, 18.40° ± 0.1°, 18.93° ± 0.1°, 20.07° ± 0.1°, 20.65° ± 0.1°, 21.71° ± 0.1°and 25.38° ± 0.1°.

2. The crystalline polymorph of Claim 1 with characteristic peaks in the powder X-ray diffraction pattern at values of two theta of 8.67° ± 0.1°, 9.51° ± 0.1°, 9.88° ± 0.1°, 10.97° ± 0.1°, 13.74° ± 0.1°, 16.11° ± 0.1°, 16.70° ± 0.1°, 17.36° ± 0.1°, 17.78° ± 0.1°, 18.40° ± 0.1°, 18.93° ± 0.1°, 19.52° ± 0.1°, 19.80° ± 0.1°, 20.07° ± 0.1°, 20.65° ± 0.1°, 21.49° ± 0.1°, 21.71° ± 0.1°, 22.23° ± 0.1°, 25.38° ± 0.1°, 26.15° ± 0.1° and 28.62° ± 0.1°.

3. The substantially pure crystalline polymorph of (2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane with characteristic peaks in the powder X-ray diffraction pattern at values of two theta of 8.67° ± 0.1°, 9.88° ± 0.1°, 16.11° ± 0.1°, 16.70° ± 0.1°, 17.36° ± 0.1°, 17.78° ± 0.1°, 18.40° ± 0.1°, 18.93° ± 0.1°, 20.07° ± 0.1°, 20.65° ± 0.1°, 21.71° ± 0.1°and 25.38° ± 0.1°.

4. The substantially pure crystalline polymorph of Claim 3 with characteristic peaks in the powder X-ray diffraction pattern at values of two theta of 8.67° ± 0.1°, 9.51° + 0.1°, 9.88° ± 0.1°, 10.97° ± 0.1°, 13.74° ± 0.1°, 16.11° ± 0.1°, 16.70° ± 0.1°, 17.36° ± 0.1°, 17.78° ± 0.1°, 18.40° ± 0.1°, 18.93° ± 0.1°, 19.52° ± 0.1°, 19.80° ± 0.1°, 20.07° ± 0.1°, 20.65° ± 0.1°, 21.49° ± 0.1°, 21.71° ± 0.1°, 22.23° ± 0.1°, 25.38° ± 0.1°, 26.15° ± 0.1° and 28.62° ± 0.1°.

5. Substantially pure amorphous ritonavir.

6. The substantially pure amorphous ritonavir of Claim 5 characterized by a glass transition from about 45°C to about 49°C.

7. A process for the preparation of the compound of Claim 5 comprising adding a solution of ritonavir to an antisolvent.

8. A process for the preparation of the compound of Claim 5 comprising adding a solution of ritonavir in methylene chloride to hexane.

9. A process for the preparation of the compound of Claim 5 comprising adding a solution of ritonavir Form I in methylene chloride at a concentration of about 1 g of ritonavir per about 1.5-2.0 mL of methylene chloride to hexane at a concentration of about 60-110 mL of hexane per gram of ritonavir.

10. A process for the preparation of the compound of Claim 5 comprising adding a solution of ritonavir Form I in methylene chloride at a concentration of

about 1 g of ritonavir per about 1.5 mL of methylene chloride to hexane at a concentration of about 85-90 mL of hexane per gram of ritonavir.

11. A process for the preparation of the compound of Claim 5 comprising adding a solution of ritonavir in methanol to methyl t-butyl ether.

12. A process for the preparation of the compound of Claim 5 comprising adding a solution of ritonavir Form I in methanol at a concentration of about 1 g of ritonavir per about 1.5-2.0 mL of methanol to hexane at a concentration of about 60-150 mL of hexane per gram of ritonavir.

13. A process for the preparation of the compound of Claim 5 comprising adding a solution of ritonavir Form I in methanol at a concentration of about 1 g of ritonavir per about 1.5 mL of methanol to hexane at a concentration of about 90-110 mL of hexane per gram of ritonavir.

14. A process for the preparation of the compound of Claim 5 comprising adding a solution of ritonavir in methanol to water.

15. A process for the preparation of the compound of Claim 5 comprising adding a solution of ritonavir Form I in methanol at a concentration of about 1 g of ritonavir per about 1.5-2.0 mL of methanol to water at a concentration of about 400-500 mL of water per gram of ritonavir.

16. A process for the preparation of the compound of Claim 5 comprising adding a solution of ritonavir Form I in methanol at a concentration of about 1 g of ritonavir per about 1.6 mL of methanol to water at a concentration of about 400 mL of water per gram of ritonavir.

17 A process for the preparation of the compound of Claim 5 comprising lyophilization of a solution of ritonavir.

18. A process for the preparation of the compound of Claim 5 comprising lyophilization of a solution of ritonavir in isobutanol.

19. A process for the preparation of the substantially pure crystalline polymorph of Claim 3 comprising seeding a solution of ritonavir with seed crystals of (2S)-N-((1S)-1-Benzyl-2-((4S,5S)-4-benzyl-2-oxo-1,3-oxazolidin-5-yl)ethyl)-2-((((2-isopropyl-1,3-thiazol-4-yl)methyl)amino)-carbonyl)amino)-3-methylbutanamide in an amount such that there are undissolved seed crystals in the solution of ritonavir.

20. A process for the preparation of the substantially pure crystalline polymorph of Claim 3 comprising seeding a solution of ritonavir in a C1-C3 alcohol with seed crystals of (2S)-N-((1S)-1-Benzyl-2-((4S,5S)-4-benzyl-2-oxo-1,3-oxazolidin-5-yl)ethyl)-2-((((2-isopropyl-1,3-thiazol-4-yl)methyl)amino)-carbonyl)amino)-3-methylbutanamide in an amount such that there are undissolved seed crystals in the solution of ritonavir.

21. The process of Claim 20 wherein the C1-C3 alcohol is ethanol.

22. A process for the preparation of the substantially pure crystalline polymorph of Claim 3 comprising seeding a solution of ritonavir with seed crystals of ritonavir Form II, followed by addition of an anti-solvent.

23. A process for the preparation of the substantially pure crystalline polymorph of Claim 3 comprising seeding a solution of ritonavir in ethyl acetate with seed crystals of ritonavir Form II, followed by addition of heptane.

24. A process for the preparation of the substantially pure crystalline polymorph of Claim 3 comprising seeding a solution of ritonavir in ethyl acetate at from about 50°C to about 55°C with seed crystals of ritonavir Form II, followed by addition of heptane and cooling to about 25°C.

25. A process for the preparation of substantially pure ritonavir crystalline polymorph Form I comprising adding a solution of ritonavir to a slurry of seed crystals of ritonavir crystalline polymorph Form I in an anti-solvent.

26. The process of Claim 25 wherein the solvent is ethyl acetate and the anti-solvent is heptane.

27. A process for the preparation of substantially pure ritonavir crystalline polymorph Form I comprising:

(a) dissolving ritonavir in ethyl acetate with heating at a concentration of about 1 kg of ritonavir/ 4 L of ethyl acetate;

(b) adding the hot solution of ritonavir of step (a) to a slurry of seed crystals of ritonavir crystalline polymorph Form I in heptane; and

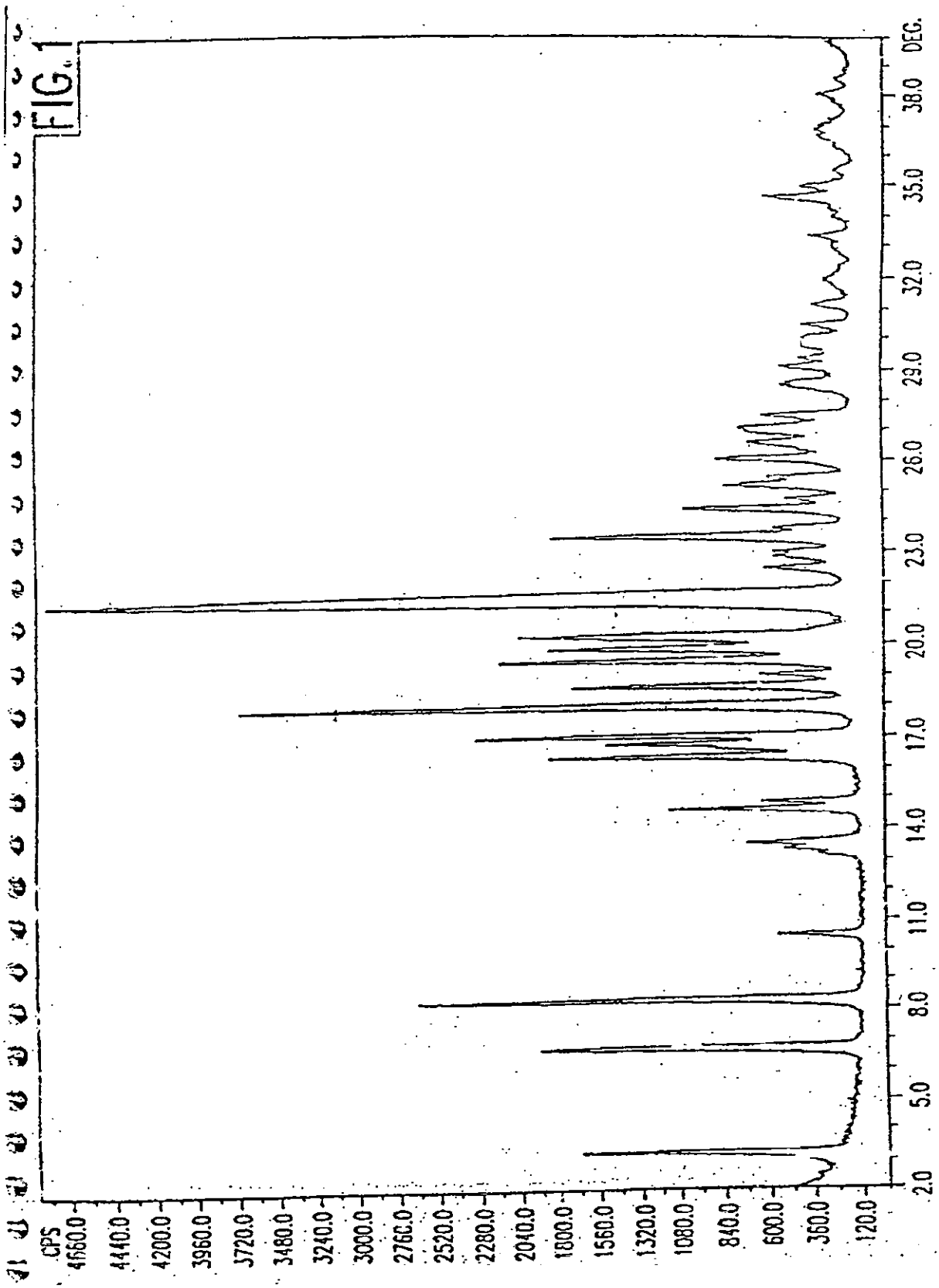
(c) cooling the resulting mixture to about 20°C.

28. The process of Claim 27 wherein the ratio of Form I seed crystals to starting ritonavir is from about 0.5% to about 10% w/w.

29. The process of Claim 27 wherein the ratio of Form I seed crystals to starting ritonavir is from about 0.5% to about 5% w/w.

30. The process of Claim 27 wherein the ratio of Form I seed crystals to starting ritonavir is from about 0.5% to about 1% w/w.

FIG. 1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5.0
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FIG.2

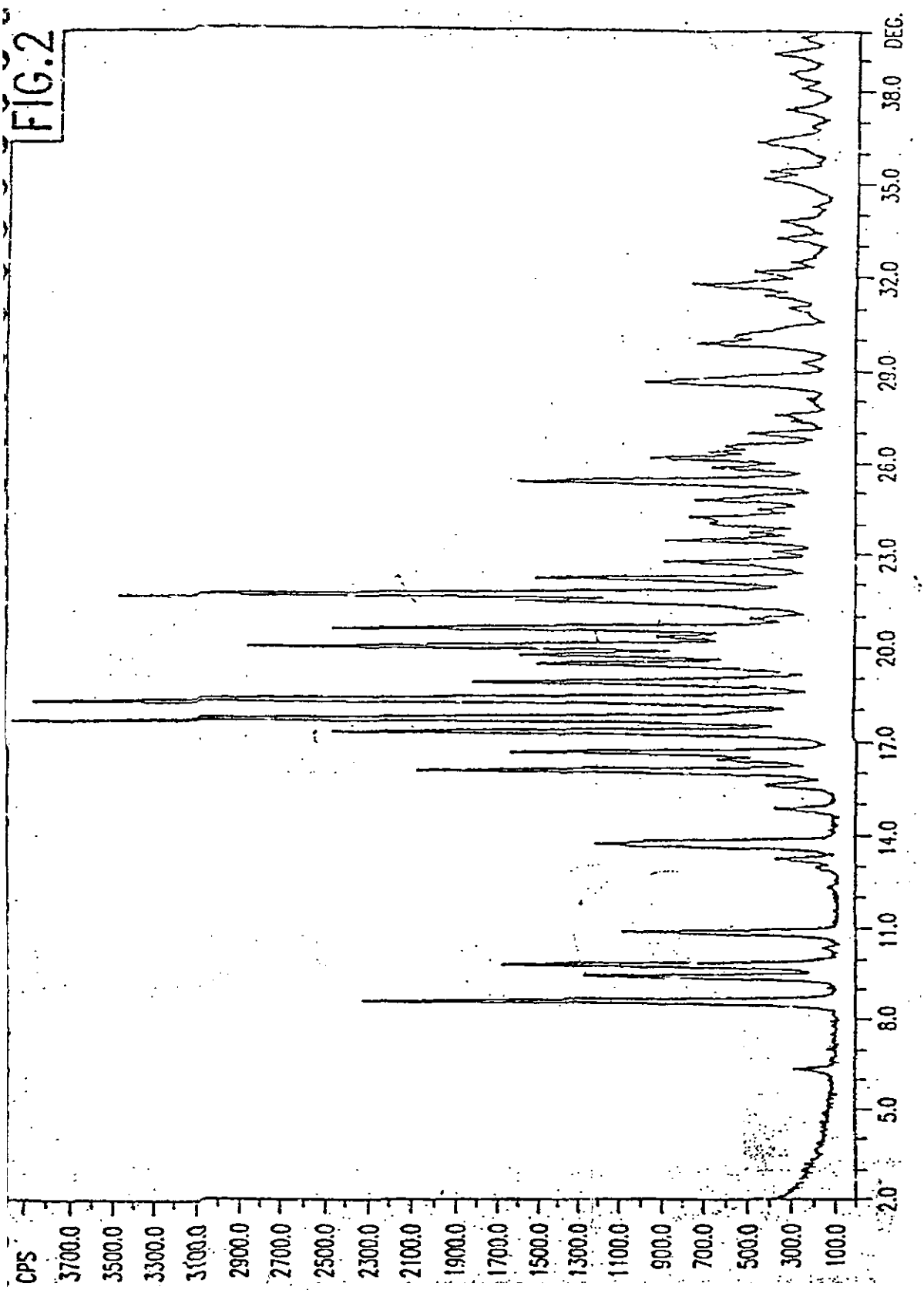
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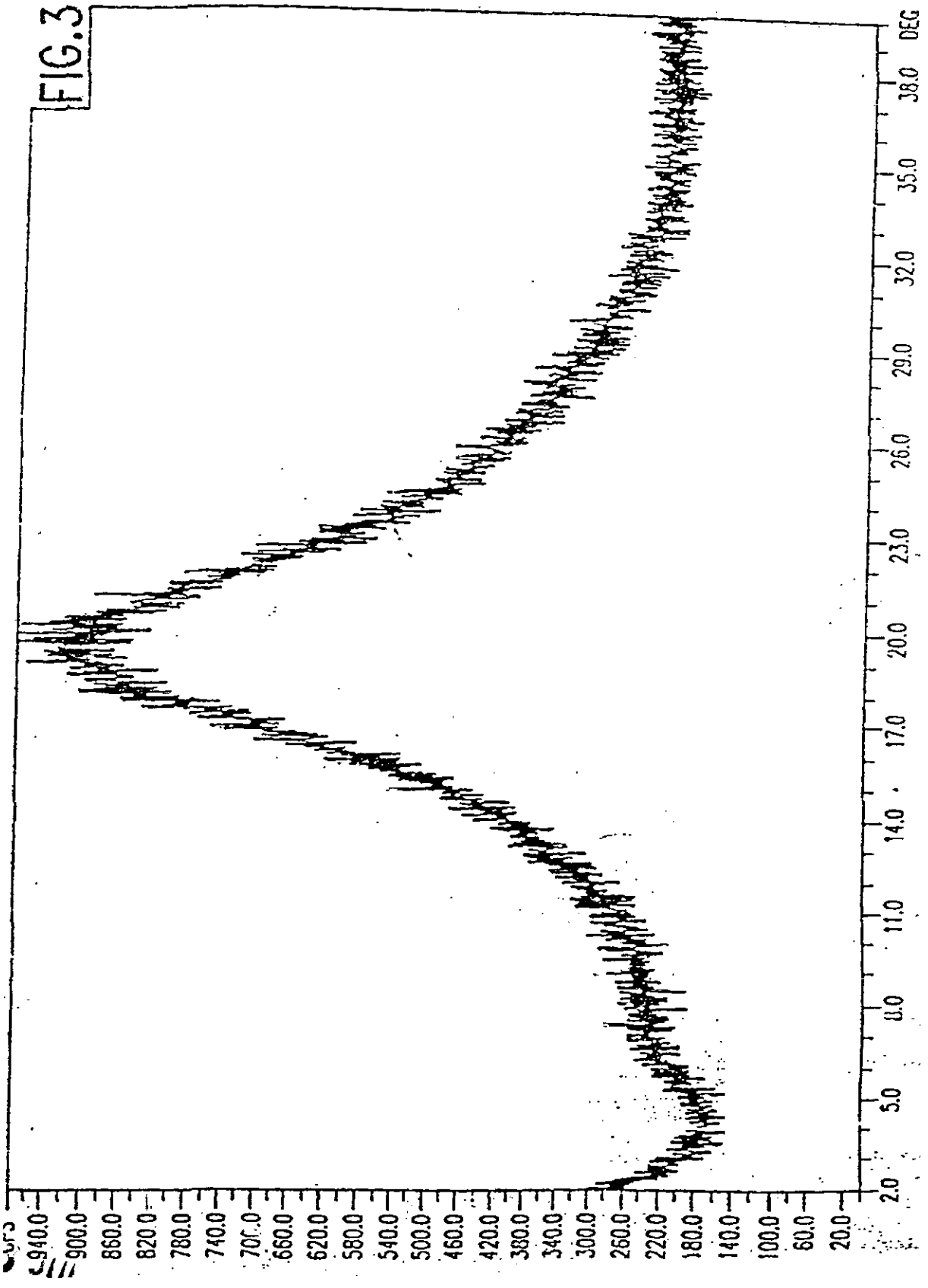
FIG.3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2.0
5.0
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38.0
DEG

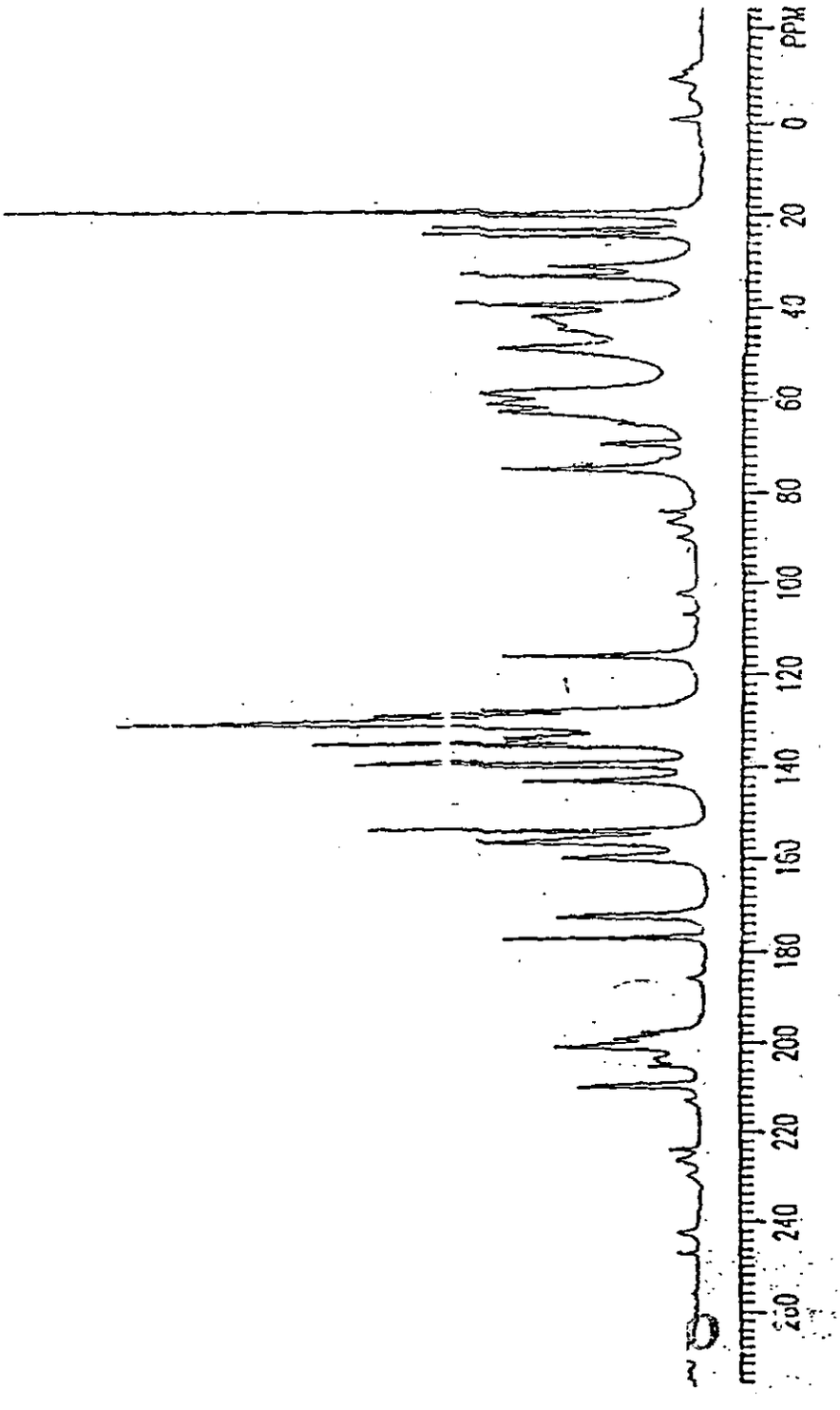


FIG.4

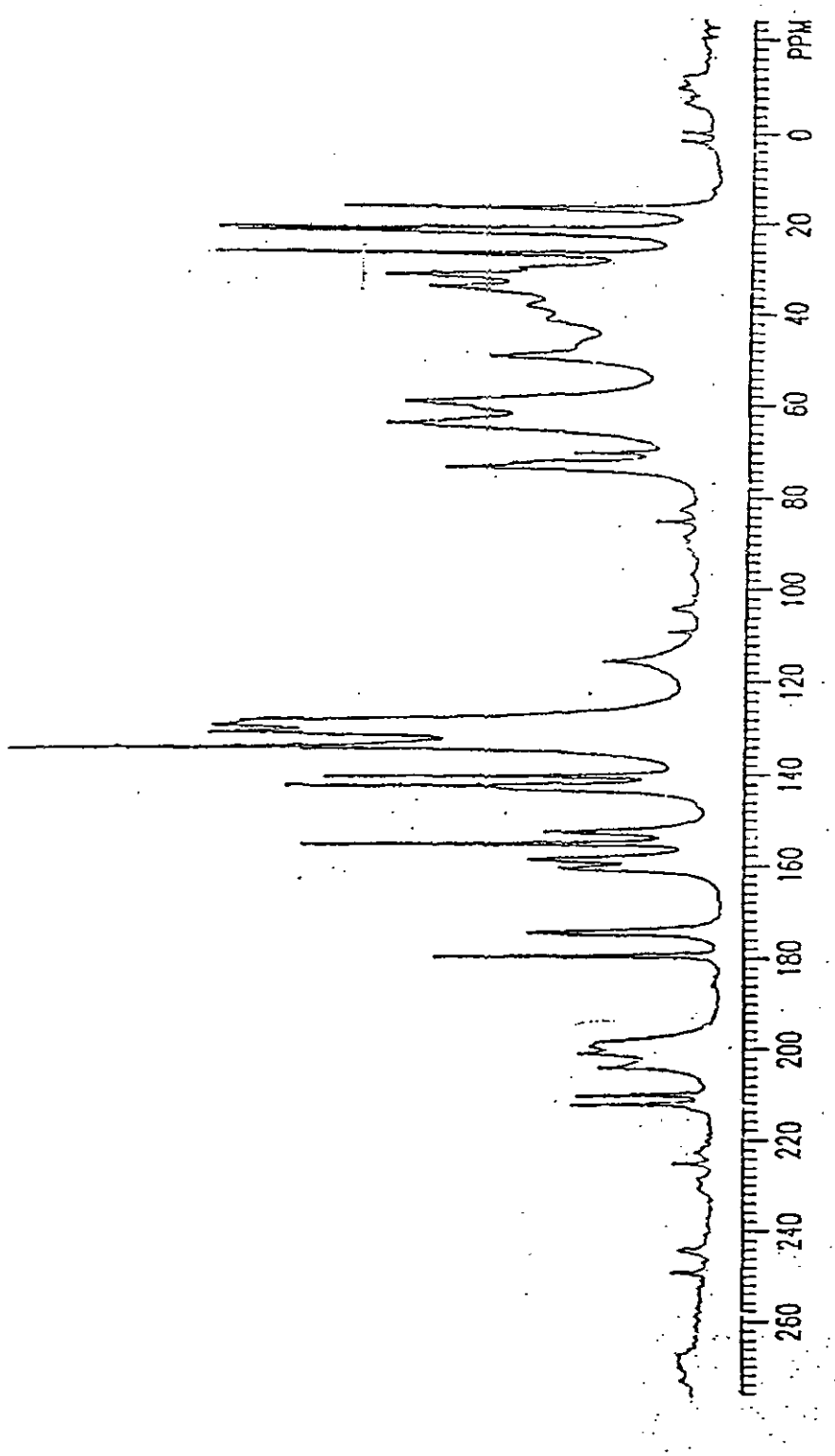
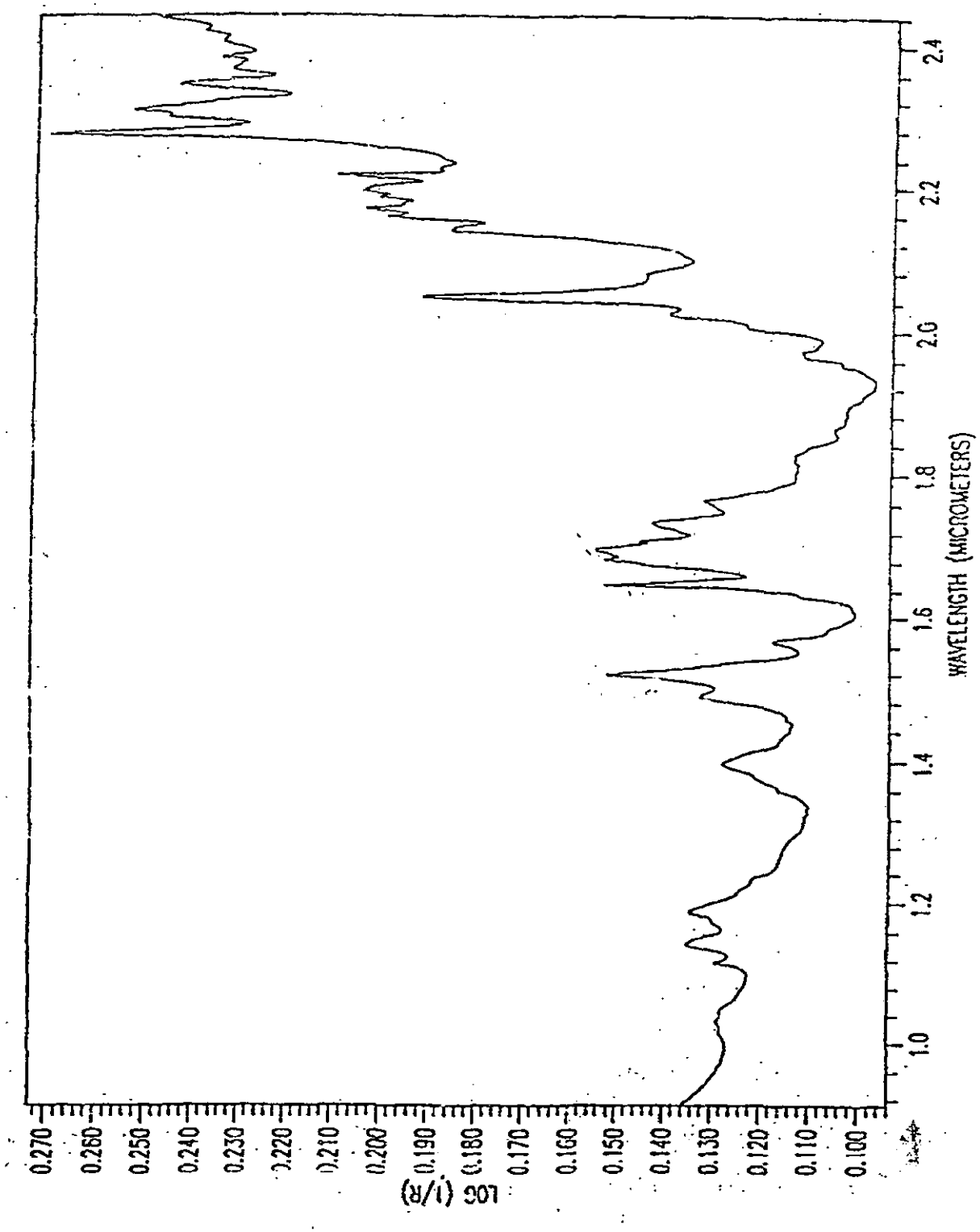


FIG.5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0.250
0.240
0.230
0.220
0.210
0.200
0.190
0.180
0.170
0.160
0.150
0.140
0.130
0.120
0.110
0.100
LOG (1/R)
1.0
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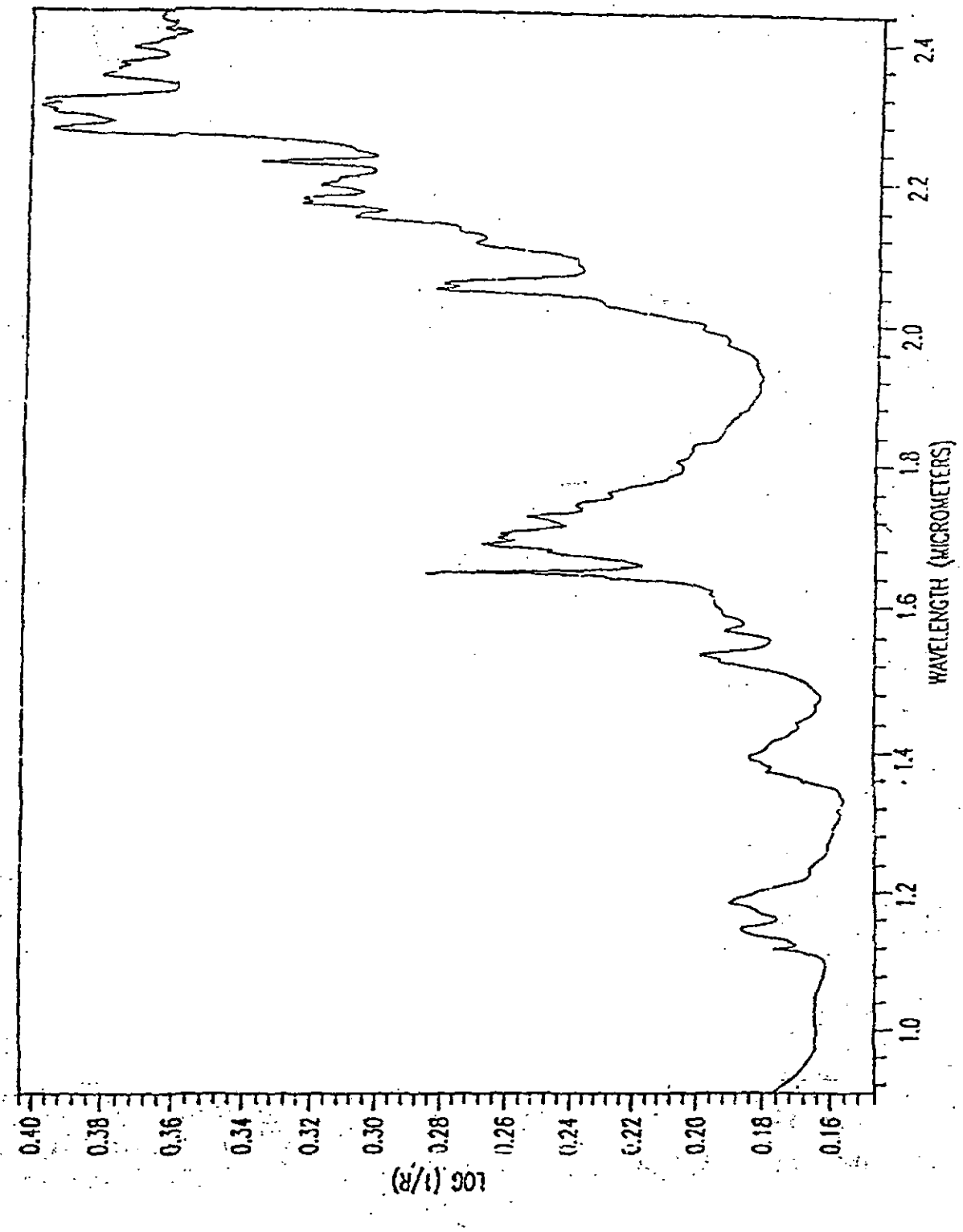
1.4
1.6
1.8
2.0
2.2
2.4
WAVELENGTH (MICROMETERS)

FIG. 6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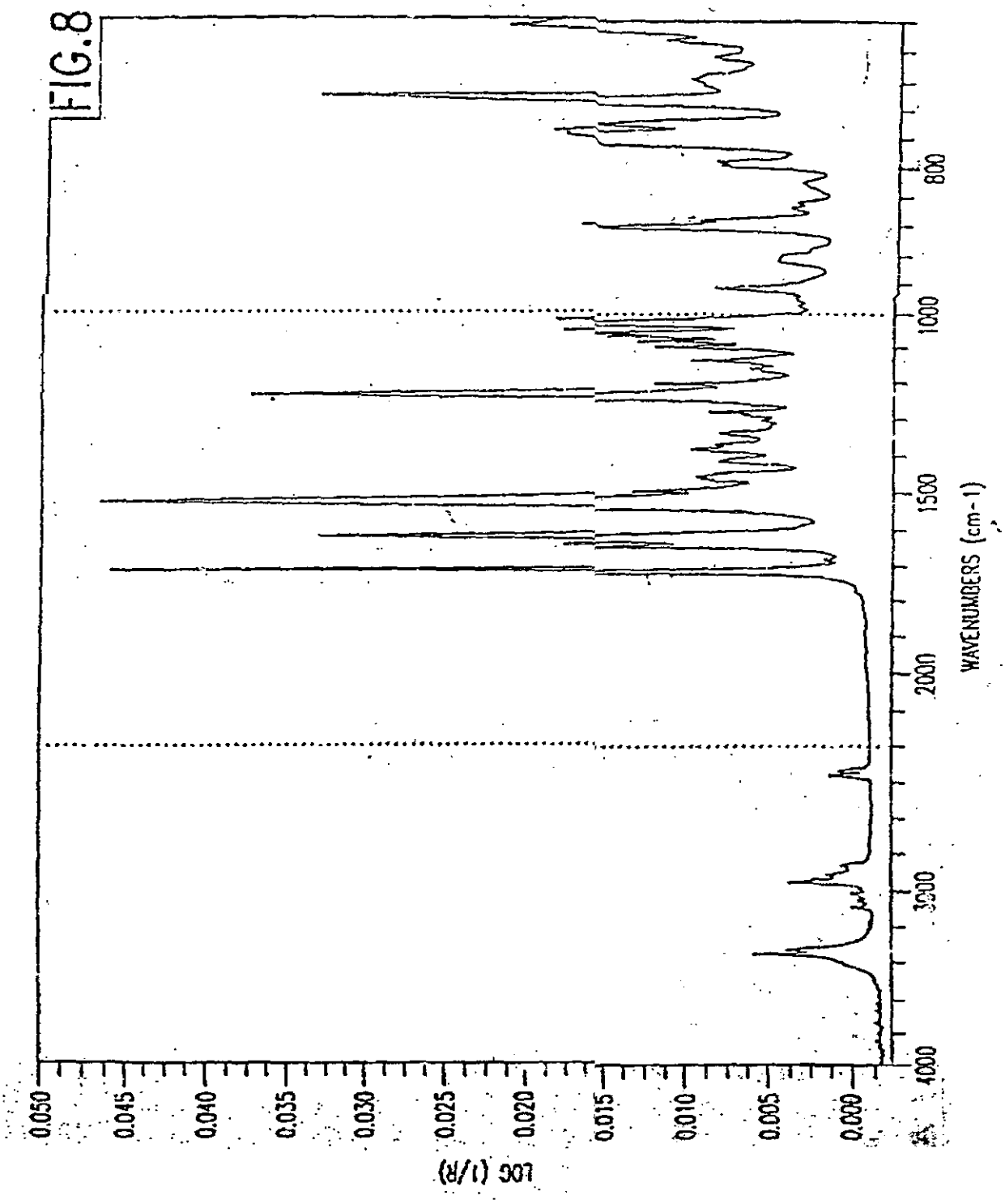
0.36
0.34
0.32
0.30
0.28
0.26
0.24
0.22
0.20
0.18
0.16
1.0
1.2
1.4
1.6
1.8
2.0
2.2
2.4
WAVELENGTH (MICROMETERS)

FIG.7

FIG.8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0.035
0.030
0.025
0.020
0.015
0.010
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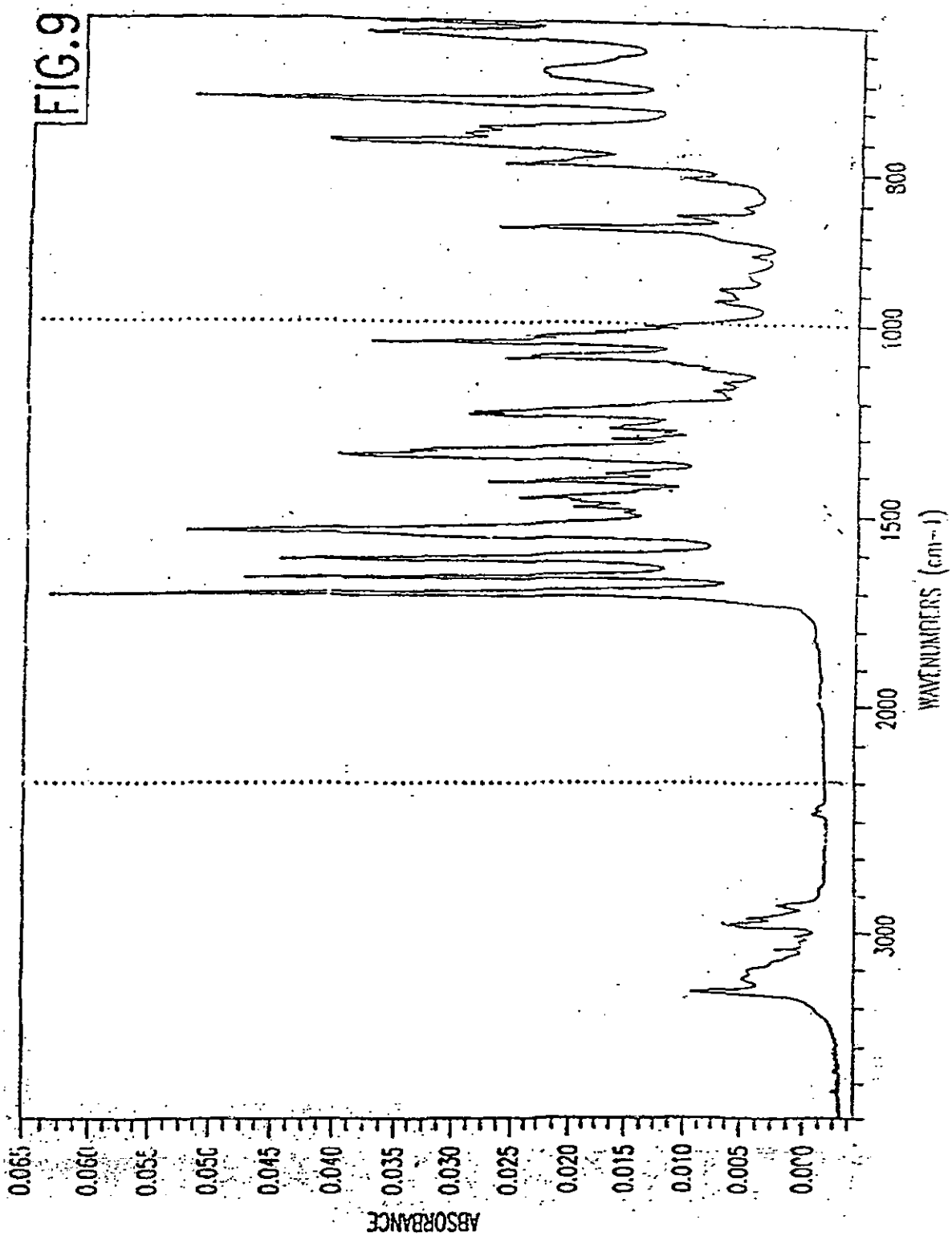
0.000
4000
3000
2000
1500
1000
800
WAVENUMBERS (cm-1)

FIG.9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0.055
0.050
0.045
0.040
0.035
0.030
0.025
0.020
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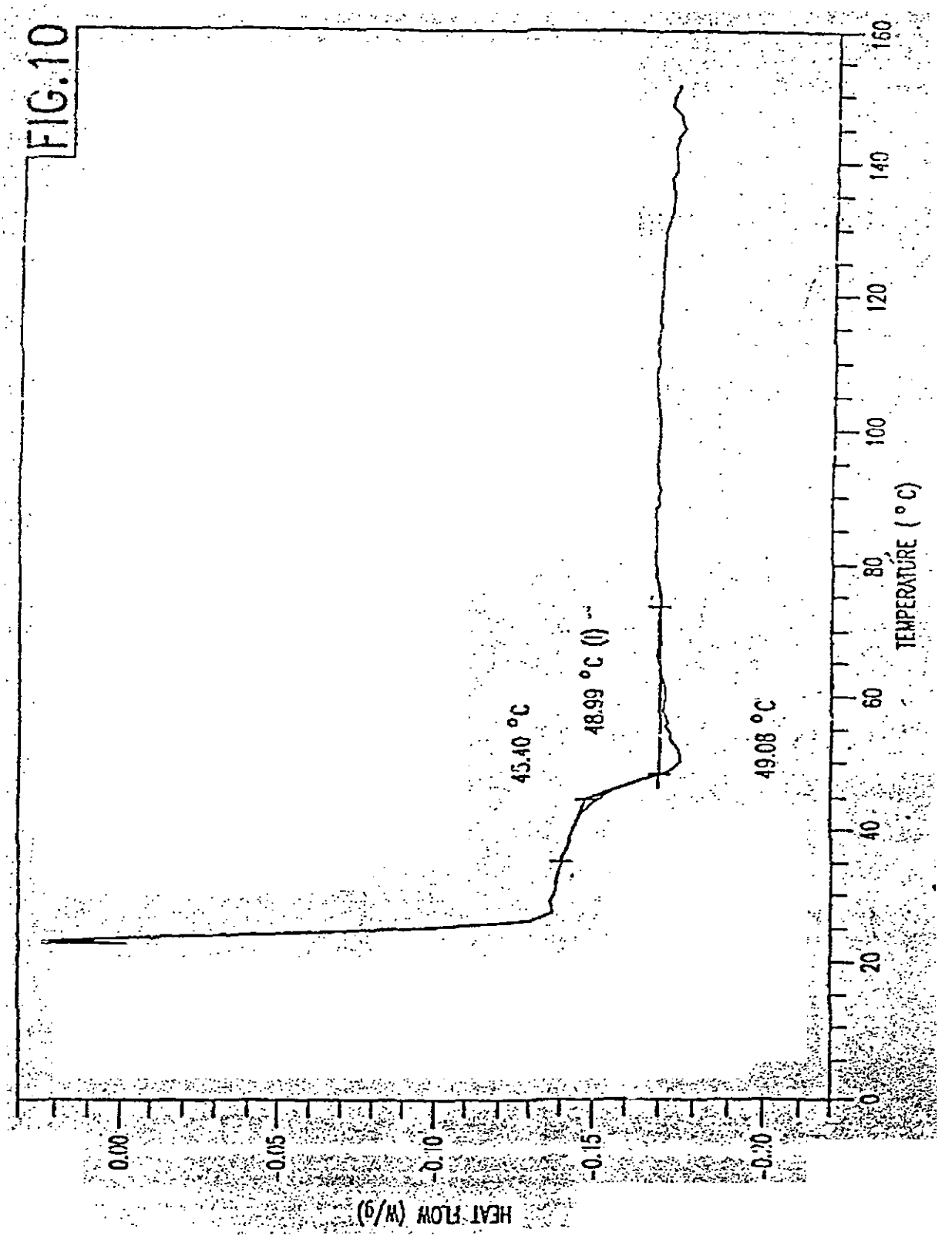
0.010
0.005
0.000
3000
2000
1500
1000
800
WAVENUMBERS (cm-1)

FIG.10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-0.00
-0.05
-0.10
-0.15
-0.20
0
20
40
60
80
100
120
140
160
TEMPERATURE (°C)
43.40 °C
48.99 °C (I)
49.08 °C

ANNEXURE-II

(a) and (b)

Annexure - II(a)

PI 138278

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office

September 01, 1999

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE UNDER 35 USC 111.

APPLICATION NUMBER: *09/119,345*
FILING DATE: *July 20, 1998*
PCT APPLICATION NUMBER: *PCT/US99/16334*

By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

T. LAWRENCE
Certifying Officer

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

23 JUL 2000

Polymorph of a Pharmaceutical

Technical Field

This invention relates to a novel crystalline polymorph of (2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)amino-1,6-diphenyl-3-hydroxyhexane, methods for its preparation, methods for its use as a pharmaceutical agent and pharmaceutical compositions comprising the novel crystalline polymorph. This invention also relates to an amorphous form of (2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-amino-1,6-diphenyl-3-hydroxyhexane and its use in the preparation of the novel crystalline polymorph.

Background of the Invention

Inhibitors of human immunodeficiency virus (HIV) protease have been approved for use in the treatment of HIV infection for several years. A particularly effective HIV protease inhibitor is (2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)amino-1,6-diphenyl-3-hydroxyhexane(ritonavir), which is marketed as NORVIR®. Ritonavir is known to have utility for the inhibition of HIV protease, the inhibition of HIV infection and the enhancement of the pharmacokinetics of compounds which are metabolized by cytochrome P450 monooxygenase. Ritonavir is particularly effective for the inhibition of HIV infection

when used alone or in combination with one or more reverse transcriptase inhibitors and/or one or more other HIV protease inhibitors.

Ritonavir and processes for its preparation are disclosed in U.S. Patent No. 5,541,206, issued July 30, 1996. This patent discloses processes for preparing ritonavir which produce a crystalline polymorph of ritonavir which is termed crystalline Form I. Form I has the powder X-ray diffraction pattern, ^{13}C solid state nuclear magnetic resonance spectrum, the FT near infrared spectrum and the FT mid infrared spectrum which appear in FIGS. 1, 4, 6 and 8, respectively. The angular positions (two theta) of the characteristic peaks in the powder X-ray diffraction pattern of Form I shown in FIG. 1 are 3.33° ± 0.1°, 6.76° ± 0.1°, 8.33° ± 0.1°, 14.61° ± 0.1°, 16.33° ± 0.1°, 16.76° ± 0.1°, 17.03° ± 0.1°, 18.02° ± 0.1°, 18.62° ± 0.1°, 19.47° ± 0.1°, 19.86° ± 0.1°, 20.25° ± 0.1°, 21.46° ± 0.1°, 23.46° ± 0.1° and 24.36° ± 0.1°.

Another process for the preparation of ritonavir is disclosed in U.S. Patent No. 5,567,823, issued October 22, 1996. The process disclosed in this patent also produces ritonavir as crystalline Form I.

Pharmaceutical compositions comprising ritonavir or a pharmaceutically acceptable salt thereof are disclosed in U.S. Patent Nos. 5,541,206, issued July 30, 1996; 5,484,801, issued January 16, 1996; 5,725,878, issued March 10, 1998; and 5,559,158, issued September 24, 1996 and in International Application No. WO98/22106, published May 28, 1998 (corresponding to U.S. Serial No. 08/966,495, filed November 7, 1997).

The use of ritonavir to inhibit an HIV infection is disclosed in in U.S. Patent No. 5,541,206, issued July 30, 1996. The use of ritonavir in combination with one or more reverse transcriptase inhibitors to inhibit an HIV infection is disclosed in U.S. Patent No. 5,635,523, issued June 3, 1997. The use of ritonavir in combination with one or more HIV protease inhibitors to inhibit an HIV infection is disclosed in U.S. Patent No. 5,674,882, issued October 7, 1997. The use of

ritonavir to enhance the pharmacokinetics of compounds metabolized by cytochrome P450 monooxygenase is disclosed in WO97/01349, published January 16, 1997 (corresponding to U.S. Serial No. 08/687,774, filed June 26, 1996).

It has now been unexpectedly discovered that ritonavir can be prepared as a new crystalline polymorph which is termed crystalline Form II.

All issued patents and patent applications cited herein are hereby incorporated by reference.

Brief Description of the Drawings

FIG. 1 is the powder X-ray diffraction pattern of the Form I crystalline polymorph of ritonavir.

FIG. 2 is the powder X-ray diffraction pattern of the Form II crystalline polymorph of ritonavir.

FIG. 3 is the powder X-ray diffraction pattern of amorphous ritonavir.

FIG. 4 is the 400 MHz solid state ^{13}C nuclear magnetic resonance spectrum of the Form I crystalline polymorph of ritonavir.

FIG. 5 is the 400 MHz solid state ^{13}C nuclear magnetic resonance spectrum of the Form II crystalline polymorph of ritonavir.

FIG. 6 is the FT near infrared spectrum of the Form I crystalline polymorph of ritonavir.

FIG. 7 is the FT near infrared spectrum of the Form II crystalline polymorph of ritonavir.

FIG. 8 is the FT mid infrared spectrum of the Form I crystalline polymorph of ritonavir.

FIG. 9 is the FT mid infrared spectrum of the Form II crystalline polymorph of ritonavir.

FIG. 10 is the differential scanning calorimetric thermogram for amorphous ritonavir.

Disclosure of the Invention

In accordance with the present invention, there is a novel crystalline polymorph of (2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)amino-1,6-diphenyl-3-hydroxyhexane (ritonavir). For the sake of identification, this crystalline polymorph is designated as the Form II crystalline polymorph of ritonavir.

Form II has the powder X-ray diffraction pattern, ^{13}C solid state nuclear magnetic resonance spectrum, the FT near infrared spectrum and the FT mid infrared spectrum which appear in FIGS. 2, 5, 7 and 9, respectively. The two-theta angle positions of the characteristic peaks in the powder X-ray diffraction pattern of Form II shown in FIG. 2 are 8.67° ± 0.1°, 9.51° ± 0.1°, 9.88° ± 0.1°, 10.97° ± 0.1°, 13.74° ± 0.1°, 16.11° ± 0.1°, 16.70° ± 0.1°, 17.36° ± 0.1°, 17.78° ± 0.1°, 18.40° ± 0.1°, 18.93° ± 0.1°, 19.52° ± 0.1°, 19.80° ± 0.1°, 20.07° ± 0.1°, 20.65° ± 0.1°, 21.49° ± 0.1°, 21.71° ± 0.1°, 22.23° ± 0.1°, 25.38° ± 0.1°, 26.15° ± 0.1° and 28.62° ± 0.1°.

The Form II crystalline polymorph of ritonavir can be prepared from amorphous ritonavir by contacting amorphous ritonavir with a C1-C3 alcohol. The method of contacting may be either by saturating the amorphous compound in the solvent at ambient temperature and then allowing the mixture to stand for an extended period of time (for example, overnight) or by dissolving the amorphous compound in the solvent at elevated temperature, preferably, at reflux, followed by cooling the solution to room temperature and isolating Form II.

In a preferred process, the Form II crystalline polymorph of ritonavir can be prepared from amorphous ritonavir by preparing a saturated solution of amorphous ritonavir in a C1-C3 alcohol at room temperature and isolating Form II which results. In practice this can be accomplished by dissolving a sufficient amount of amorphous ritonavir in the C1-C3 alcohol at elevated temperature (up to reflux) such that when the solution is allowed to cool to room temperature a saturated solution is obtained, from which Form II precipitates and can be isolated. A preferred solvent for the preparation of Form II is anhydrous ethanol. Isolation of the resulting solid provides Form II.

Amorphous ritonavir is prepared from the Form I crystalline polymorph of ritonavir by melting Form I ritonavir and rapidly cooling the melt. Isolation of the resulting solid provides amorphous ritonavir.

The following examples will serve to further illustrate the preparation of the novel forms of ritonavir of the invention.

Example 1

Preparation of Amorphous Ritonavir

Form I crystalline polymorph of ritonavir (100 g) was melted at 125°C by heating Form I. The melt was maintained at a temperature of 125°C for 3 hours. The melt was rapidly cooled by placing the container holding the melt into a Dewar flask containing liquid nitrogen. The resulting glass was ground with a mortar and pestle to provide amorphous ritonavir (100 g). Powder X-ray diffraction analysis confirmed that the product was amorphous. Differential scanning calorimetric analysis determined that the glass transition point from about 45°C to about 49°C. (Measured onset at 45.4°C and which ends at 49.08°C, with a midpoint of 48.99°C).

Example 2

Preparation of Crystalline Ritonavir (Form II)

Amorphous ritonavir (40.0 g) was dissolved in boiling anhydrous ethanol (100 mL). Upon allowing this solution to cool to room temperature, a saturated solution was obtained. After standing overnight at room temperature, the resulting solid was isolated from the mixture by filtration and was air dried to provide Form II (approximately 24.0 g).

Powder X-ray diffraction analysis of samples was conducted in the following manner. Samples for X-ray diffraction analysis were prepared by spreading the sample powder (with no prior grinding required) in a thin layer on the sample holder and gently flattening the sample with a microscope slide.
A Nicolet 12/V X-ray Diffraction System was used with the following parameters: X-ray source: Cu-Kα1; Range: 2.00-40.00° Two Theta; Scan Rate: 1.00 degree/minute; Step Size: 0.02 degrees; Wavelength: 1.540562 angstroms.

Characteristic powder X-ray diffraction pattern peak positions are reported for polymorphs in terms of the angular positions (two theta) with an allowable variability of ± 0.1°. This allowable variability is specified by the U.S. Pharmacopeia, pages 1843-1844 (1995). The variability of ± 0.1° is intended to be used when comparing two powder X-ray diffraction patterns. In practice, if a diffraction pattern peak from one pattern is assigned a range of angular positions (two theta) which is the measured peak position ± 0.1° and a diffraction pattern peak from the other pattern is assigned a range of angular positions (two theta) which is the measured peak position ± 0.1° and if those ranges of peak positions overlap, then the two peaks are considered to have the same angular position (two theta). For example, if a diffraction pattern peak from one pattern is determined to have a peak position of 5.20°, for comparison purposes the allowable variability allows the peak to be assigned a position in the range of 5.10° – 5.30°. If a

comparison peak from the other diffraction pattern is determined to have a peak position of 5.35°, for comparison purposes the allowable variability allows the peak to be assigned a position in the range of 5.25° – 5.45°. Because there is overlap between the two ranges of peak positions (i.e., 5.10° - 5.30° and 5.25° – 5.45°) the two peaks being compared are considered to have the same angular position (two theta).

Solid state nuclear magnetic resonance analysis of samples was conducted in the following manner. A Bruker AMX-400 MHz instrument was used with the following parameters: CP- MAS (cross-polarized magic angle spinning); spectrometer frequency for ^{13}C was 100.627952576 MHz; pulse sequence was cp2lev; contact time was 2.5 milliseconds; temperature was 27.0 °C; spin rate was 7000 Hz; relaxation delay was 6.000 sec; 1st pulse width was 3.8 microseconds; 2nd pulse width was 8.6 microseconds; acquisition time was 0.034 seconds; sweep width was 30303.0 Hz; 2000 scans.

FT near infrared analysis of samples was conducted in the following manner. Samples were analyzed as neat, undiluted powders contained in a clear glass 1 dram vial. A Nicolet Magna System 750 FT-IR spectrometer with a Nicolet SabIR near infrared fiber optic probe accessory was used with the following parameters: the source was white light; the detector was PbS; the beamsplitter was CaF2; sample spacing was 1.0000; digitizer bits was 20; mirror velocity was 0.3165; the aperture was 50.00; sample gain was 1.0; the high pass filter was 200.0000; the low pass filter was 11000.0000; the number of sample scans was 64; the collection length was 75.9 seconds; the resolution was 8.000; the number of scan points was 8480; the number of FFT points was 8192; the laser frequency was 15798.0 cm -1; the interferogram peak position was 4096; the apodization was Happ-Genzel; the number of background scans was 64 and the background gain was 1.0.

FT mid infrared analysis of samples was conducted in the following manner. Samples were analyzed as neat, undiluted powders. A Nicolet Magna System 750 FT-IR spectrometer with a Spectra-Tech InspectIR video microanalysis accessory and a Germanium attenuated total reflectance (Ge ATR) crystal was used with the following parameters: the source was infrared; the detector was MCT/A; the beamsplitter was KBr; sample spacing was 2.0000; digitizer bits was 20; mirror velocity was 1.8988; the aperture was 100.00; sample gain was 1.0; the high pass filter was 200.0000; the low pass filter was 20000.0000; the number of sample scans was 128; the collection length was 79.9 seconds; the resolution was 4.000; the number of scan points was 8480; the number of FFT points was 8192; the laser frequency was 15798.0 cm -1; the interferogram peak position was 4096; the apodization was triangular; the number of background scans was 128 and the background gain was 1.0.

Differential scanning calorimetric analysis of samples was conducted in the following manner. A T.A. Instruments Thermal Analyzer 3100 with Differential Scanning Calorimetry module 2910 was used, along with Modulated DSC software version 1.1A. The analysis parameters were: Sample weight: 2.28 mg, placed in a covered, uncrimped aluminum pan; Heating rate: room temperature to 150°C at 5°C/minute under a nitrogen purge.

The foregoing is merely illustrative of the invention and is not intended to limit the invention to the disclosed embodiments. Variations and changes which are obvious to one skilled in the art are intended to be within the scope and nature of the invention which are defined in the appended claims.

CLAIMS

What is claimed is:

1. The crystalline polymorph of (2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-amino-1,6-diphenyl-3-hydroxyhexane which is characterized by peaks in the powder X-ray diffraction pattern at values of two theta of 8.67° ± 0.1°, 9.51° ± 0.1°, 9.38° ± 0.1°, 10.97° ± 0.1°, 13.74° ± 0.1°, 16.11° ± 0.1°, 16.70° ± 0.1°, 17.36° ± 0.1°, 17.78° ± 0.1°, 18.40° ± 0.1°, 18.93° ± 0.1°, 19.52° ± 0.1°, 19.80° ± 0.1°, 20.07° ± 0.1°, 20.65° ± 0.1°, 21.49° ± 0.1°, 21.71° ± 0.1°, 22.23° ± 0.1°, 25.38° ± 0.1°, 26.15° ± 0.1° and 28.62° ± 0.1°.

2. A pharmaceutical composition for inhibiting HIV protease comprising a pharmaceutical carrier and a pharmaceutically effective amount of the crystalline polymorph of Claim 1.

3. A method for inhibiting HIV protease comprising administering to a human in need thereof a therapeutically effective amount of the crystalline polymorph of Claim 1.

4. A pharmaceutical composition for inhibiting an HIV infection comprising a pharmaceutical carrier and a pharmaceutically effective amount of the crystalline polymorph of Claim 1.

5. A method for inhibiting an HIV infection comprising administering to a human in need thereof a therapeutically effective amount of the crystalline polymorph of Claim 1.

6. A process for the preparation of the crystalline polymorph of Claim 1 comprising contacting amorphous ritonavir with a C1-C3 alcohol.

7. The process of Claim 4 wherein amorphous ritonavir is refluxed in the C1-C3 alcohol.

8. The process of Claim 6 wherein the alcohol is absolute ethanol.

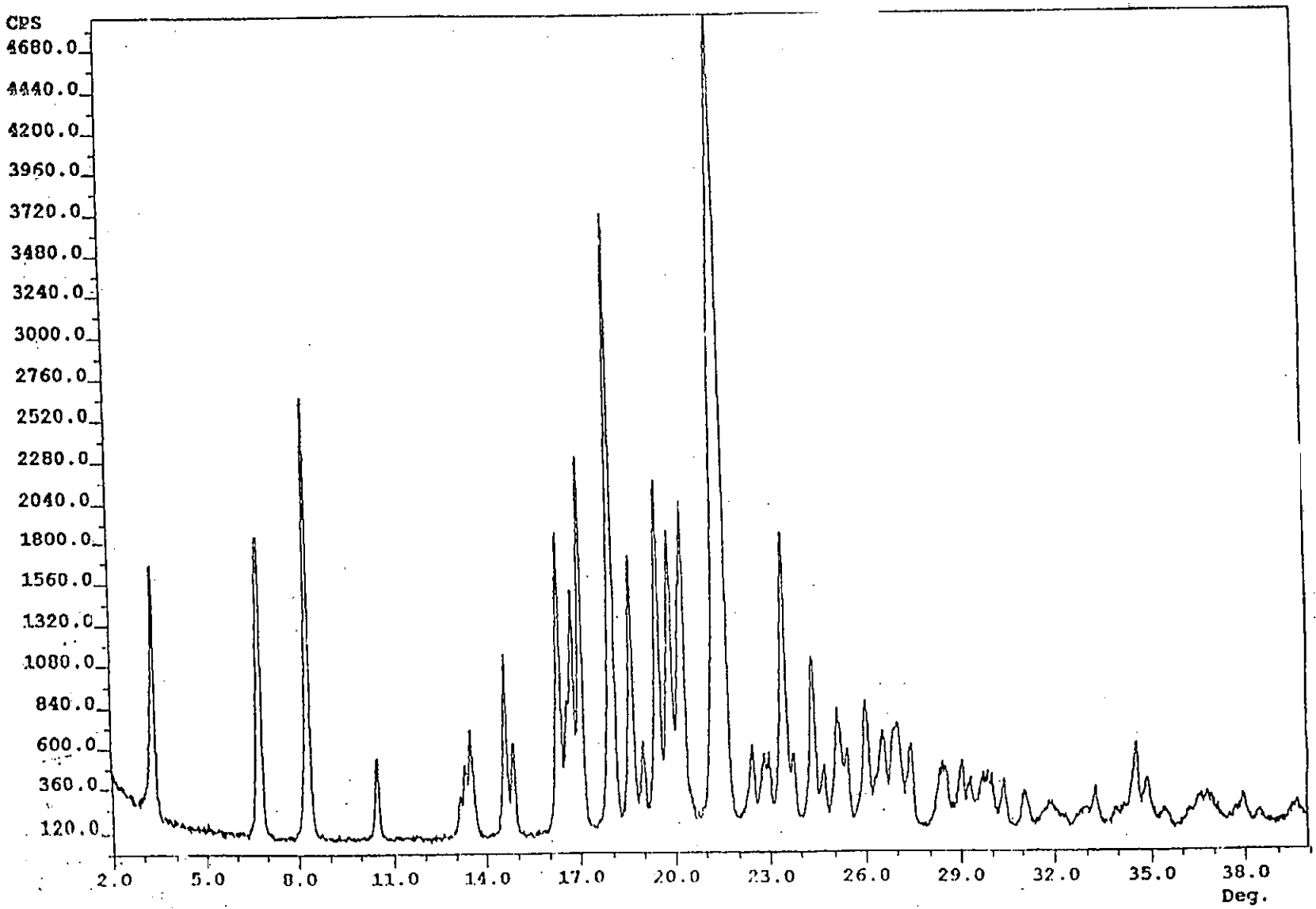
9. Amorphous ritonavir.

10. Amorphous ritonavir characterized by a glass transition from about 45°C to about 49°C.

Polymorph of a Pharmaceutical

Abstract of the Invention

A new crystalline polymorph of ritonavir and methods for its use and preparation are disclosed.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1320.0
1080.0
840.0
600.0
360.0
120.0
2.0
5.0
8.0
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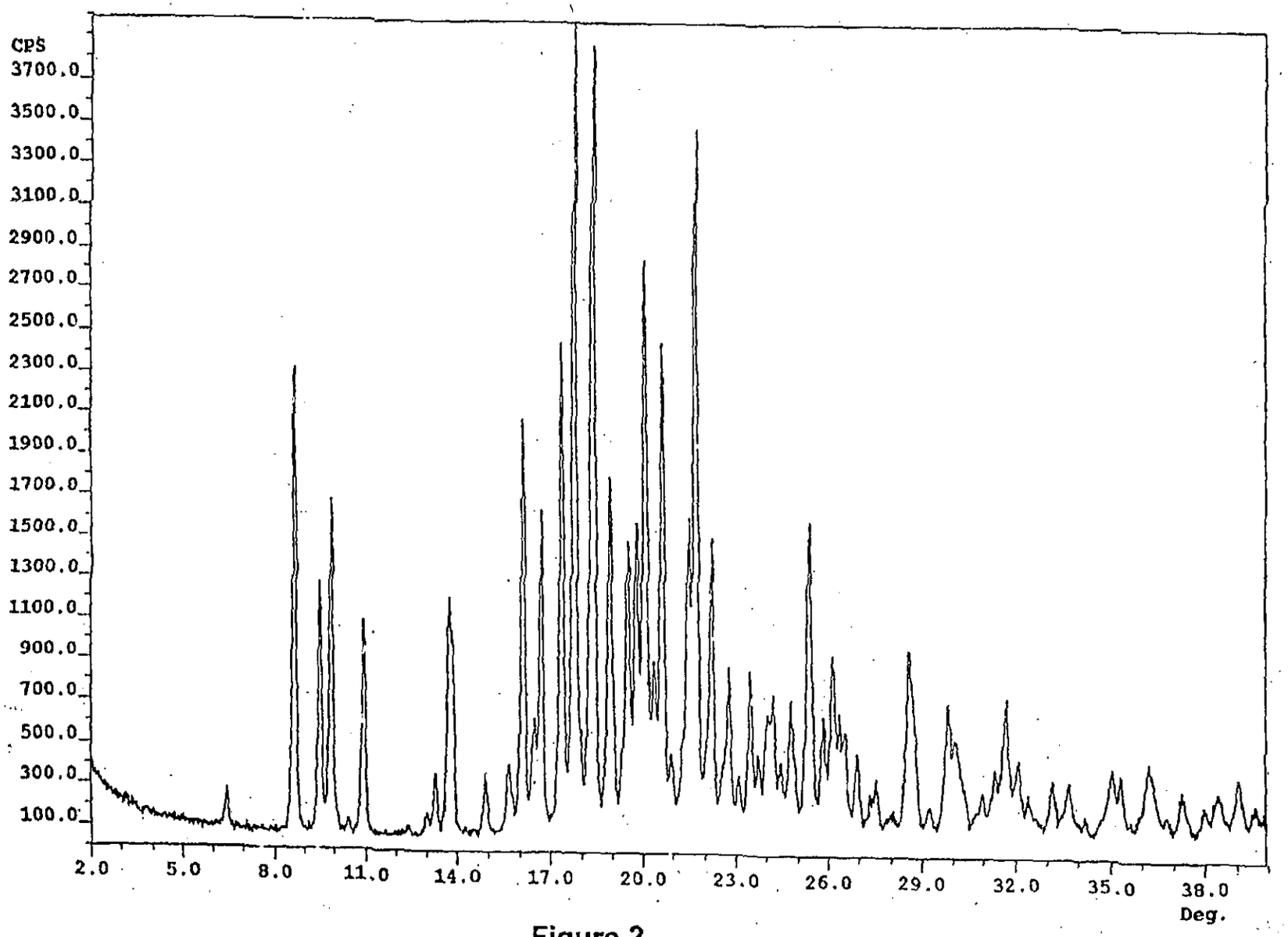
Deg.

Figure 1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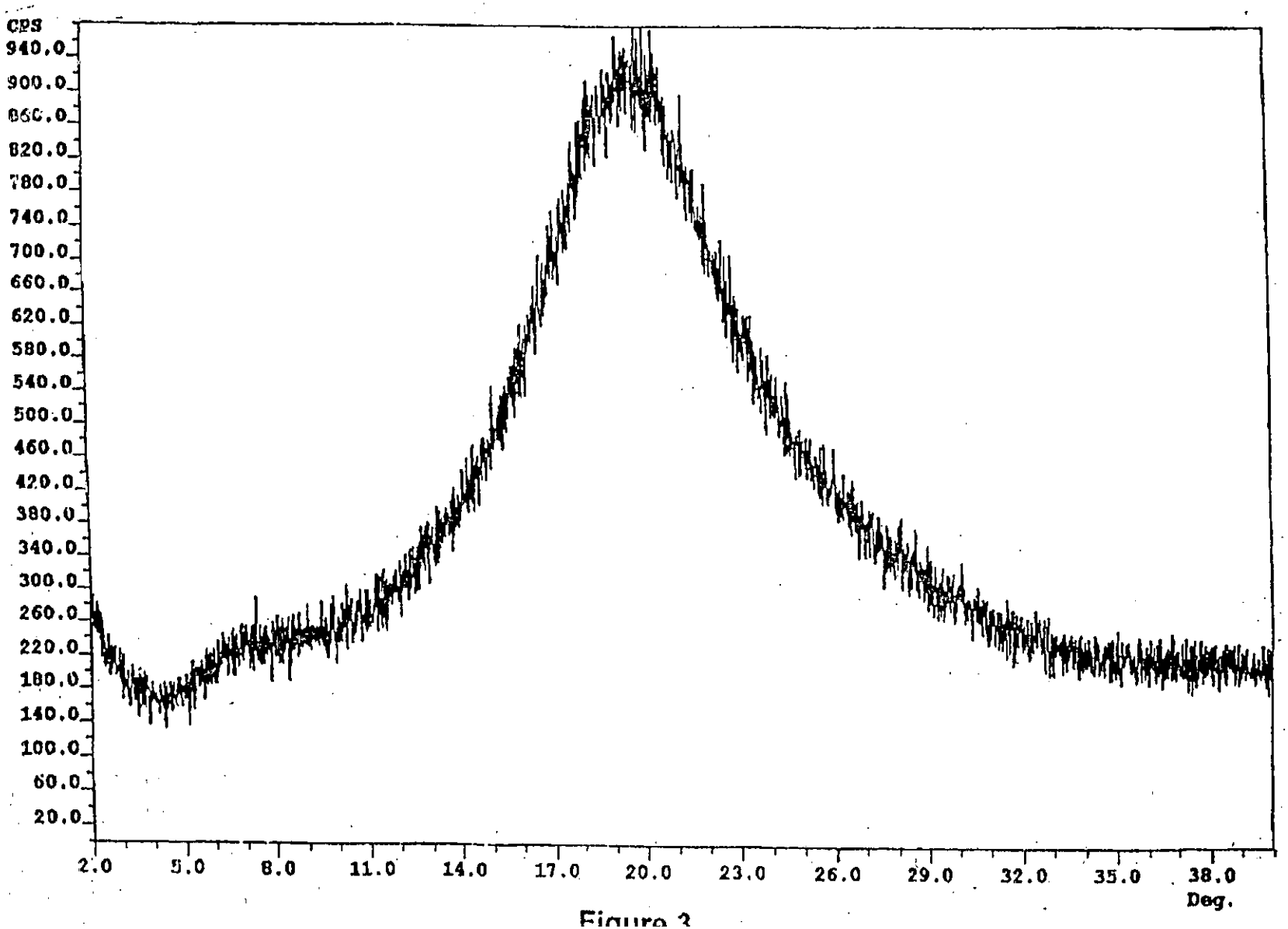
Deg.

Figure 2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300.0
260.0
220.0
180.0
140.0
100.0
60.0
20.0
2.0
5.0
8.0
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29.0
32.0
35.0
38.0
Deg.

Figure 3

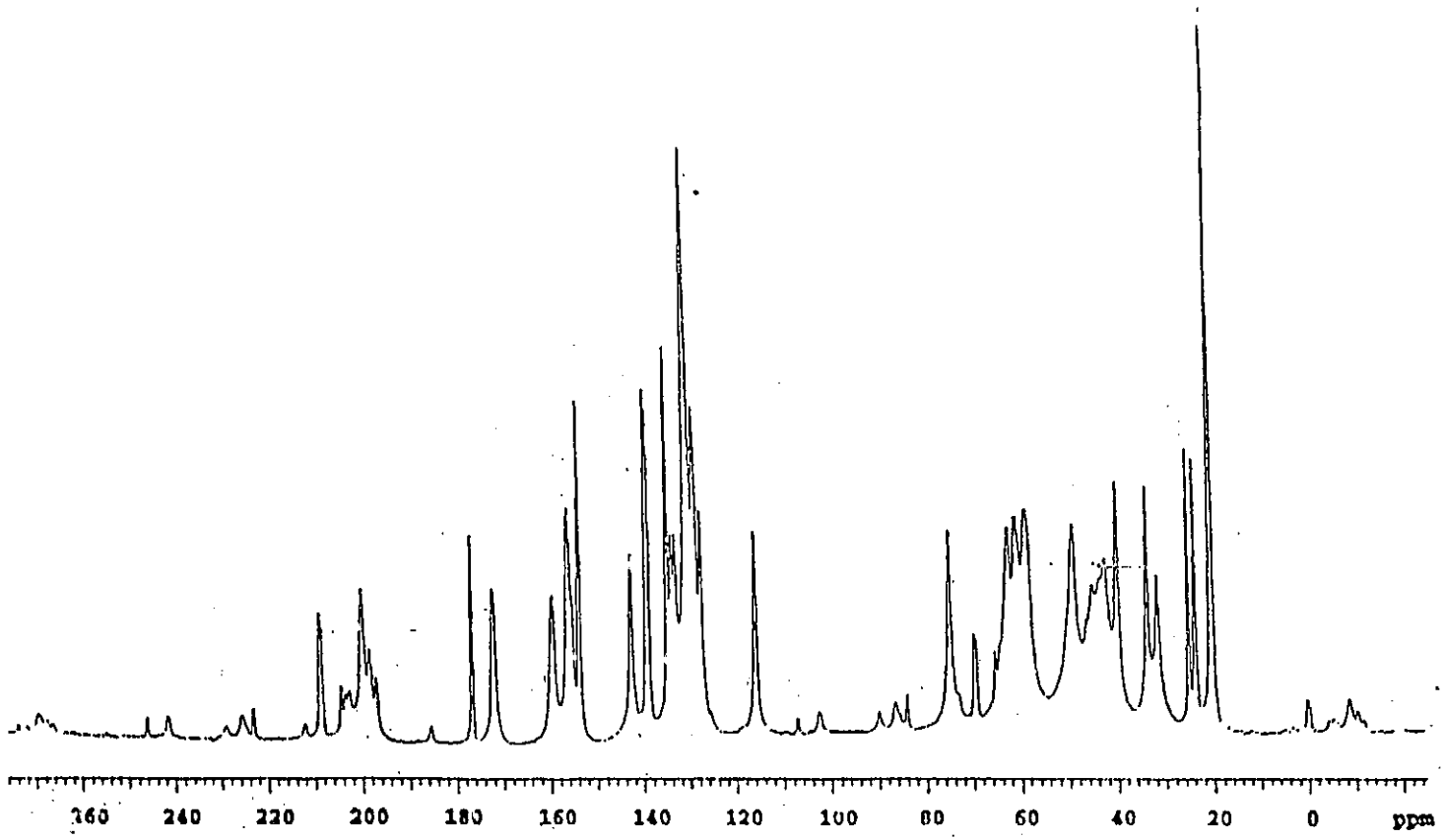
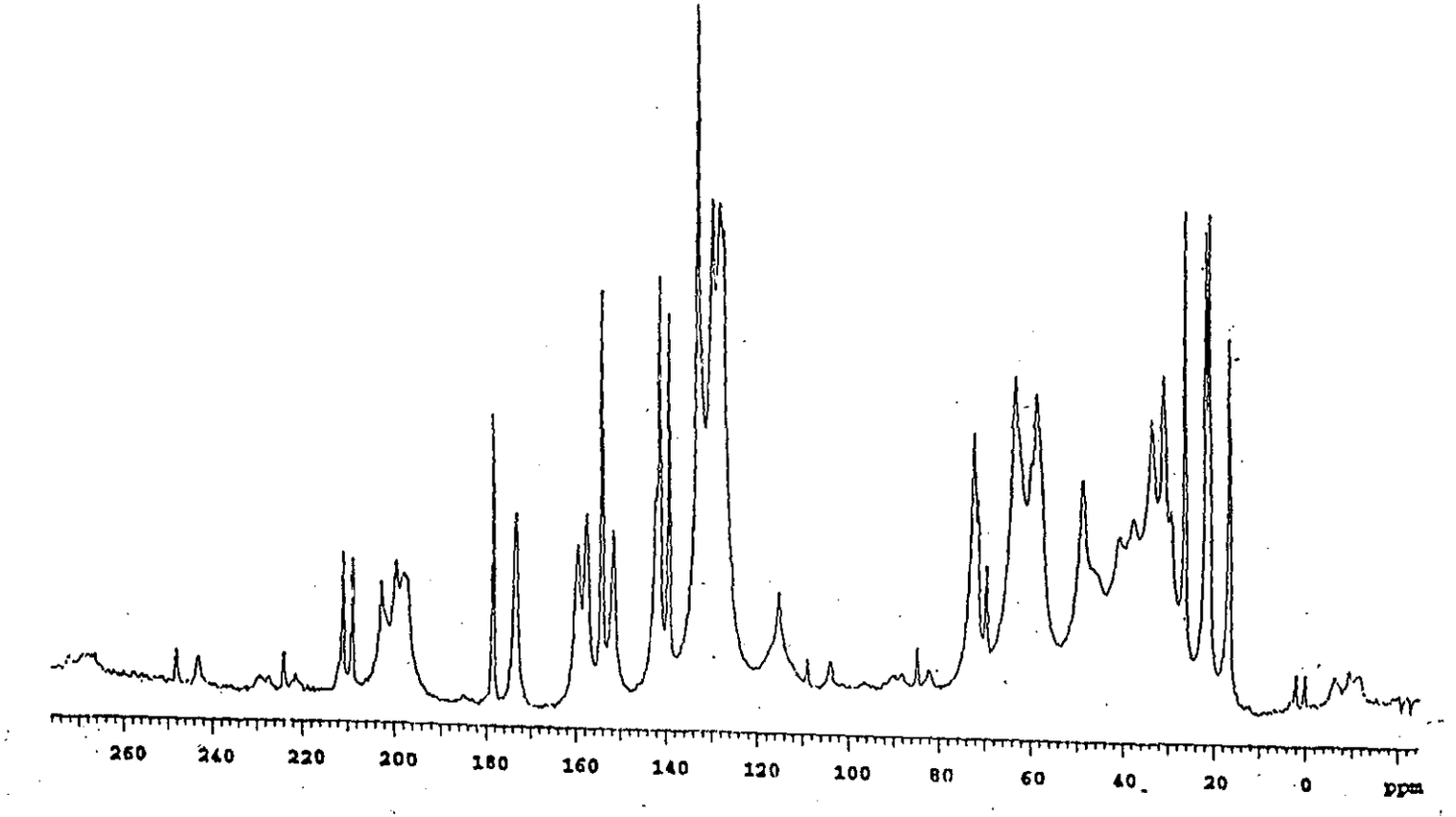


Figure 4



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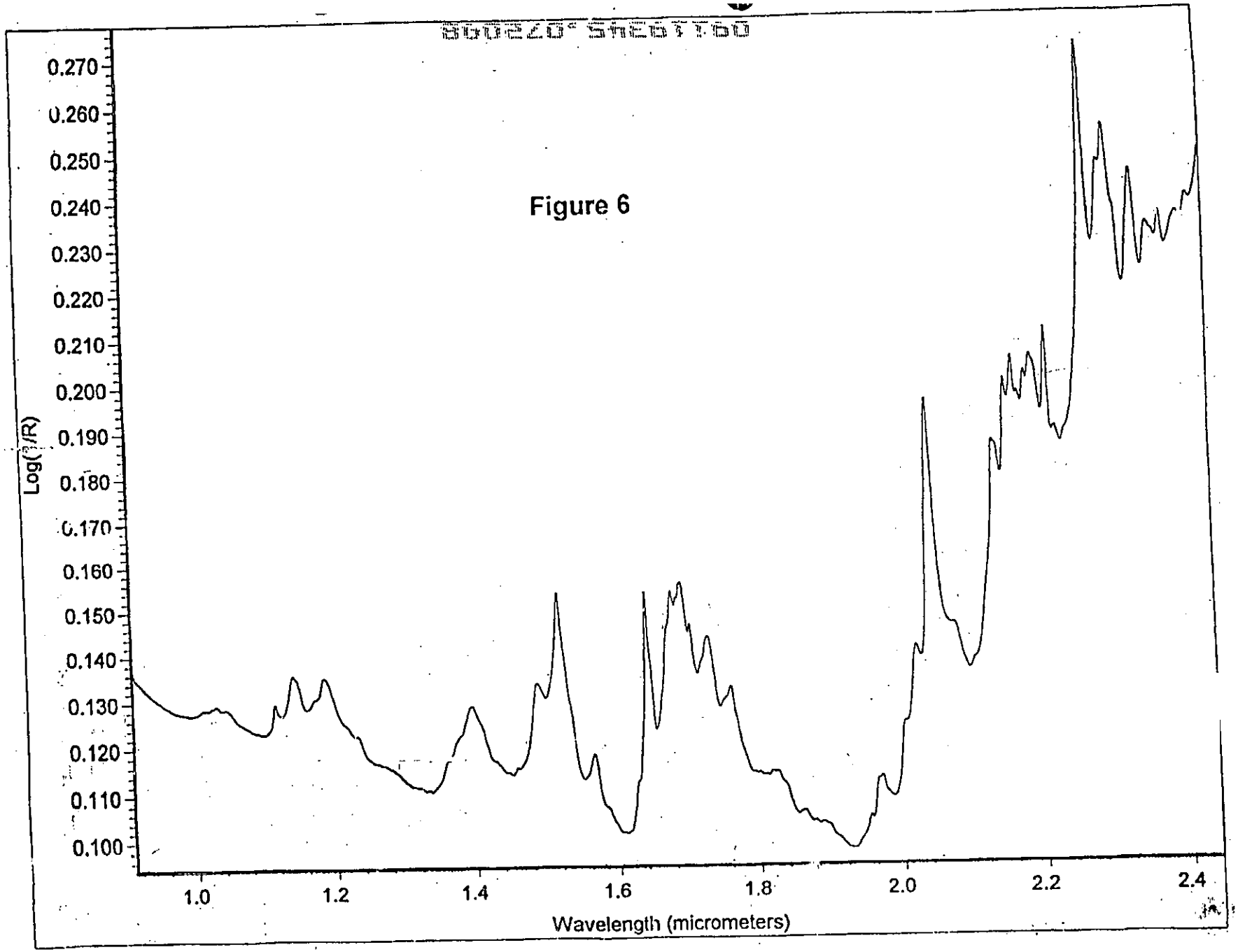
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0.220
0.210
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0.180
0.170
0.160
0.150
0.140
0.130
0.120
0.110
0.100
Log(1/R)
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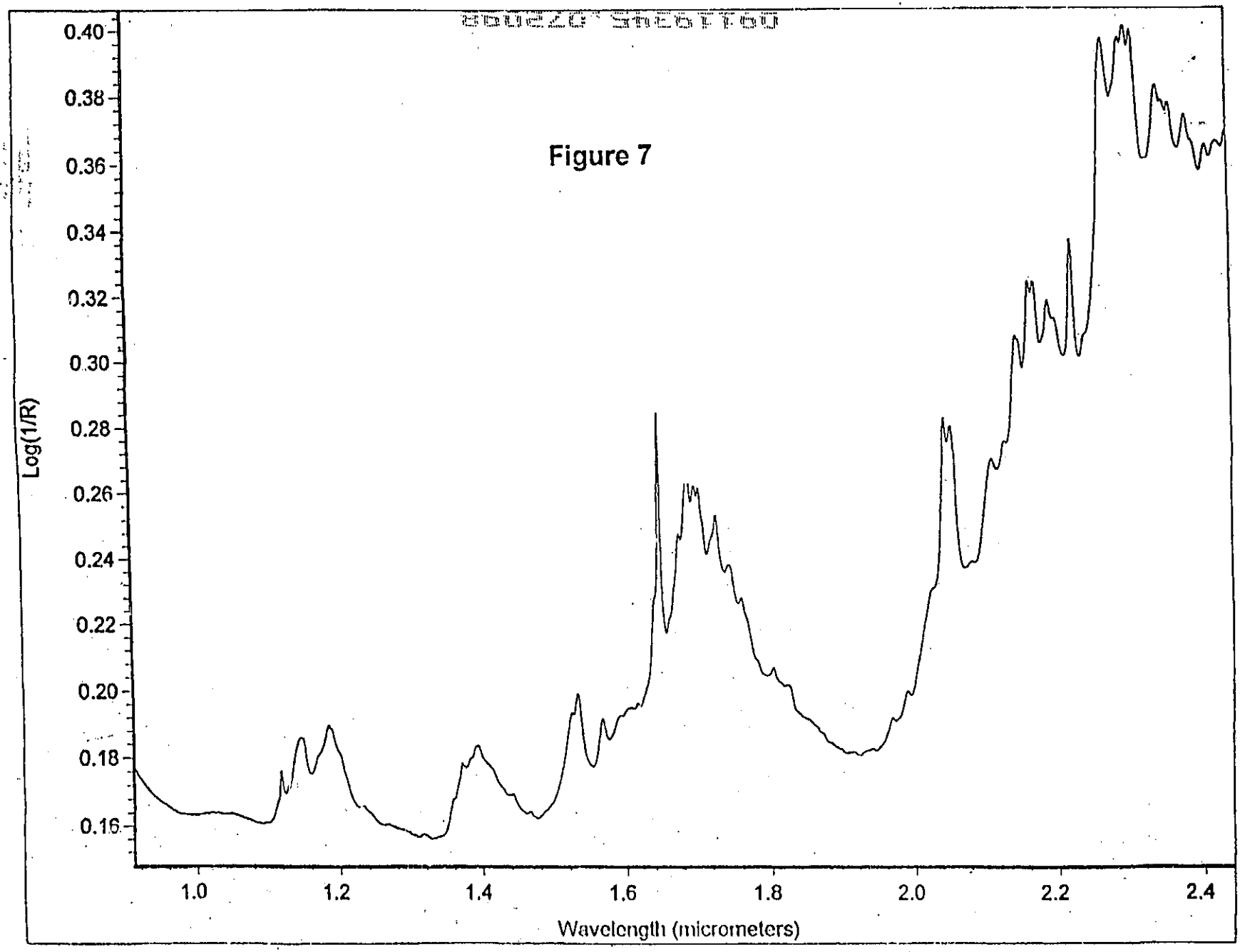
1.2
1.4
1.6
1.8
2.0
2.2
2.4
Wavelength (micrometers)

Figure 6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0.38
0.36
0.34
0.32
0.30
0.28
0.26
0.24
0.22
0.20
0.18
0.16
Log(1/R)
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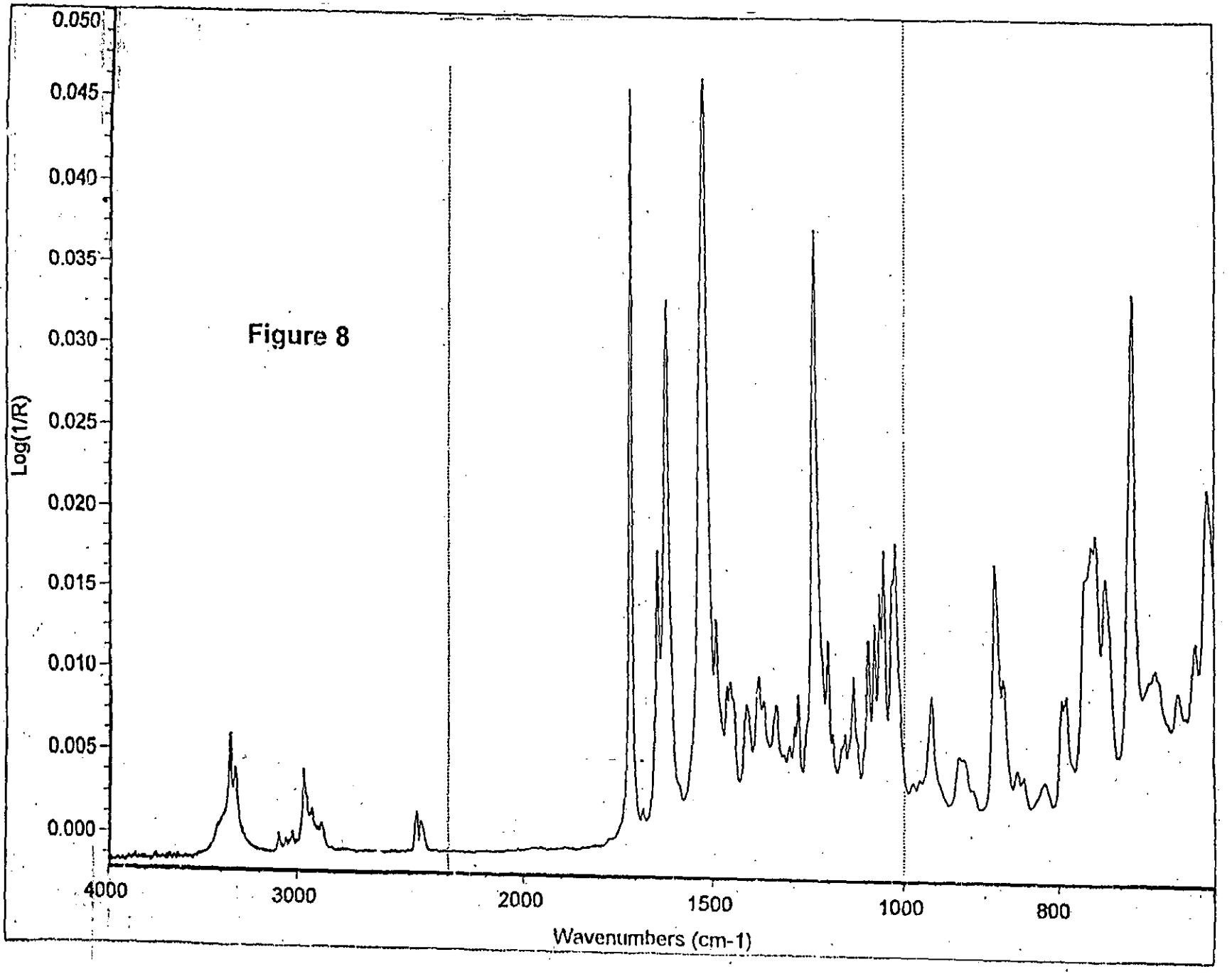
1.2
1.4
1.6
1.8
2.0
2.2
2.4
Wavelength (micrometers)

Figure 7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0.045
0.040
0.035
0.030
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0.020
0.015
0.010
0.005
0.000
Log(1/R)
4000
3000
2000
1500
1000
800
Wavenumbers (cm-1)

Figure 8

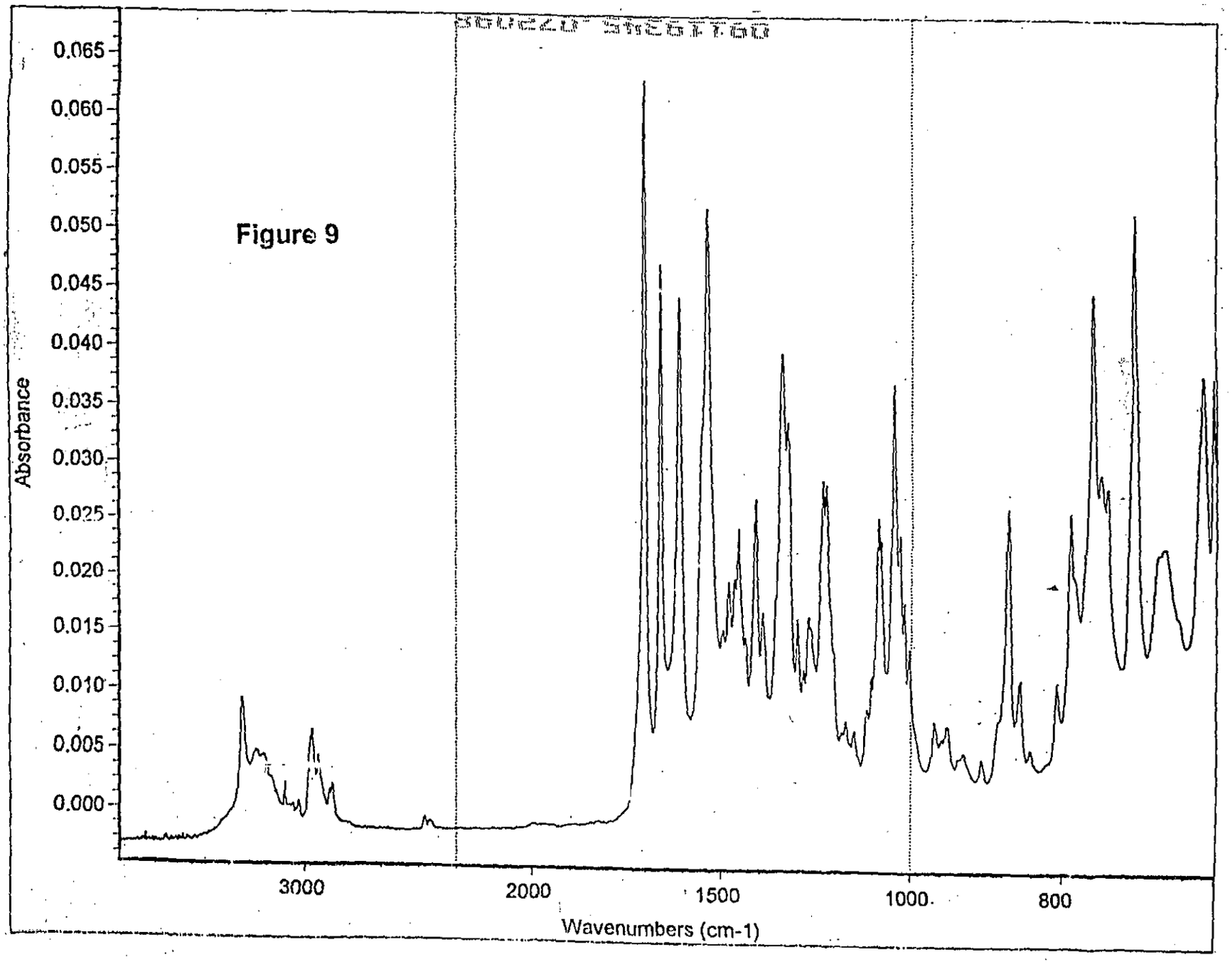
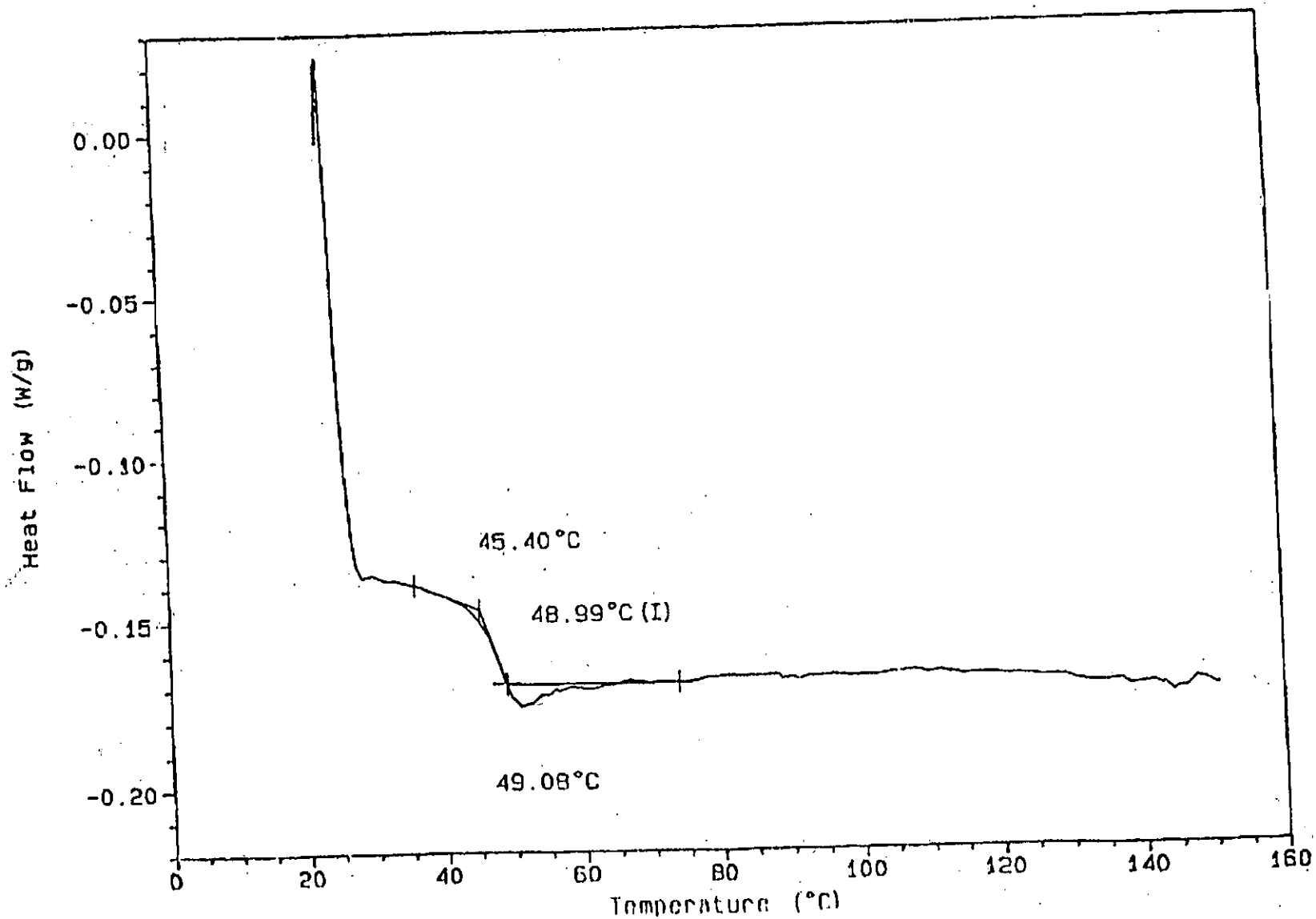


Figure 9
Absorbance
0.065
0.060
0.055
0.050
0.045
0.040
0.035
0.030
0.025
0.020
0.015
0.010
0.005
0.000
3000
2000
1500
1000
800
Wavenumbers (cm-1)

Figure 10


0.00
-0.05
-0.10
-0.15
-0.20
Heat Flow (W/g)
45.40°C
48.99°C (I)
49.08°C
0
20
40
60
80
100
120
140
160
Temperature (°C)

Annexure - II(b)

PI 138279

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office

September 01, 1999

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE UNDER 35 USC 111.

APPLICATION NUMBER: *09/326,093*
FILING DATE: *June 04, 1999*
PCT APPLICATION NUMBER: *PCT/US99/16334*

By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

T. LAWRENCE
Certifying Officer

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SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

23 JUL 2008

Polymorph of a Pharmaceutical

This is a continuation-in-part of U.S. Patent Application No. 09/119,345, filed July 20, 1998.

Technical Field

This invention relates to a novel crystalline polymorph of (2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)amino-1,6-diphenyl-3-hydroxyhexane, methods for its preparation, methods for its use as a pharmaceutical agent and pharmaceutical compositions comprising the novel crystalline polymorph. This invention also relates to an amorphous form of (2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-amino-1,6-diphenyl-3-hydroxyhexane and its use in the preparation of the novel crystalline polymorph.

Background of the Invention

Inhibitors of human immunodeficiency virus (HIV) protease have been approved for use in the treatment of HIV infection for several years. A particularly effective HIV protease inhibitor is (2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)amino-1,6-diphenyl-3-hydroxyhexane (ritonavir), which is marketed as NORVIR®. Ritonavir is known to have utility for the inhibition of HIV protease, the inhibition of HIV infection and the enhancement of the pharmacokinetics of compounds which are metabolized by cytochrome P450 monooxygenase. Ritonavir is particularly effective for the inhibition of HIV

infection when used alone or in combination with one or more reverse transcriptase inhibitors and/or one or more other HIV protease inhibitors.

Ritonavir and processes for its preparation are disclosed in U.S. Patent No. 5,541,206, issued July 30, 1996. This patent discloses processes for preparing ritonavir which produce a crystalline polymorph of ritonavir which is termed crystalline Form I. Substantially pure Form I has the powder X-ray diffraction pattern, ^{13}C solid state nuclear magnetic resonance spectrum, the FT near infrared spectrum and the FT mid infrared spectrum which appear in FIGS. 1, 4, 6 and 8, respectively. The angular positions (two theta) of the characteristic peaks in the powder X-ray diffraction pattern of substantially pure Form I shown in FIG. 1 are 3.33° ± 0.1°, 6.76° ± 0.1°, 8.33° ± 0.1°, 14.61° ± 0.1°, 16.33° ± 0.1°, 16.76° ± 0.1°, 17.03° ± 0.1°, 18.02° ± 0.1°, 18.62° ± 0.1°, 19.47° ± 0.1°, 19.86° ± 0.1°, 20.25° ± 0.1°, 21.46° ± 0.1°, 23.46° ± 0.1° and 24.36° ± 0.1°.

Another process for the preparation of ritonavir is disclosed in U.S. Patent No. 5,567,823, issued October 22, 1996. The process disclosed in this patent also produces ritonavir as crystalline Form I.

Pharmaceutical compositions comprising ritonavir or a pharmaceutically acceptable salt thereof are disclosed in U.S. Patent Nos. 5,541,206, issued July 30, 1996; 5,484,801, issued January 16, 1996; 5,725,878, issued March 10, 1998; and 5,559,158, issued September 24, 1996 and in International Application No. WO98/22106, published May 28, 1998 (corresponding to U.S. Serial No. 08/966,495, filed November 7, 1997).

The use of ritonavir to inhibit an HIV infection is disclosed in U.S. Patent No. 5,541,206, issued July 30, 1996. The use of ritonavir in combination with one or more reverse transcriptase inhibitors to inhibit an HIV infection is disclosed in U.S. Patent No. 5,635,523, issued June 3, 1997. The use of ritonavir in combination with one or more HIV protease inhibitors to inhibit an HIV infection is disclosed in U.S. Patent No. 5,674,882, issued October 7, 1997. The use of

ritonavir to enhance the pharmacokinetics of compounds metabolized by cytochrome P450 monooxygenase is disclosed in WO97/01349, published January 16, 1997 (corresponding to U.S. Serial No. 08/687,774, filed June 26, 1996).

It has now been unexpectedly discovered that ritonavir can be prepared as a new crystalline polymorph which is termed crystalline Form II.

All publications, issued patents and patent applications cited herein are hereby incorporated by reference.

Brief Description of the Drawings

FIG. 1 is the powder X-ray diffraction pattern of the substantially pure Form I crystalline polymorph of ritonavir.

FIG. 2 is the powder X-ray diffraction pattern of the substantially pure Form II crystalline polymorph of ritonavir.

FIG. 3 is the powder X-ray diffraction pattern of substantially pure amorphous ritonavir.

FIG. 4 is the 400 MHz solid state ^{13}C nuclear magnetic resonance spectrum of the substantially pure Form I crystalline polymorph of ritonavir.

FIG. 5 is the 400 MHz solid state ^{13}C nuclear magnetic resonance spectrum of the substantially pure Form II crystalline polymorph of ritonavir.

FIG. 6 is the FT near infrared spectrum of the substantially pure Form I crystalline polymorph of ritonavir.

FIG. 7 is the FT near infrared spectrum of the substantially pure Form II crystalline polymorph of ritonavir.

FIG. 8 is the FT mid infrared spectrum of the substantially pure Form I crystalline polymorph of ritonavir.

FIG. 9 is the FT mid infrared spectrum of the substantially pure Form II crystalline polymorph of ritonavir.

FIG. 10 is the differential scanning calorimetric thermogram for substantially pure amorphous ritonavir.

Disclosure of the Invention

In accordance with the present invention, there is a novel substantially pure crystalline polymorph of (2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)amino-1,6-diphenyl-3-hydroxyhexane (ritonavir). For the sake of identification, this crystalline polymorph is designated as the Form II crystalline polymorph of ritonavir.

Substantially pure Form II has the powder X-ray diffraction pattern, ^{13}C solid state nuclear magnetic resonance spectrum, the FT near infrared spectrum and the FT mid infrared spectrum which appear in FIGS. 2, 5, 7 and 9, respectively. The two-theta angle positions of characteristic peaks in the powder X-ray diffraction pattern of substantially pure Form II as shown in FIG. 2 are: 8.67° ± 0.1°, 9.88° ± 0.1°, 16.11° ± 0.1°, 16.70° ± 0.1°, 17.36° ± 0.1°, 17.78° ± 0.1°, 18.40° ± 0.1°, 18.93° ± 0.1°, 20.07° ± 0.1°, 20.65° ± 0.1°, 21.71° ± 0.1°and 25.38° ± 0.1°.

More preferably, substantially pure Form II is characterized by peaks in the powder X-ray diffraction pattern having two-theta angle positions as shown in FIG. 2 of:
8.67° ± 0.1°, 9.51° ± 0.1°, 9.88° ± 0.1°, 10.97° ± 0.1°, 13.74° ± 0.1°, 16.11° ± 0.1°, 16.70° ± 0.1°, 17.36° ± 0.1°, 17.78° ± 0.1°, 18.40° ± 0.1°, 18.93° ± 0.1°, 19.52° ± 0.1°, 19.80° ± 0.1°, 20.07° ± 0.1°, 20.65° ± 0.1°, 21.49° ± 0.1°, 21.71° ± 0.1°, 22.23° ± 0.1°, 25.38° ± 0.1°, 26.15° ± 0.1° and 28.62° ± 0.1°.

The substantially pure Form II crystalline polymorph of ritonavir can be prepared from amorphous ritonavir by contacting amorphous ritonavir with a

C1-C3 alcohol. The method of contacting may be either by saturating the amorphous compound in the solvent at ambient temperature and then allowing the mixture to stand for an extended period of time (for example, overnight) or by dissolving the amorphous compound in the solvent at elevated temperature, preferably, at reflux, followed by cooling the solution to room temperature and isolating Form II.

In a preferred process, the substantially pure Form II crystalline polymorph of ritonavir can be prepared from amorphous ritonavir by preparing a saturated solution of amorphous ritonavir in a C1-C3 alcohol at room temperature and isolating Form II which results. In practice this can be accomplished by dissolving a sufficient amount of amorphous ritonavir in the C1-C3 alcohol at elevated temperature (up to reflux) such that when the solution is allowed to coo to room temperature a saturated solution is obtained, from which Form II precipitates and can be isolated. A preferred solvent for the preparation of Form II is anhydrous ethanol. Isolation of the resulting solid provides Form II.

Substantially pure amorphous ritonavir is prepared from the Form I crystalline polymorph of ritonavir by melting Form I ritonavir and rapidly cooling the melt. Isolation of the resulting solid provides amorphous ritonavir.

Substantially pure amorphous ritonavir can also be prepared by slowly adding a solution of ritonavir Form I in a suitable solvent (methylene chloride and the like, preferably, methylene chloride) at a concentration of, preferably, about 1 g of ritonavir/1.5 mL of methylene chloride) to an anti-solvent (for example, hexane and the like; preferably, hexane) at a concentration of, preferably, about 85-90 mL of hexane/ g of ritonavir, followed by isolation (for example, by filtration) of the resulting solid.

Substantially pure amorphous ritonavir can also be prepared by slowly adding a solution of ritonavir Form I in a suitable solvent (for example, methanol and the like; preferably, methanol) at a concentration of, preferably, about 1 g of

ritonavir/ 1.6 mL of methanol) to water at about 0°C at a concentration of, preferably, about 400 mL of water/ g of ritonavir, followed by isolation (for example, by filtration) and drying of the resulting solid.

Alternatively, substantially pure Form II can be prepared by seeding a solution of ritonavir Form I in a C1-C3 alcohol (preferably, ethanol) with (2S)-N-((1S)-1-Benzyl-2-((4S,5S)-4-benzyl-2-oxo-1,3-oxazolidin-5-yl)ethyl)-2-((((2-isopropyl-1,3-thiazol-4-yl)methyl)amino)-carbonyl)amino)-3-methylbutanamide. In a preferred method, ritonavir Form I is dissolved in ethanol (preferably, 200 proof ethanol). To the solution is added seed crystals of (2S)-N-((1S)-1-Benzyl-2-((4S,5S)-4-benzyl-2-oxo-1,3-oxazolidin-5-yl)ethyl)-2-((((2-isopropyl-1,3-thiazol-4-yl)*methyl)amino)carbonyl)-amino)-3-methylbutanamide. The mixture is allowed* to stand at a temperature of about 5° C for about 24 hours. The resulting crystalline ritonavir Form II is isolated by filtration.

In yet another alternative method, substantially pure Form II can be prepared by recrystallization of Form I or mixtures of Form I and Form II from a suitable solvent (for example, ethyl acetate or isopropyl acetate or chloroform and the like other solvents with like dielectric constant; preferably, ethyl acetate), with *seeding with Form II crystals, followed by addition of an anti-solvent (for example,* heptane, hexane, toluene, petroleum ether and the like other anti-solvents with like dielectric constant; preferably, heptane). In a preferred method, ritonavir (Form I or a mixture of Form I and Form II) is dissolved in ethyl acetate (from about 4.0 L to about 6.0 L/kg of ritonavir) with heating (at from about 65°C to about 70°C). The solution is slowly cooled to from about 55°C to about 50°C, preferably about 52°C. Seed crystals of ritonavir Form II (from about 0.5 g of Form II seed crystals/kg of ritonavir to about 10.0 g of Form II seed crystals/kg of ritonavir, preferably about 1.25 g of Form II seed crystals/kg of ritonavir) are added and the mixture is stirred for about 1 hour at a temperature of from about 55°C to about 50°C, preferably about 52°C. Heptane (from about 1.0 L/kg of

ritonavir to about 4.0 L/kg of ritonavir, preferably about 2.8 L/kg of ritonavir) is added with mixing and the mixture is allowed to slowly cool to about 25°C and is then stirred for at least 12 hours at about 25°C. The product is isolated by filtration/centrifugation and is dried under vacuum with heating. On a manufacturing scale (300-400 kg batches), it has been observed that isolation by filtration/centrifugation is considerably faster for Form II than for the corresponding amount of Form I (16 hours versus 24-30 hours).

It has also been found that Form II or mixtures of Form II and Form I can be converted to substantially pure Form I by dissolving the Form II or mixture of Form II and Form I in a suitable solvent (for example, ethyl acetate and the like; preferably ethyl acetate) at a concentration of about 1 kg of ritonavir/4 L of solvent (preferably, ethyl acetate) with heating. The hot solution of ritonavir is slowly added (preferably, through a filter) to a slurry of seed crystals of ritonavir Form I (from about 0.5% to about 10% by weight relative to amount of ritonavir Form II or mixture of Form II and Form I, preferably from about 0.5% to about 5% by weight and, most preferably, from about 0.5% to about 1% by weight) in an anti-solvent (for example, heptane and the like; preferably, heptane) at a concentration of about 1 kg of ritonavir (Form II or mixture of Form II and Form I)/ 4 L of antisolvent (preferably, heptane). The mixture is cooled to about 20°C and stirred for at least 3 hours. Isolation (for example, by filtration) and drying of the resulting solid provides ritonavir Form I.

The following examples will serve to further illustrate the preparation of the novel forms of ritonavir of the invention and the conversion of Form II to Form I.

Example 1

Preparation of Amorphous Ritonavir

Form I crystalline polymorph of ritonavir (100 g) was melted at 125°C by heating Form I. The melt was maintained at a temperature of 125°C for 3 hours. The melt was rapidly cooled by placing the container holding the melt into a Dewar flask containing liquid nitrogen. The resulting glass was ground with a mortar and pestle to provide amorphous ritonavir (100 g). Powder X-ray diffraction analysis confirmed that the product was amorphous. Differential scanning calorimetric analysis determined that the glass transition point was from about 45°C to about 49°C. (Measured onset at 45.4°C and which ends at 49.08°C, with a midpoint of 48.99°C).

Example 2

Preparation of Crystalline Ritonavir (Form II)

Amorphous ritonavir (40.0 g) was dissolved in boiling anhydrous ethanol (100 mL). Upon allowing this solution to cool to room temperature, a saturated solution was obtained. After standing overnight at room temperature, the resulting solid was isolated from the mixture by filtration and was air dried to provide Form II (approximately 24.0 g).

Example 3

Preparation of (2S)-N-((1S)-1-Benzyl-2-((4S,5S)-4-benzyl-2-oxo-1,3-oxazolidin-5-yl)ethyl)-2-((((2-isopropyl-1,3-thiazol-4-yl)methyl)amino)carbonyl)amino)-3-methylbutanamide

Example 3a

Preparation of (4S,5S)-5-((2S)-2-t-butyloxycarbonylamino-3-phenylpropyl)-4-benzyl-1,3-oxazolidin-2-one

(2S,3S,5S)-2-Amino-3-hydroxy-5-t-butyloxycarbonylamino-1,6-diphenylhexane succinate salt (30 g, 63 mmol; U.S. Patent No. 5,654,466), ((5-thiazolyl)methyl)-(4-nitrophenyl)carbonate hydrochloride (22.2 g; U.S. Patent No. 5,597,926) and sodium bicarbonate (16.2 g) were mixed with 300mL of water and 300 mL of ethyl acetate and the mixture was stirred at room temperature for about 30 minutes. The organic layer was then separated and heated at about 60°C for 12 hours, and then stirred at 20-25°C for 6 hours. 3 mL of ammonium hydroxide (29% ammonia in water) was added and the mixture stirred for 1.5 hours. The resulting mixture was washed with 4 x 200 mL of 10% aqueous potassium carbonate and the organic layer was separated and evaporated under vacuum to provide an oil. The oil was suspended in about 250 mL of heptane. The heptane was evaporated under vacuum to provide a yellow solid. The yellow solid was dissolved in 300 mL of THF and 25 mL of 10% aqueous sodium hydroxide was added. After stirring for about 3 hours, the mixture was adjusted to pH 7 by addition of 4N HCl (about 16 mL). The THF was evaporated under vacuum to leave an aqueous residue, to which was added 300 mL of distilled water. After stirring this mixture, a fine suspension of solids resulted. The solid was collected by filtration and the filtered solid was washed with water (1400 mL) in several portions, resulting in the desired product.

Example 3b

Preparation of (4S,5S)-5-((2S)-2-amino-3-phenylpropyl)-4-benzyl-1,3-oxazolidin-2-one

The crude, wet product of Example 3a was slurried in 1N HCl (192 mL) and the slurry was heated to 70°C with stirring. After 1 hour, THF (100 mL) was

added and stirring at 65°C was continued for 4 hours. The mixture was then allowed to cool to 20-25°C and was stirred overnight at 20-25°C. The THF was removed by evaporation under vacuum and the resulting aqueous solution was cooled to about 5°C, causing some precipitation to occur. The aqueous mixture was adjusted to pH 7 by addition of 50% aqueous sodium hydroxide (about 18.3 g). The resulting mixture was extracted with ethyl acetate (2 x 100 mL) at about 15°C. The combined organic extracts were washed with 100 mL of brine and the organic layer was separated and stirred with sodium sulfate (5 g) and Darco G-60 (3 g). This mixture was warmed on a hot plate for 1 hour at 45°C. The hot mixture was then filtered through a bed of diatomaceous earth and the filter pad was washed with ethyl acetate (100 mL). The filtrate was evaporated under vacuum to provide an oil. The oil was redissolved in methylene chloride (300 mL) and the solvent was evaporated under vacuum. The resulting oil was dried at room temperature under vacuum to provide the desired product (18.4 g) as a glassy syrup.

Example 3c

Preparation of (2S)-N-((1S)-1-Benzyl-2-((4S,5S)-4-benzyl-2-oxo-1,3-oxazolidin-5-yl)ethyl)-2-((((2-isopropyl-1,3-thiazol-4-yl)methyl)amino)carbonyl)amino)-3-methylbutanamide

N-((N-Methyl-N((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine (10.6 g, 33.9 mmol; U.S. Patent No. 5,539,122 and International Patent Application No. WO98/00410), the product of Example 3b (10.0 g, 32.2 mmol) and

1-hydroxybenzotriazole (5.2 g, 34 mmol) were dissolved in THF (200 mL). 1,3-dicylcohexylcarbodiimide (DCC, 7.0 g, 34 mmol) was then added to the THF mixture and the mixture was stirred at 22°C for 4 hours. Citric acid (25 mL of

10% aqueous solution) was added and stirring continued for 30 minutes. The THF was then evaporated under vacuum. The residue was dissolved in ethyl acetate (250 mL) and washed with 10% citric acid solution (175 mL). NaCl (5 g) was added to accelerate the separation of the layers. The organic layer was sequentially washed with 10% aq. sodium carbonate (2 x 200 mL) and water (200 mL). The organic layer was then dried over sodium sulfate (20 g), filtered and evaporated under vacuum. The resulting product (20.7 g of a foam) was dissolved in hot ethyl acetate (150 mL) and then heptane (75 mL) was added. Upon cooling, another 75 mL of heptane was added and the mixture was heated to reflux. Upon cooling to room temperature, no precipitate formed. The solvents were evaporated under vacuum and the residue was redissolved in a mixture of 200 mL ethyl acetate/100 mL heptane. The small amount of undissolved solid was removed by filtration. The filtrate was evaporated under vacuum and the residue was dissolved in a mixture of 100 mL ethyl acetate/ 50 mL heptane, giving a clear solution. The solution was cooled to –10°C and a white precipitate formed. The mixture was allowed to sit at –15°C for 24 hours. The resulting solid was collected by filtration, washed with 1:1 ethyl acetate/heptane (2 x 24 mL) and dried in a vacuum oven at 55°C to provide the desired product as a beige solid (16.4 g).

Example 4

Preparation of Crystalline Ritonavir (Form II)

To a solution of 1.595 g of ritonavir Form I in 10 mL of 200 proof ethanol was added approximately 50 micrograms of the product of Example 3c. This mixture was allowed to stand at about 5°C for 24 hours. The resulting crystals were isolated by filtration through 0.45 micron nylon filter and air-dried to provide ritonavir Form II.

INDEX OF IN/PCT/2001/00018/MUM A

SR. NO.	ANNEXURE	TITLE
1.	**Annexure I**	Indian Patent Application No. IN/PCT/2001/00018/MUM
2.	**Annexure II (a)**	Priority document – US Patent Application No. 09/119,345
3.	**Annexure II (b)**	Priority document – US Patent Application No. 09/326,093
4.	**Annexure III**	Corresponding PCT International Application No. PCT/US99/16334 (WO 00/04016)
5.	**Annexure IV**	**First Patent Ritonavir:** PCT International Application No. PCT/US1993/012326 (WO94/14436)
6.	**Annexure V**	**First Patent Ritonavir:** US Patent No. 5541206
7.	**Annexure VI**	Gleevec Case relating to Patent Application No. 1602/MAS/1998 decided by Chennai Patent Office
8.	**Annexure VII**	Judgment of the Chennai High Court upholding the constitutional validity of 3 (d) f The Patents Act, 1970, (W. P. Nos. 24759 and 24760 of 2006 dated 06/08/2007)
9.	**Annexure VIII**	GB Patent No.761163
10.	**Annexure IX**	*Pfizer v. Apotex (Amlodipine case)*

Dr. Gopakumar G Nair

Ritonavir Form II	100.0 mg
Ethanol, dehydrated	120.0 mg
Oleic acid	709.75 mg
Butylated hydroxytoluene	0.25 mg
Polyoxyl 35 castor oil (Cremophor EL®)	60.0 mg
Water	10.0 mg

The preferred composition can be prepared according to the following method.

The following protocol is employed in the preparation of 1000 soft gelatin capsules:

Scale (mg/capsule)	Name	Amount (g)
Q.S.	Nitrogen, N.F.	Q.S.
118.0	Ethanol, dehydrated, USP, 200 Proof	118.0
2.0	Ethanol, dehydrated, USP, 200 Proof	2.0
0.25	Butylated Hydroxytoluene, NF	0.25
704.75	Oleic Acid, NF	704.75
100.0	Ritonavir Form II	100.0
10.0	Water, purified; USP (distilled)	10.0
60.0	Polyoxyl 35 Castor Oil, NF	60.0
5.000	Oleic Acid, NF	5.000

A mixing tank and suitable container are purged with nitrogen. 118.0 g of ethanol is weighed, blanketed with nitrogen, and held for later use. The second

aliquot of ethanol (2 g) is then weighed, and mixed with 0.25 g of butylated hydroxytoluene until clear. The mixture is blanketed with nitrogen and held. The main mixing tank is heated to 28 °C (not to exceed 30 °C). 704.75 g of oleic acid is then charged into the mixing tank. 100.0 g of ritonavir Form II is then added to the oleic acid with mixing. The ethanol/butylated hydroxytoluene is then added to the mixing tank, followed by the 118.0 g of ethanol measured previously, and mixed for at least 10 minutes. 10 g of water is then charged into the tank and mixed until the solution is clear (for not less than 30 minutes). 60.0 g of Polyoxyl 35 castor oil is charged into the tank and mixed until uniform. The solution is stored at 2-8 °C until encapsulation. According to the procedures described in International Patent Application WO98/22106, 1.0 g of the solution is filled into each soft gelatin capsule and the soft gelatin capsules are then dried, and stored at 2-8 °C.

As used herein, the term "substantially pure", when used in reference to a polymorph of ritonavir, refers to a polymorph of ritonavir, Form I or Form II, which is greater than about 90% pure. This means that the polymorph of ritonavir 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 ritonavir. More preferably, the term "substantially pure" refers to a polymorph of ritonavir, Form I or Form II, which is greater than about 95% pure. This means that the polymorph of ritonavir does not contain more than about 5% of any other compound and, in particular, does not contain more than about 5% of any other form of ritonavir. Even more preferably, the term "substantially pure" refers to a polymorph of ritonavir, Form I or Form II, which is greater than about 97% pure. This means that the polymorph of ritonavir does not contain more than about 3% of any other compound and, in particular, does not contain more than about 3% of any other form of ritonavir.

As used herein, the term "substantially pure", when used in reference to amorphous ritonavir, refers to amorphous ritonavir which is greater than about 90% pure. This means that the amorphous ritonavir 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 ritonavir. More preferably, the term "substantially pure", when used in reference to amorphous ritonavir, refers to amorphous ritonavir which is greater than about 95% pure. This means that the amorphous ritonavir does not contain more than about 5% of any other compound and, in particular, does not contain more than about 5% of any other form of ritonavir. Even more preferably, the term "substantially pure", when used in reference to amorphous ritonavir, refers to amorphous ritonavir which is greater than about 97% pure. This means that the amorphous ritonavir does not contain more than about 3% of any other compound and, in particular, does not contain more than about 3% of any other form of ritonavir.

Powder X-ray diffraction analysis of samples was conducted in the following manner. Samples for X-ray diffraction analysis were prepared by spreading the sample powder (with no prior grinding required) in a thin layer on the sample holder and gently flattening the sample with a microscope slide. A Nicolet 12/V X-ray Diffraction System was used with the following parameters: X-ray source: Cu-Kα1; Range: 2.00-40.00° Two Theta; Scan Rate: 1.00 degree/minute; Step Size: 0.02 degrees; Wavelength: 1.540562 angstroms.

Characteristic powder X-ray diffraction pattern peak positions are reported for polymorphs in terms of the angular positions (two theta) with an allowable variability of ± 0.1°. This allowable variability is specified by the U.S. Pharmacopeia, pages 1843-1844 (1995). The variability of ± 0.1° is intended to be used when comparing two powder X-ray diffraction patterns. In practice, if a

diffraction pattern peak from one pattern is assigned a range of angular positions (two theta) which is the measured peak position ± 0.1° and a diffraction pattern peak from the other pattern is assigned a range of angular positions (two theta) which is the measured peak position ± 0.1° and if those ranges of peak positions overlap, then the two peaks are considered to have the same angular position (two theta). For example, if a diffraction pattern peak from one pattern is determined to have a peak position of 5.20°, for comparison purposes the allowable variability allows the peak to be assigned a position in the range of 5.10° – 5.30°. If a comparison peak from the other diffraction pattern is determined to have a peak position of 5.35°, for comparison purposes the allowable variability allows the peak to be assigned a position in the range of 5.25° – 5.45°. Because there is overlap between the two ranges of peak positions (i.e., 5.10° - 5.30° and 5.25° – 5.45°) the two peaks being compared are considered to have the same angular position (two theta).

Solid state nuclear magnetic resonance analysis of samples was conducted in the following manner. A Bruker AMX-400 MHz instrument was used with the following parameters: CP- MAS (cross-polarized magic angle spinning); spectrometer frequency for ^{13}C was 100.627952576 MHz; pulse sequence was cp2lev; contact time was 2.5 milliseconds; temperature was 27.0 °C; spin rate was 7000 Hz; relaxation delay was 6.000 sec; 1st pulse width was 3.8 microseconds; 2nd pulse width was 8.6 microseconds; acquisition time was 0.034 seconds; sweep width was 30303.0 Hz; 2000 scans.

FT near infrared analysis of samples was conducted in the following manner. Samples were analyzed as neat, undiluted powders contained in a clear glass 1 dram vial. A Nicolet Magna System 750 FT-IR spectrometer with a Nicolet SabIR near infrared fiber optic probe accessory was used with the following parameters: the source was white light; the detector was PbS; the beamsplitter was CaF2; sample spacing was 1.0000; digitizer bits was 20; mirror

velocity was 0.3165; the aperture was 50.00; sample gain was 1.0; the high pass filter was 200.0000; the low pass filter was 11000.0000; the number of sample scans was 64; the collection length was 75.9 seconds; the resolution was 8.000; the number of scan points was 8480; the number of FFT points was 8192; the laser frequency was 15798.0 cm -1; the interferogram peak position was 4096; the apodization was Happ-Genzel; the number of background scans was 64 and the background gain was 1.0.

FT mid infrared analysis of samples was conducted in the following manner. Samples were analyzed as neat, undiluted powders. A Nicolet Magna System 750 FT-IR spectrometer with a Spectra-Tech InspectIR video microanalysis accessory and a Germanium attenuated total reflectance (Ge ATR) crystal was used with the following parameters: the source was infrared; the detector was MCT/A; the beamsplitter was KBr; sample spacing was 2.0000; digitizer bits was 20; mirror velocity was 1.8988; the aperture was 100.00; sample gain was 1.0; the high pass filter was 200.0000; the low pass filter was 20000.0000; the number of sample scans was 128; the collection length was 79.9 seconds; the resolution was 4.000; the number of scan points was 8480; the number of FFT points was 8192; the laser frequency was 15798.0 cm -1; the interferogram peak position was 4096; the apodization was triangular; the number of background scans was 128 and the background gain was 1.0.

Differential scanning calorimetric analysis of samples was conducted in the following manner. A T.A. Instruments Thermal Analyzer 3100 with Differential Scanning Calorimetry module 2910 was used, along with Modulated DSC software version 1.1A. The analysis parameters were: Sample weight: 2.28 mg, placed in a covered, uncrimped aluminum pan; Heating rate: room temperature to 150°C at 5°C/minute under a nitrogen purge.

The foregoing is merely illustrative of the invention and is not intended to limit the invention to the disclosed embodiments. Variations and changes which are obvious to one skilled in the art are intended to be within the scope and nature of the invention which are defined in the appended claims.

CLAIMS

What is claimed is:

1. The crystalline polymorph of (2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-amino-1,6-diphenyl-3-hydroxyhexane with characteristic peaks in the powder X-ray diffraction pattern at values of two theta of 8.67° ± 0.1°, 9.88° ± 0.1°, 16.11° ± 0.1°, 16.70° ± 0.1°, 17.36° ± 0.1°, 17.78° ± 0.1°, 18.40° ± 0.1°, 18.93° ± 0.1°, 20.07° ± 0.1°, 20.65° ± 0.1°, 21.71° ± 0.1°and 25.38° ± 0.1°.

2. The crystalline polymorph of Claim 1 with characteristic peaks in the powder X-ray diffraction pattern at values of two theta of 8.67° ± 0.1°, 9.51° ± 0.1°, 9.88° ± 0.1°, 10.97° ± 0.1°, 13.74° ± 0.1°, 16.11° ± 0.1°, 16.70° ± 0.1°, 17.36° ± 0.1°, 17.78° ± 0.1°, 18.40° ± 0.1°, 18.93° ± 0.1°, 19.52° ± 0.1°, 19.80° ± 0.1°, 20.07° ± 0.1°, 20.65° ± 0.1°, 21.49° ± 0.1°, 21.71° ± 0.1°, 22.23° ± 0.1°, 25.38° ± 0.1°, 26.15° ± 0.1° and 28.62° ± 0.1°.

3. The substantially pure crystalline polymorph of (2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-amino-1,6-diphenyl-3-hydroxyhexane with characteristic peaks in the powder X-ray diffraction pattern at values of two theta of 8.67° ± 0.1°, 9.88° ± 0.1°, 16.11° ± 0.1°, 16.70° ± 0.1°, 17.36° ± 0.1°, 17.78° ± 0.1°, 18.40° ± 0.1°, 18.93° ± 0.1°, 20.07° ± 0.1°, 20.65° ± 0.1°, 21.71° ± 0.1°and 25.38° ± 0.1°.

4. The substantially pure crystalline polymorph of Claim 3 with characteristic peaks in the powder X-ray diffraction pattern at values of two theta of 8.67° ± 0.1°, 9.51° ± 0.1°, 9.88° ± 0.1°, 10.97° ± 0.1°, 13.74° ± 0.1°, 16.11° ± 0.1°, 16.70° ± 0.1°, 17.36° ± 0.1°, 17.78° ± 0.1°, 18.40° ± 0.1°, 18.93° ± 0.1°, 19.52° ± 0.1°, 19.80° ± 0.1°, 20.07° ± 0.1°, 20.65° ± 0.1°, 21.49° ± 0.1°, 21.71° ± 0.1°, 22.23° ± 0.1°, 25.38° ± 0.1°, 26.15° ± 0.1° and 28.62° ± 0.1°.

5. Substantially pure amorphous ritonavir.

6. The substantially pure amorphous ritonavir of Claim 5 characterized by a glass transition from about 45°C to about 49°C.

7. A process for the preparation of the substantially pure crystalline polymorph of Claim 3 comprising contacting amorphous ritonavir with a C1-C3 alcohol.

8. The process of Claim 7 wherein a saturated solution of amorphous ritonavir in the C1-C3 alcohol is prepared.

9. The process of Claim 8 wherein amorphous ritonavir is dissolved by refluxing in the C1-C3 alcohol.

10. The process of Claim 8 wherein the alcohol is absolute ethanol.

11. A process for the preparation of the substantially pure amorphous ritonavir of Claim 5 comprising adding a solution of ritonavir in methylene chloride to hexane.

12. A process for the preparation of the substantially pure amorphous ritonavir of Claim 5 comprising adding a solution of ritonavir in methanol to water.

13. A process for the preparation of the substantially pure crystalline polymorph of Claim 3 comprising seeding a solution of ritonavir in a C1-C3 alcohol with seed crystals of (2S)-N-((1S)-1-Benzyl-2-((4S,5S)-4-benzyl-2-oxo-1,3-oxazolidin-5-yl)ethyl)-2-((((2-isopropyl-1,3-thiazol-4-yl)methyl)amino)-carbonyl)amino)-3-methylbutanamide.

14. The process of Claim 13 wherein the C1-C3 alcohol is ethanol.

15. A process for the preparation of the substantially pure crystalline polymorph of Claim 3 comprising seeding a solution of ritonavir in ethyl acetate with seed crystals of ritonavir Form II, followed by addition of heptane.

16. A process for the preparation of substantially pure ritonavir crystalline polymorph Form I comprising:

(a) dissolving ritonavir in ethyl acetate with heating at a concentration of about 1 kg of ritonavir/ 4 L of ethyl acetate; and
(b) adding the hot solution of ritonavir of step (b) to a slurry of seed crystals of ritonavir crystalline polymorph Form I in heptane; and
(c) cooling the resulting mixture to about 20°C.

17. The process of Claim 16 wherein the ratio of Form I seed crystals to starting ritonavir is from about 0.5% to about 10% w/w.

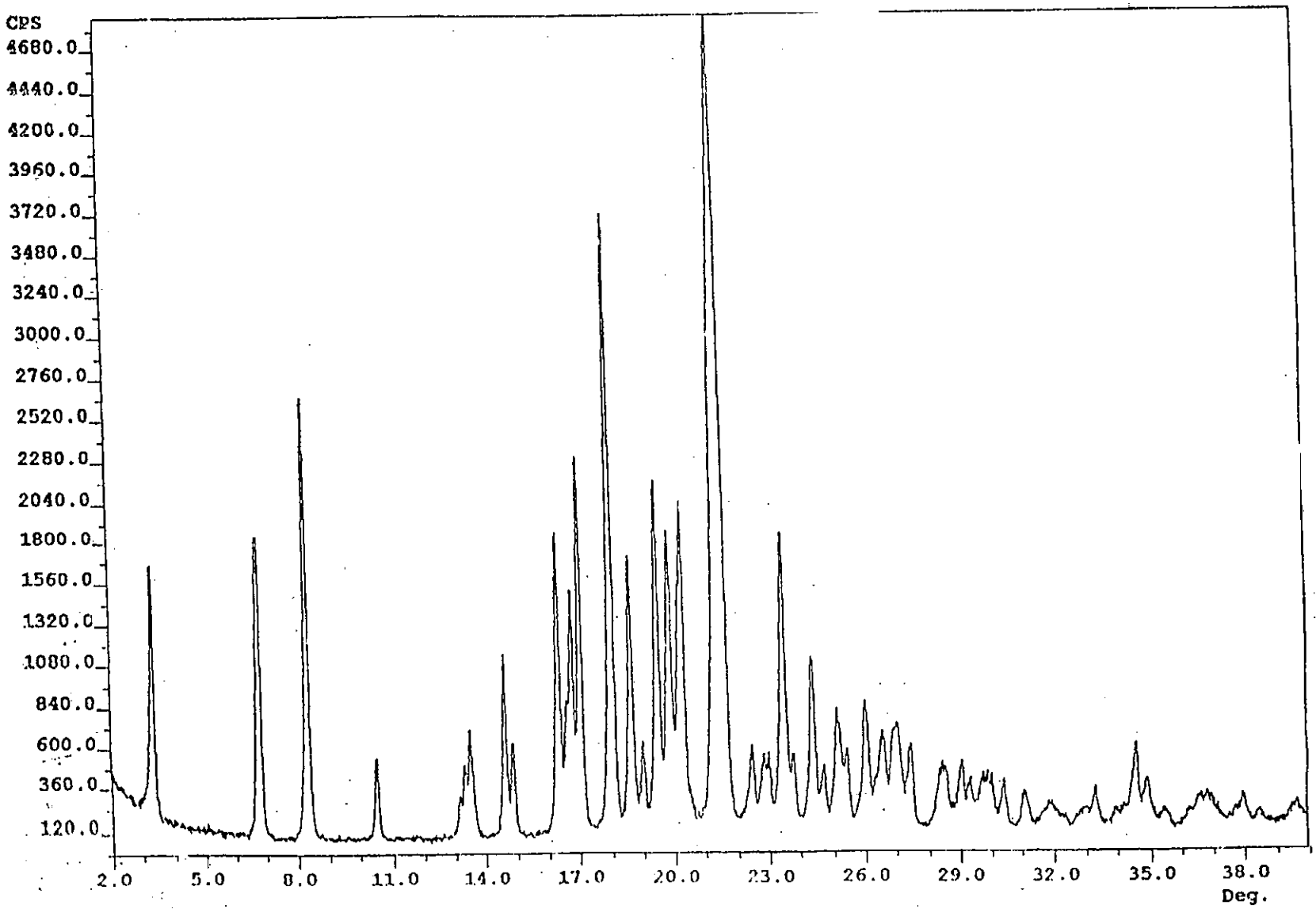
18. The process of Claim 16 wherein the ratio of Form I seed crystals to starting ritonavir is from about 0.5% to about 5% w/w.

19. The process of Claim 16 wherein the ratio of Form I seed crystals to starting ritonavir is from about 0.5% to about 1% w/w.

Polymorph of a Pharmaceutical

Abstract of the Invention

A new crystalline polymorph of ritonavir and methods for its use and preparation are disclosed.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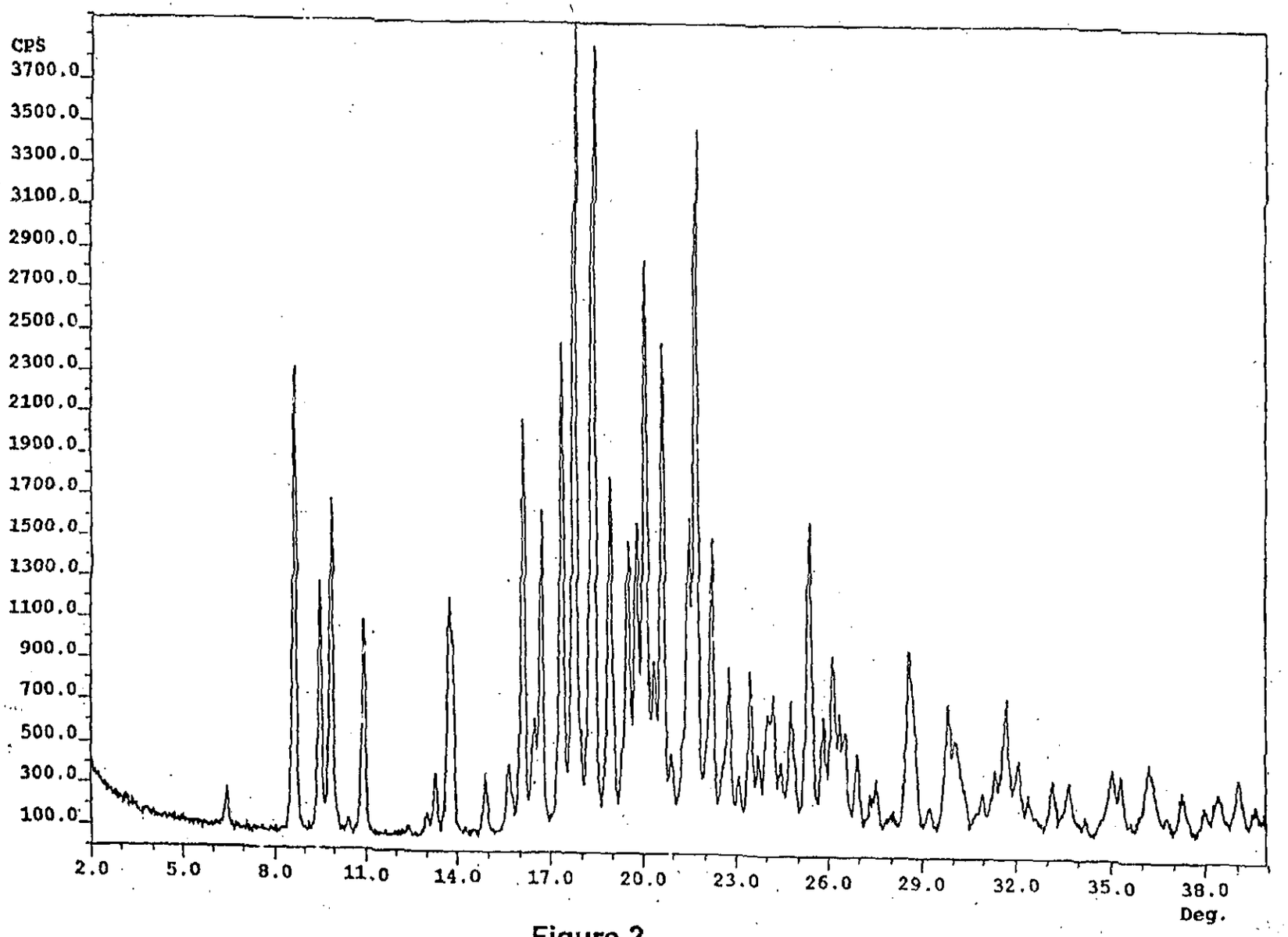
2520.0
2280.0
2040.0
1800.0
1560.0
1320.0
1080.0
840.0
600.0
360.0
120.0
2.0
5.0
8.0
11.0
14.0
17.0
20.0
23.0
26.0
29.0
32.0
35.0
38.0
Deg.

Figure 1


CPS
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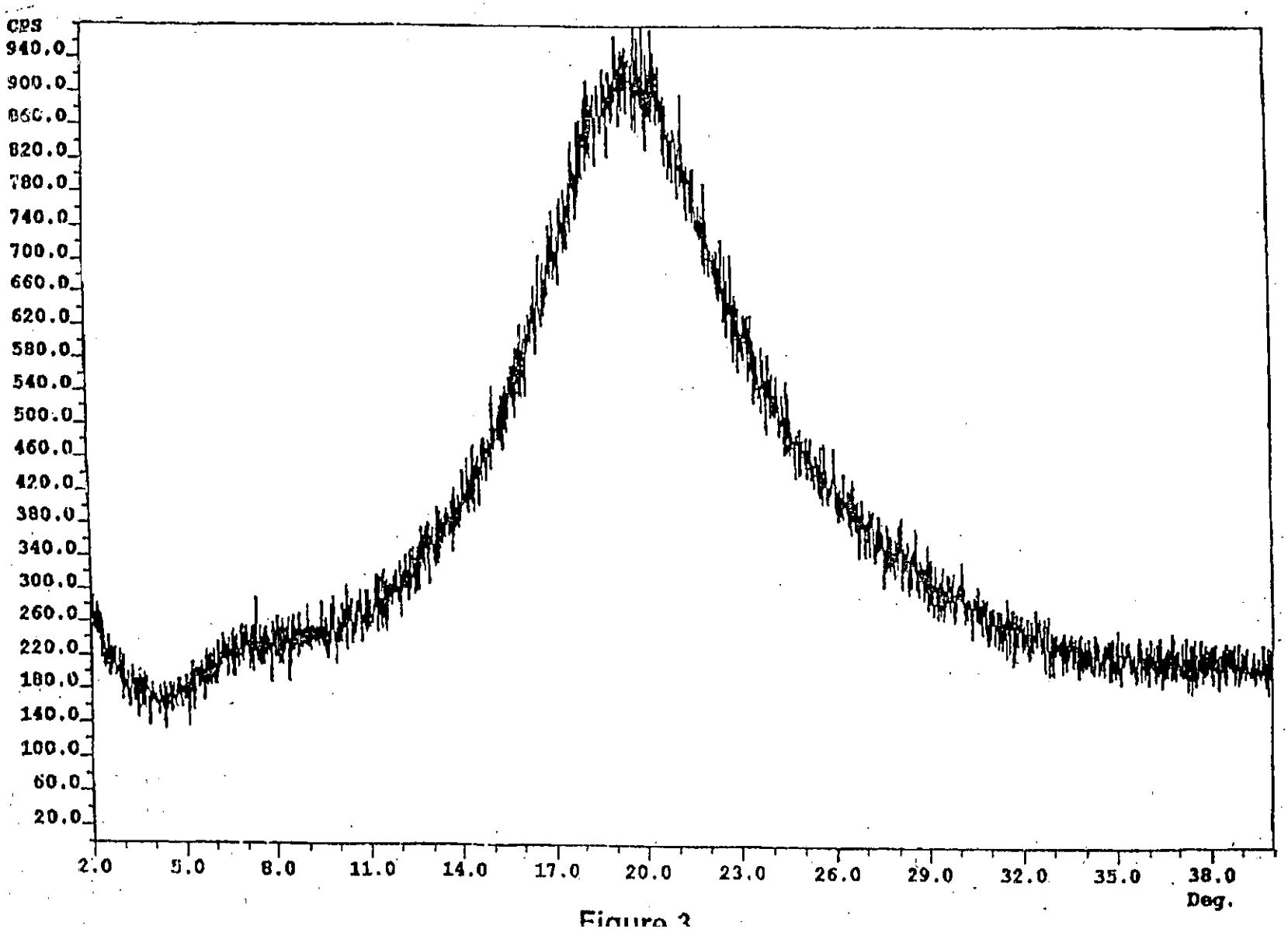
3500.0
3300.0
3100.0
2900.0
2700.0
2500.0
2300.0
2100.0
1900.0
1700.0
1500.0
1300.0
1100.0
900.0
700.0
500.0
300.0
100.0
2.0
5.0
8.0
11.0
14.0
17.0
20.0
23.0
26.0
29.0
32.0
35.0
38.0
Deg.

Figure 2


CPS
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900.0
860.0
820.0
780.0
740.0
700.0
660.0
620.0
580.0
540.0
500.0
460.0
420.0
380.0
340.0
300.0
260.0
220.0
180.0
140.0
100.0
60.0
20.0
2.0
5.0
8.0
11.0
14.0
17.0
20.0
23.0
26.0
29.0
32.0
35.0
38.0
Deg.

Figure 3

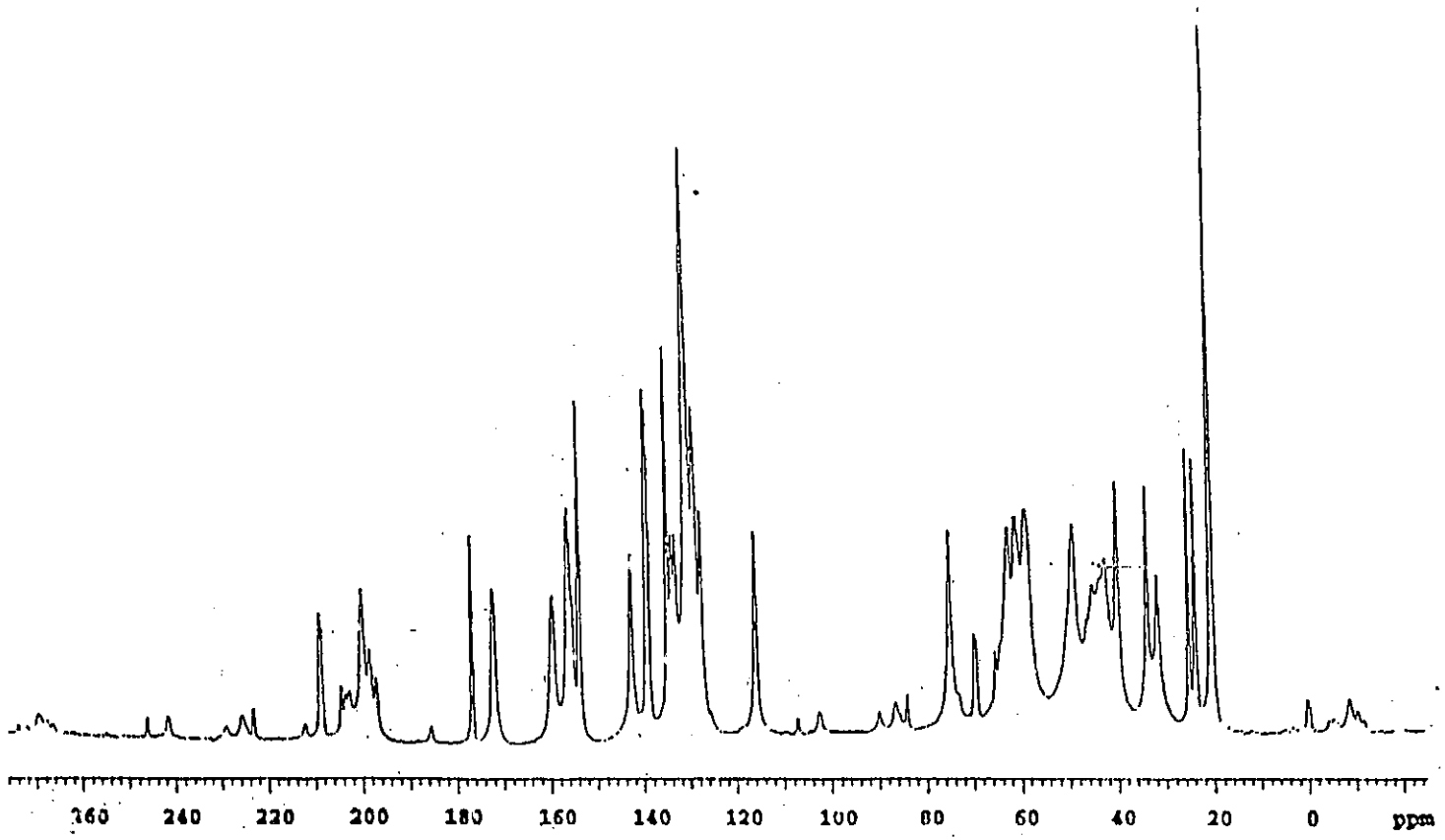


Figure 4

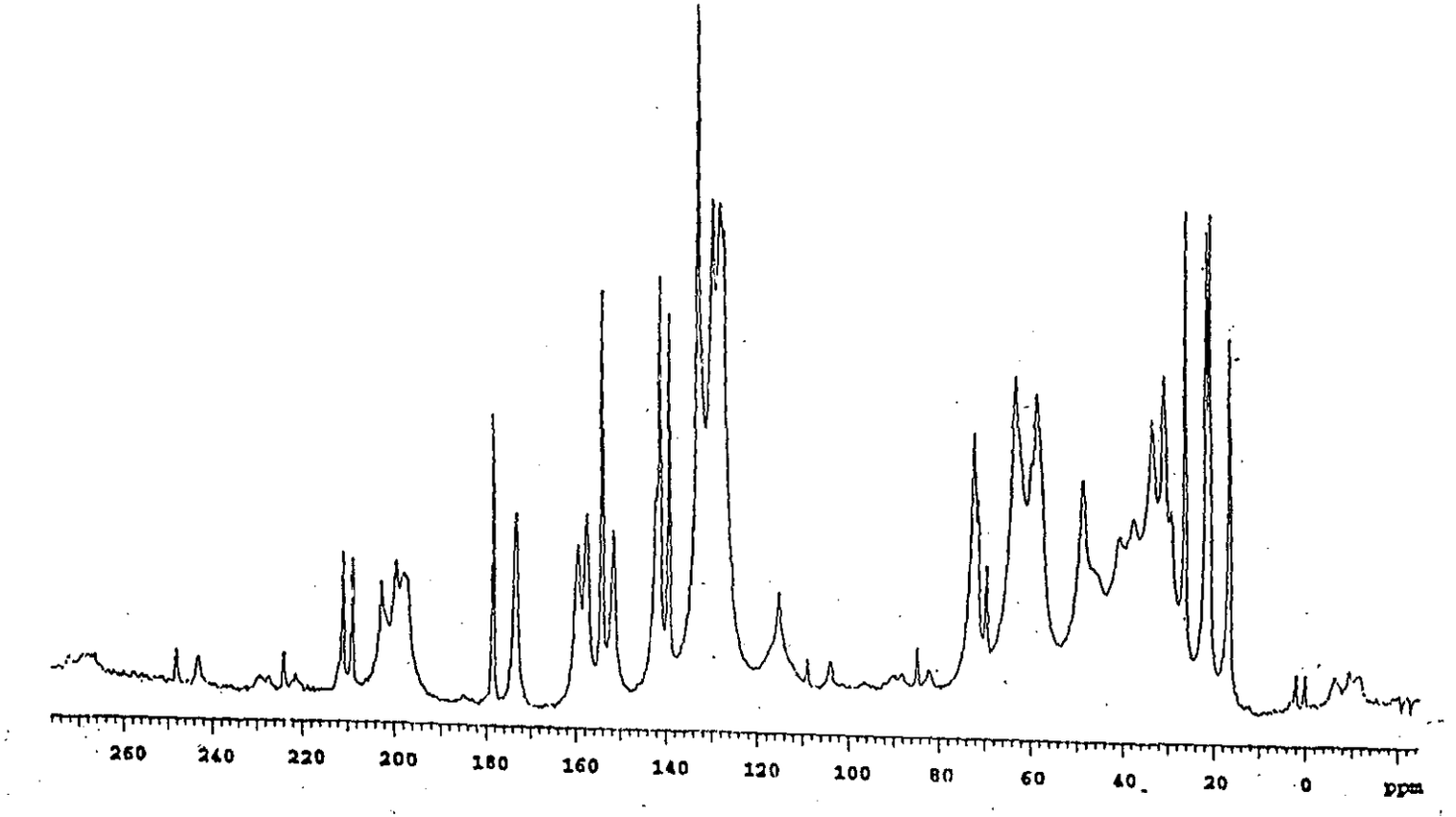


Figure 5

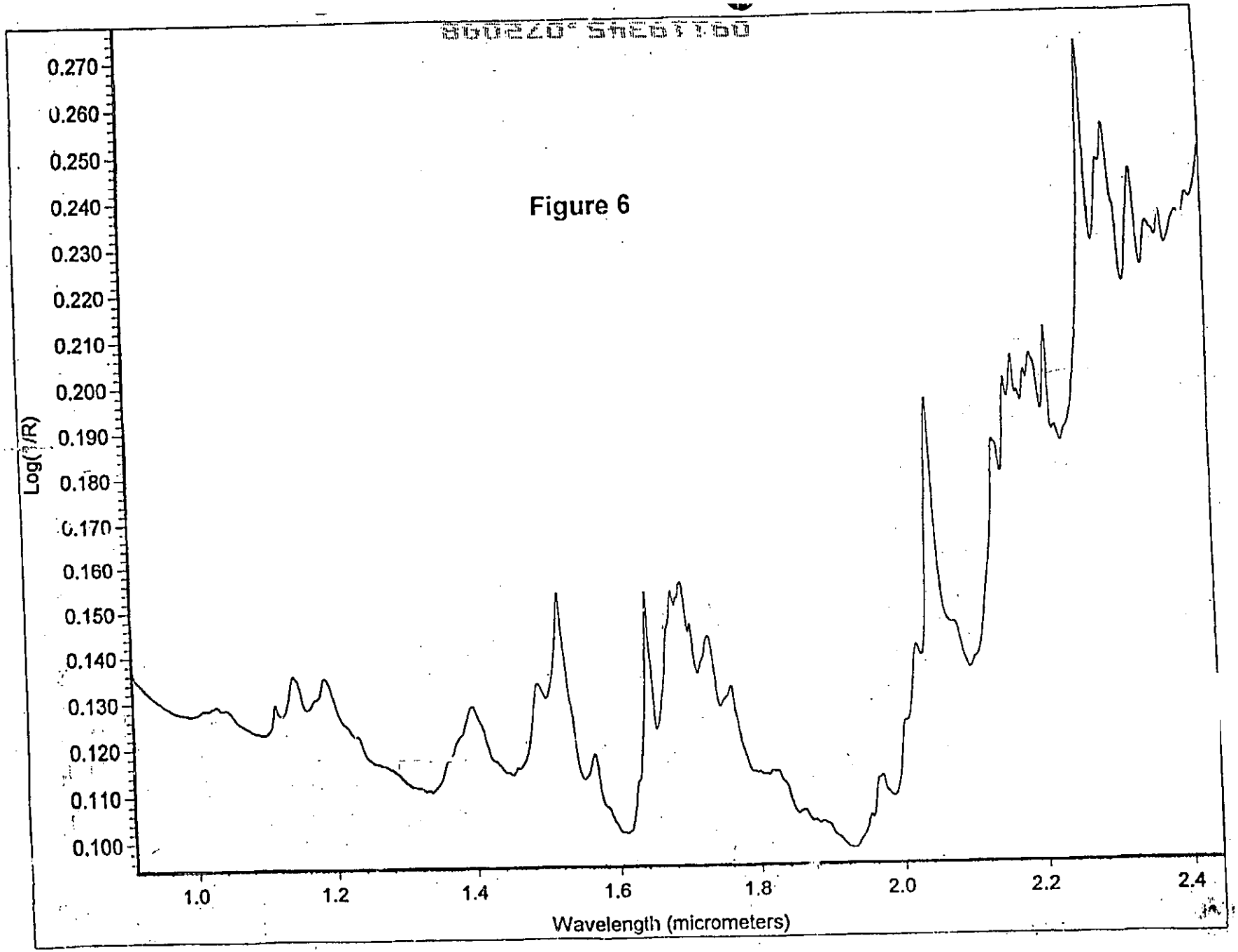

0.270
0.260
0.250
0.240
0.230
0.220
0.210
0.200
0.190
0.180
0.170
0.160
0.150
0.140
0.130
0.120
0.110
0.100
Log(1/R)
1.0
1.2
1.4
1.6
1.8
2.0
2.2
2.4
Wavelength (micrometers)

Figure 6

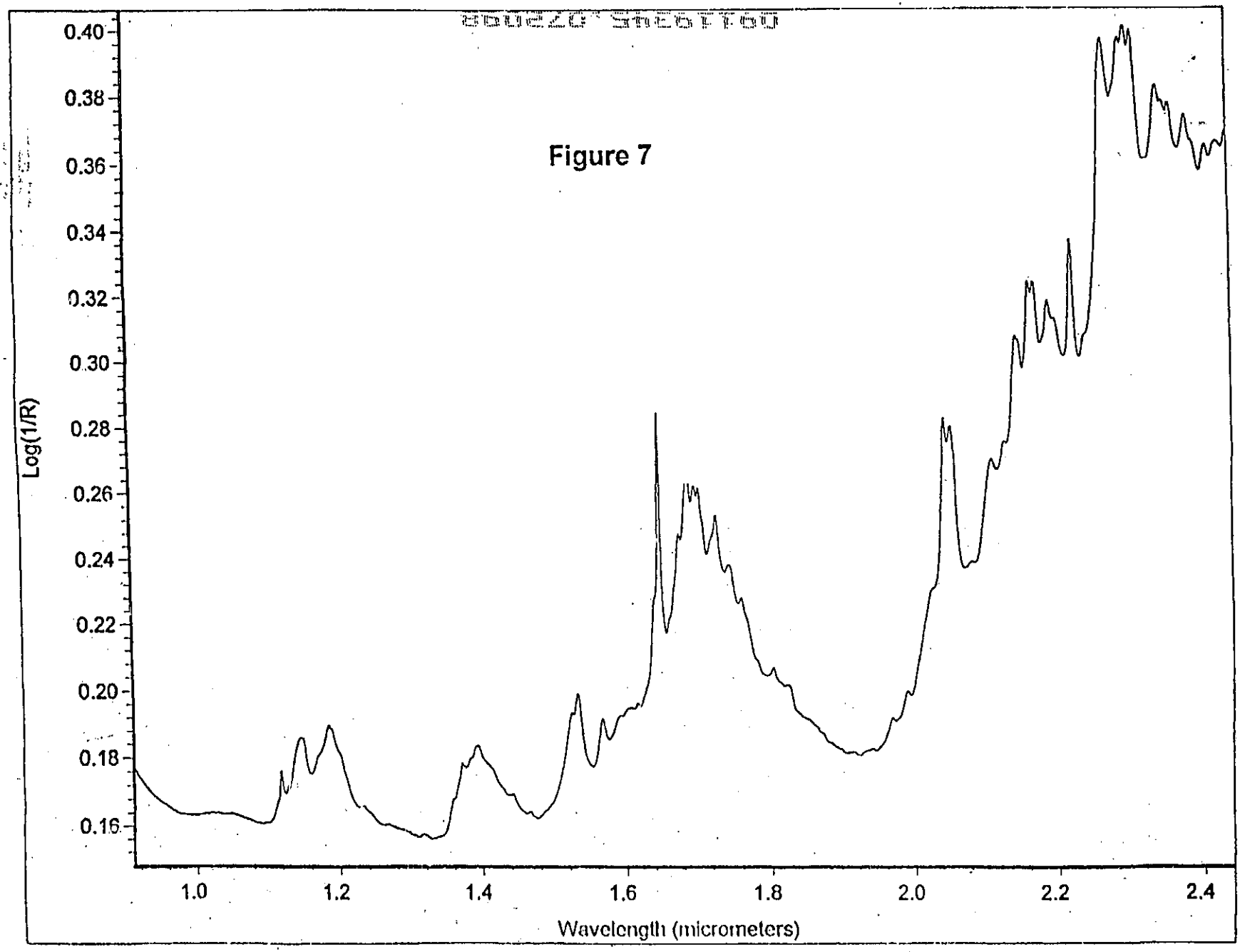

0.40
0.38
0.36
0.34
0.32
0.30
0.28
0.26
0.24
0.22
0.20
0.18
0.16
Log(1/R)
1.0
1.2
1.4
1.6
1.8
2.0
2.2
2.4
Wavelength (micrometers)

Figure 7

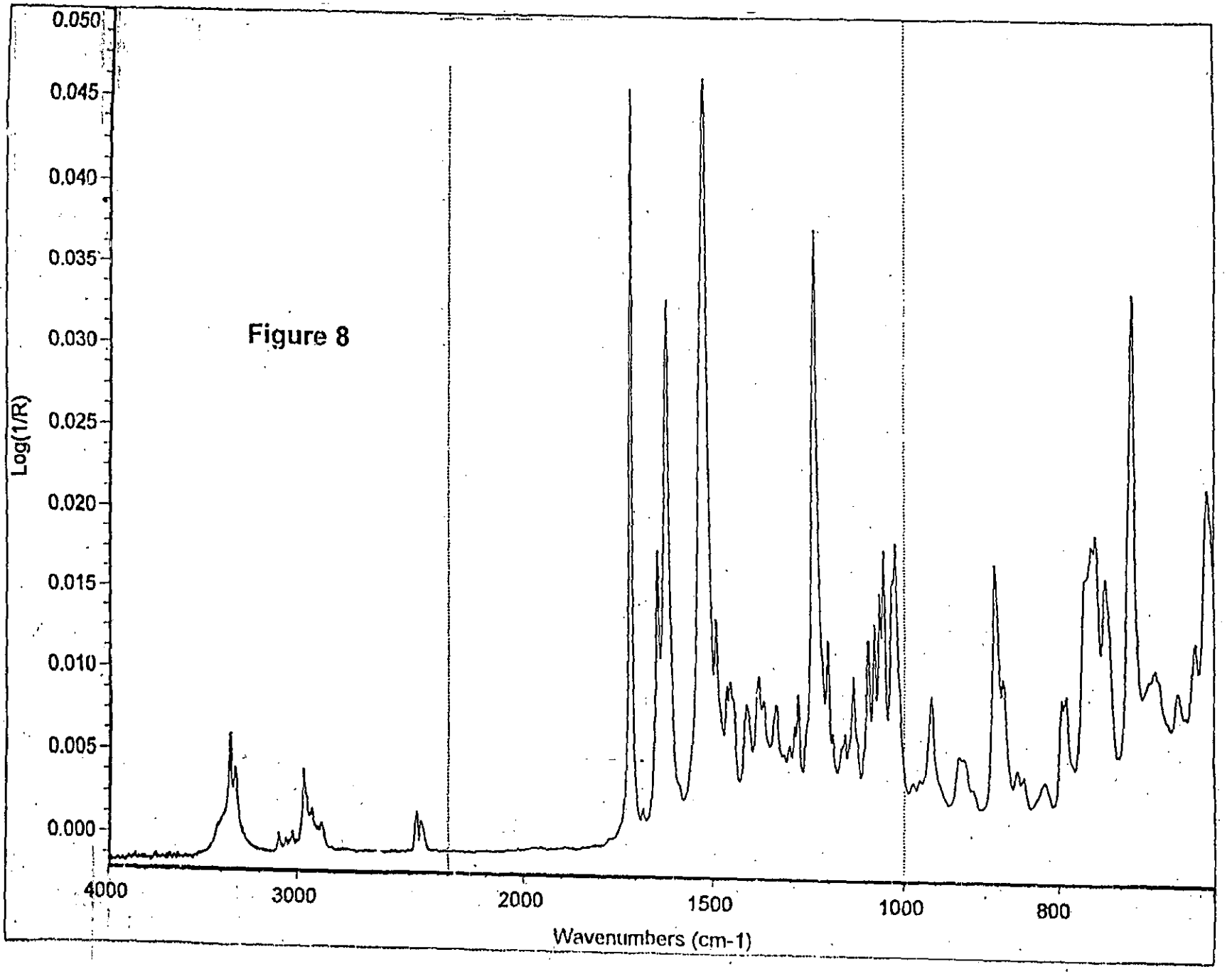

0.050
0.045
0.040
0.035
0.030
0.025
0.020
0.015
0.010
0.005
0.000
Log(1/R)
4000
3000
2000
1500
1000
800
Wavenumbers (cm-1)

Figure 8

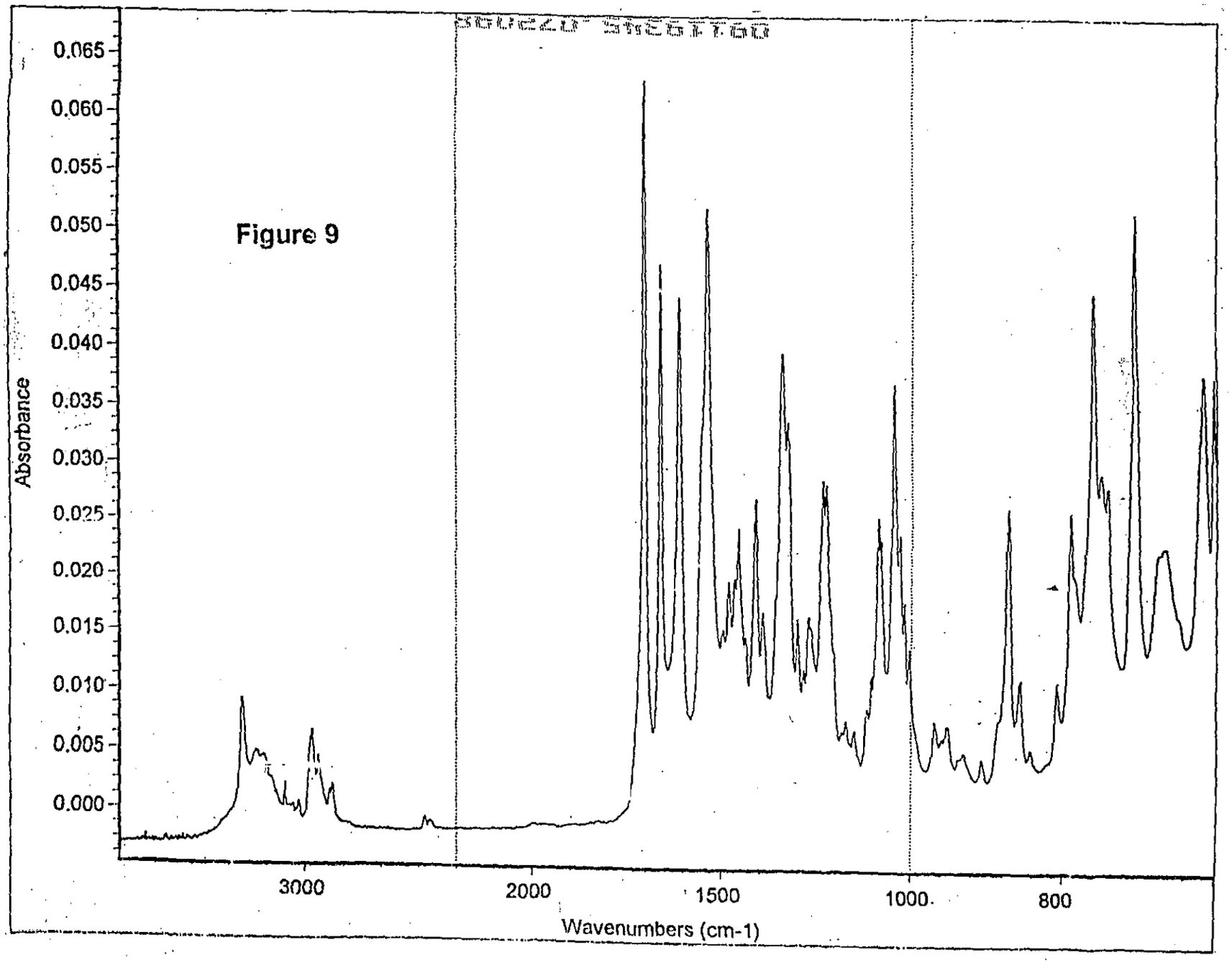
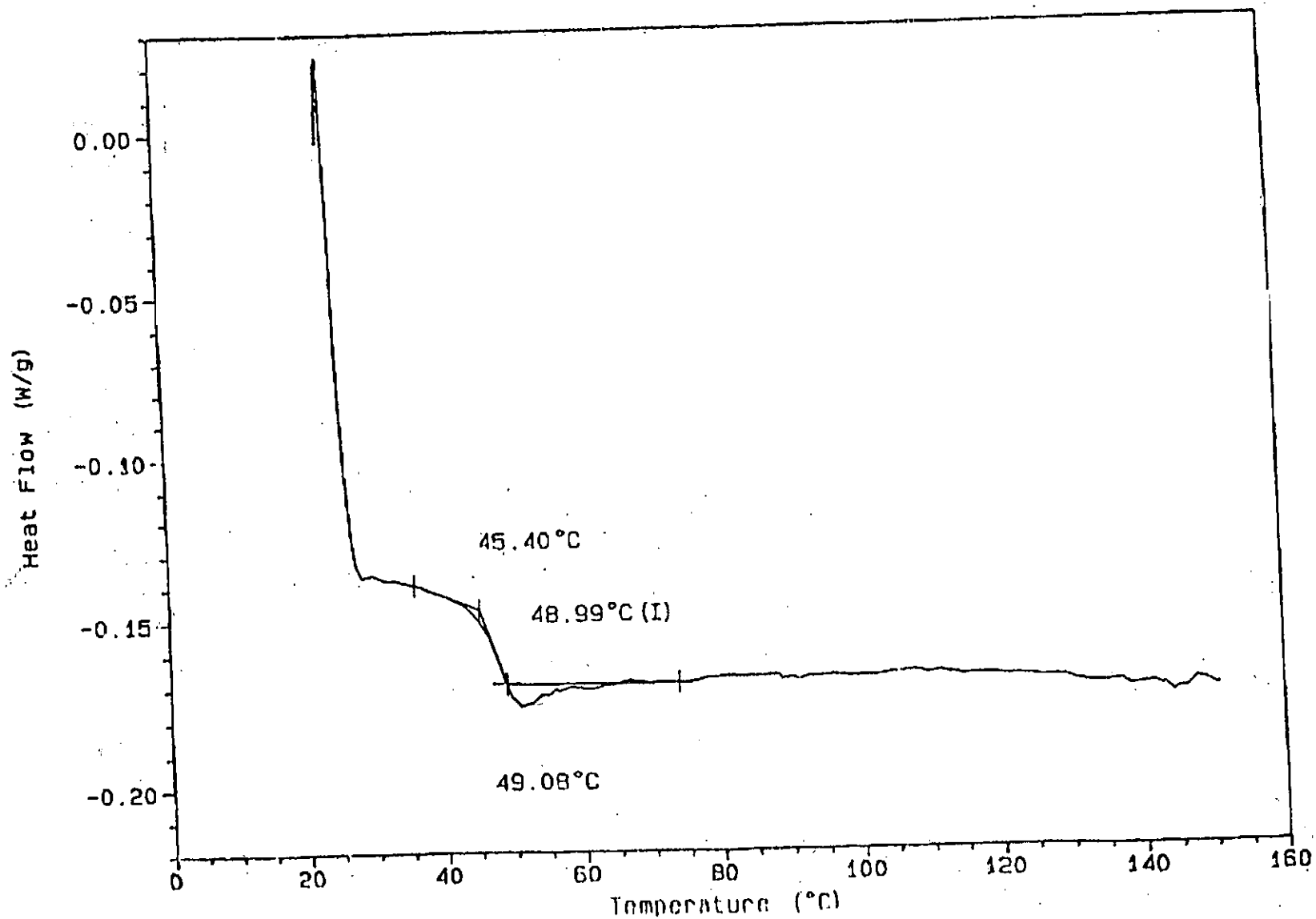


Figure 9
Absorbance
0.065
0.060
0.055
0.050
0.045
0.040
0.035
0.030
0.025
0.020
0.015
0.010
0.005
0.000
3000
2000
1500
1000
800
Wavenumbers (cm-1)

Figure 10


0.00
-0.05
-0.10
-0.15
-0.20
Heat Flow (W/g)
45.40°C
48.99°C (I)
49.08°C
0
20
40
60
80
100
120
140
160
Temperature (°C)

ANNEXURE-III

23 JUL 2008

Annexure-II

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : C07D 417/00 — A2

(11) International Publication Number: WO 00/04016

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(71) Applicant: ABBOTT LABORATORIES [US/US]; CHAD 0377/AP6D–2, 100 Abbott Park Road, Abbott Park, IL 60064–6050 (US).

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(74) Agents: CROWLEY, Steven, R. et al.; Abbott Laboratories, Chad 0377/AP6D–2, 100 Abbott Park Road, Abbott Park, IL 60064–6050 (US).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published

Without international search report and to be republished upon receipt of that report.

(54) Title: POLYMORPH OF A PHARMACEUTICAL

(57) Abstract

A new crystalline polymorph of ritonavir and methods for its use and preparation are disclosed.

ANNEXURE-IV

'23 JUL 2008

Annexure-IV Ritonavir 1st patent

PCT

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International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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A61K 31/425, 31/42, C07D 277/24, 275/02, 261/08, 263/32

A1

(11) International Publication Number: WO 94/14436

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(22) International Filing Date: 16 December 1993 (16.12.93)

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(81) Designated States: AU, CA, JP, KR, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

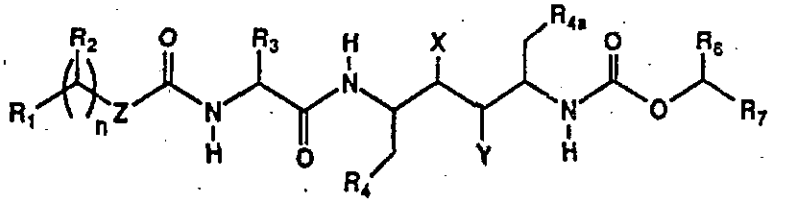
Published
With international search report.

(71) Applicant: ABBOTT LABORATORIES [US/US]; CHAD 0377/AP6D-2, One Abbott Park Road, Abbott Park, IL 60064-3500 (US).

(72) Inventors: KEMPF, Dale, J.; 256 Tyler, Libertyville, IL 60048 (US). NORBECK, Daniel, W.; 2810 Federal Court, Crystal Lake, IL 60012 (US). SHAM, Hing, Leung; 5109 Pembrook Court, Gurnee, IL 60031 (US). ZHAO, Chen; 5241 Conifer Lane, Gurnee, IL 60031 (US). SOWIN, Thomas, J.; 17502 West Huntington Circle, Grayslake, IL 60030 (US). RENO, Daniel, S.; 4318 25th Street, Kenosha, WI 53144 (US). HAIGHT, Anthony, R.; 4252 Greenleaf Ct., Apartment 111, Park City, IL 60085 (US). COOPER, Arthur, J.; 65 Wesley Avenue, Lake Villa, IL 60046 (US).

(74) Agents: GORMAN, Edward, H., Jr. et al.; Abbott Laboratories, CHAD 0377/AP6D-2, One Abbott Park Road, Abbott Park, IL 60064-3500 (US).

(54) Title: RETROVIRAL PROTEASE INHIBITING COMPOUNDS



(A)

(57) Abstract

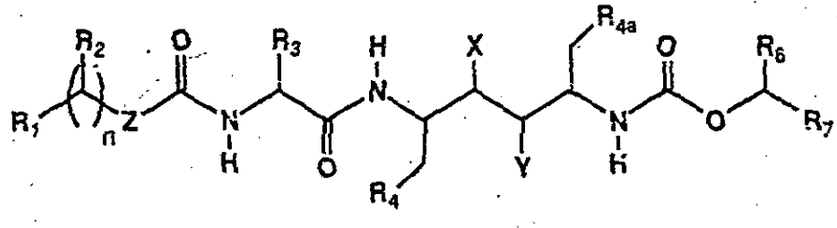
A retroviral protease inhibiting compound of formula (A) is disclosed.

9. (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-oxazolyl)methyl)-amino)-carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane; or a pharmaceutically acceptable salt, ester or prodrug thereof.

10. A compound selected from the group consisting of:
(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)-amino)carbonyl)alaninyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;
(2S,3S,5S)-5-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;
(2S,3S,5S)-2-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)valinyl)amino)-5-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;
(2S,3S,5S)-5-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)alaninyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;
(2S,3S,5S)-5-(N-(N-((2-(N,N-Dimethylamino)-4-thiazolyl)methoxycarbonyl)-valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;
(2S,3S,5S)-2-(N-(N-((2-(N,N-Dimethylamino)-4-thiazolyl)methoxycarbonyl)-valinyl)amino)-5-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;
(2S,3S,5S)-5-(N-(N-((2-(4-Morpholinyl)-4-thiazolyl)methoxycarbonyl)-valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;
(2S,3S,5S)-2-(N-(N-((2-(4-Morpholinyl)-4-thiazolyl)-methoxycarbonyl)valinyl)-amino)-5-(N-((5-thiazolyl)-methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;
(2S,3S,5S)-5-(N-(N-((2-(1-Pyrrolidinyl)-4-thiazolyl)methoxycarbonyl)-valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

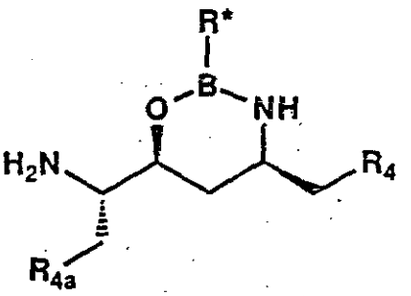
(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;
(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;
(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane; and
(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane; or a pharmaceutically acceptable salt, ester or prodrug thereof.

11. A compound of the formula:



wherein R_1 is monosubstituted thiazolyl, monosubstituted oxazolyl, monosubstituted isoxazolyl or monosubstituted isothiazolyl wherein the substituent is selected from (i) loweralkyl, (ii) loweralkenyl, (iii) cycloalkyl, (iv) cycloalkylalkyl, (v) cycloalkenyl, (vi)cycloalkenylalkyl, (vii) heterocyclic wherein the heterocyclic is selected from aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, pyridinyl, pyrimidinyl, pyridazinyl and pyrazinyl and wherein the heterocyclic is unsubstituted or substituted with a substituent selected from halo, loweralkyl, hydroxy, alkoxy and thioalkoxy, (viii) (heterocyclic)alkyl wherein heterocyclic is defined as above, (ix) alkoxyalkyl, (x) thioalkoxyalkyl, (xi) alkylamino, (xii) dialkylamino, (xiii) phenyl wherein the phenyl ring is unsubstituted or substituted with a substituent selected

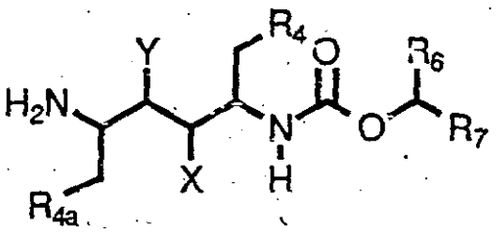
17. A compound of the formula:



wherein R_4 and R_{4a} are independently selected from phenyl, thiazolyl and oxazolyl wherein the phenyl, thiazolyl or oxazolyl ring is unsubstituted or substituted with a substituent selected from
(i) halo, (ii) loweralkyl, (iii) hydroxy, (iv) alkoxy and (v) thioalkoxy; and
R* is loweralkyl, phenyl, halo-substituted phenyl, dihalo-substituted phenyl, alkoxy-substituted phenyl, loweralkyl-substituted phenyl, bis-trifluormethyl-substituted phenyl or naphthyl; or an acid addition salt thereof.

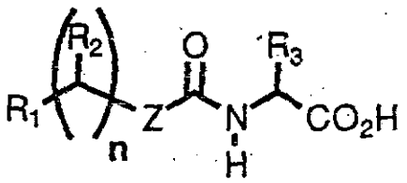
18. The compound of Claim 17 R_4 and R_{4a} are phenyl and R* is phenyl.

19. A process for the preparation of a compound of any one of Claims 1-11 comprising (a) reacting a compound of the formula:

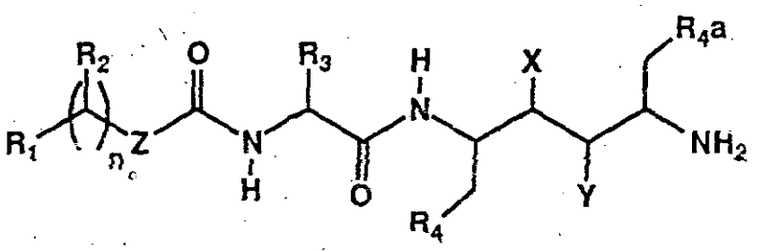


wherein R_4, R_{4a}, R_6, R_7, X and Y are as defined therein with a compound of the formula:

cycloalkylalkyl, (v) cycloalkenyl, (vi)cycloalkenylalkyl, (vii) heterocyclic wherein the heterocyclic is selected from aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, pyridinyl, pyrimidinyl, pyridazinyl and pyrazinyl and wherein the heterocyclic is unsubstituted or substituted with a substituent selected from halo, loweralkyl, hydroxy, alkoxy and thioalkoxy, (viii) (heterocyclic)alkyl wherein heterocyclic is defined as above, (ix) alkoxyalkyl, (x) thioalkoxyalkyl, (xi) alkylamino, (xii) dialkylamino, (xiii) phenyl wherein the phenyl ring is unsubstituted or substituted with a substituent selected from halo, loweralkyl, hydroxy, alkoxy and thioalkoxy, (xiv) phenylalkyl wherein the phenyl ring is unsubstituted or substituted as defined above, (xv) dialkylaminoalkyl, (xvi) alkoxy and (xvii) thioalkoxy; n is 1 ; R2 is hydrogen; R4 is phenyl; R5 is hydrogen; R is hydrogen and R7 is 5- thiazolyl, 5-oxazolyl, 5-isothiazolyl or 5-isoxazolyl. 5. The compound of Claim 2 wherein Ri is 2-monosubstituted-4- thiazolyl or 2-monosubstituted-4-oxazolyl wherein the substituent is loweralkyl; n is 1 ; R2 is hydrogen; R4 is phenyl; R5 is hydrogen; Re is hydrogen; R7 is 5-thiazolyl, 5-oxazolyl, 5-isothiazolyl or 5-isoxazolyl; and Z is -O- or -N(Rβ)- wherein Re is loweralkyl. 6. The compound of Claim 2 wherein Ri is 2-monosubstituted-4- thiazolyl or 2-monosubstituted-4-oxazolyl wherein the substituent is ethyl or isopropyl; n is 1 ; R2 is hydrogen; R3 is methyl or isopropyl; R4 is phenyl; R5 is hydrogen; Re is hydrogen; R7 is 5-thiazolyl, 5-oxazolyl, 5-isothiazolyl or 5- isoxazolyl; and Z is -0-. 7. The compound of Claim 2 wherein Ri is 2-monosubstituted-4- thiazolyl or 2-monosubstituted-4-oxazolyl wherein the substituent is ethyl or isopropyl; n is 1 ; R2 is hydrogen; R3 is isopropyl; R4 is phenyl; R5 is hydrogen; R is hydrogen; R7 is 5-thiazolyl, 5-oxazolyl, 5-isothiazolyl or 5-isoxazolyl; Z is -N(Rs)- wherein Rs is methyl; X is hydrogen and Y is -OH. 8. (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)- amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)- 1 ,6-diphenyl-3-hydroxyhexane; or a pharmaceutically acceptable salt, ester or prodrug thereof. 9. (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-oxazolyl)methyl)- amino)-carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)- 1 ,6-diphenyl-3-hydroxyhexane; or a pharmaceutically acceptable salt, ester or prodrug thereof. 10. A compound selected from the group consisting of: (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)- amino)carbonyl)alaninyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)- 1 ,6-diphenyl-3-hydroxyhexane; (2S,3S,5S)-5-(N-(N-((2-Isopropyl-4- thiazolyl) methoxycarbonyl)valinyl)amino)-2-(N-((5- thiazolyl)methoxycarbonyl)amino)-1 ,6-diphenyl-3-hydroxyhexane; (2S,3S,5S)-2-(N-(N-((2-Isopropyl-4- thiazolyl)methoxycarbonyl)valinyl)amino)-5-(N-((5- thiazolyl)methoxycarbonyl)amino)-1 ,6-diphenyl-3-hydroxyhexane; (2S,3S,5S)-5-(N-(N-((2-Isopropyl-4- thiazolyl)methoxycarbonyl)alaninyl)amino)-2-(N-((5- thiazolyl) methoxycarbonyl)amino)-1 ,6-diphenyl-3-hydroxyhexane; (2S,3S,5S)-5-(N-(N-((2-(N,N-Dimethylamino)-4-thiazolyl) methoxycarbonyl)- valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1 ,6-diphenyl-3- hydroxyhexane; (2S,3S,5S)-2-(N-(N-((2-(N,N-Dimethylamino)-4-thiazolyl)methoxycarbonyl)- valinyl)amino)-5-(N-((5-thiazolyl)methoxycarbonyl)amino)-1 ,6-diphenyl-3- hydroxyhexane; (2S,3S,5S)-5-(N-(N-((2-(4-Morpholinyl)-4-thiazolyl)methoxycarbonyl)- valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1 ,6-diphenyl-3- hydroxyhexane; (2S,3S,5S)-2-(N-(N-((2-(4-Morpholinyl)-4-thiazolyl)-methoxycarbonyl)valinyl)amino)-5-(N-((5-thiazolyl)- methoxycarbonyl)amino)-1 ,6-diphenyl-3-hydroxyhexane; (2S,3S,5S)-5-(N-(N-((2-(1-Pyrrolidinyl)-4-thiazolyl)methoxycarbonyl)- valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1 ,6-diphenyl-3- hydroxyhexane; (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)- carbonyl)valinyl) amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1 ,6- diphenyl-3-hydroxyhexane; (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)- carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1 ,6- diphenyl-3-hydroxyhexane; (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)- carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1 ,6- diphenyl-3-hydroxyhexane; and (2S,3S,5S)-5-(N-(N-((N-Methy -N-((2-isopropyl-4-oxazolyl)methyl)amino)- carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1 6- diphenyl-3-hydroxyhexane; or a pharmaceutically acceptable salt, ester or prodrug thereof. 11. A compound of the formula: wherein Ri is monosubstituted thiazolyl, monosubstituted oxazolyl, monosubstituted isoxazolyl or monosubstituted isothiazolyl wherein the substituent is selected from (i) loweralkyl, (ii) loweralkenyl, (iii) cycloalkyl, (iv) cycloalkylalkyl, (v) cycloalkenyl, (vi)cycloalkenylalkyl, (vii) heterocyclic wherein the heterocyclic is selected from aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, pyridinyl, pyrimidinyl, pyridazinyl and pyrazinyl and wherein the heterocyclic is unsubstituted or substituted with a substituent selected from halo, loweralkyl, hydroxy, alkoxy and thioalkoxy, (viii) (heterocyclic)alkyl wherein heterocyclic is defined as above, (ix) alkoxyalkyl, (x) thioalkoxyalkyl, (xi) alkylamino, (xii) dialkylamino, (xiii) phenyl wherein the phenyl ring is unsubstituted or substituted with a substituent selected from halo, loweralkyl, hydroxy, alkoxy and thioalkoxy, (xiv) phenylalkyl wherein the phenyl ring is unsubstituted or substituted as defined above, (xv) dialkylaminoalkyl, (xvi) alkoxy and (xvii) thioalkoxy; n is 1 , 2 or 3; R2 is hydrogen or loweralkyl; R3 is loweralkyl; R4 and R_{4a} are independently selected from phenyl, thiazolyl and oxazolyl wherein the phenyl, thiazolyl or oxazolyl ring is unsubstituted or substituted with a substituent selected from (i) halo, (ii) loweralkyl, (iii) hydroxy, (iv) alkoxy and (v) thioalkoxy; Rβ is hydrogen or loweralkyl; R7 is thiazolyl, oxazolyl, isoxazolyl or isothiazolyl wherein the thiazolyl, oxazolyl, isoxazolyl or isothiazolyl ring is unsubstituted or substituted with loweralkyl; X is -OH and Y is -OH; and Z is absent, -0-, -S-, -CH2- or -N(Rs)- wherein Rs is loweralkyl, cycloalkyl, -OH or -NHR_{8a} wherein R_{8a} is hydrogen, loweralkyl or an N-protecting group; or a pharmaceutically acceptable salt, ester or prodrug thereof. 12. A method for inhibiting HIV protease comprising administering to a human in need thereof a therapeutically effective amount of a compound of any one of Claims 1-11. 13. A method for inhibiting HIV comprising

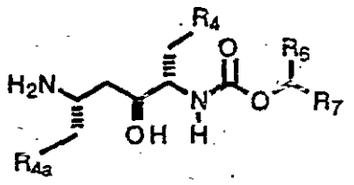


or an activated ester derviative thereof, wherein n, R_1, R_2, Z and R_3 are as defined therein; or (b) acylating a compound of the formula:



wherein n, R_1, R_2, R_3, R_4, R_{4a}, X and Y are as defined therein with a compound of the formula $(R_6)(R_7)CHOC(O)OL$ wherein L is an activating group for the acylation reaction and wherein R_6 is and R_7 are defined as therein.

20. A process for the preparation of a compound of the formula:



wherein R_4 and R_{4a} are independently selected from phenyl, thiazolyl and oxazolyl wherein the phenyl, thiazolyl or oxazolyl ring is unsubstituted or substituted with a substituent selected from
(i) halo, (ii) loweralkyl, (iii) hydroxy, (iv) alkoxy and (v) thioalkoxy;

R_6 is hydrogen or loweralkyl; and

WO/98/057648

Search result: 1 of 1

(WO/1994/014436) RETROVIRAL PROTEASE INHIBITING COMPOUNDS

Biblio. Data | Description | Claims | National Phase | Notices | Documents

Note: OCR Text

WO 1994014436 19940707 CLAIMS What is claimed is: 1. A compound of the formula: wherein Ri is monosubstituted thiazolyl, monosubstituted oxazolyl, monosubstituted isoxazolyl or monosubstituted isothiazolyl wherein the substituent is selected from (i) loweralkyl, (ii) loweralkenyl, (iii) cycloalkyl, (iv) cycloalkylalkyl, (v) cycloalkenyl, (vi) cycloalkenylalkyl, (vii) heterocyclic wherein the heterocyclic is selected from aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, pyridinyl, pyrimidinyl, pyridazinyl and pyrazinyl and wherein the heterocyclic is unsubstituted or substituted with a substituent selected from halo, loweralkyl, hydroxy, alkoxy and thioalkoxy, (viii) (heterocyclic)alkyl wherein heterocyclic is defined as above, (ix) alkoxyalkyl, (x) thioalkoxyalkyl, (xi) alkylamino, (xii) dialkylamino, (xiii) phenyl wherein the phenyl ring is unsubstituted or substituted with a substituent selected from halo, loweralkyl, hydroxy, alkoxy and thioalkoxy, (xiv) phenylalkyl wherein the phenyl ring is unsubstituted or substituted as defined above, (xv) dialkylaminoalkyi, (xvi) alkoxy and (xvii) thioalkoxy; n is 1 , 2 or 3; R2 is hydrogen or loweralkyl; R3 is loweralkyl; R4 and R_{4a} are independently selected from phenyl, thiazolyl and oxazolyl wherein the phenyl, thiazolyl or oxazolyl ring is unsubstituted or substituted with a substituent selected from (i) halo, (ii) loweralkyl, (iii) hydroxy, (iv) alkoxy and (v) thioalkoxy; Re is hydrogen or loweralkyl; R7 is thiazolyl, oxazolyl, isoxazolyl or isothiazolyl wherein the thiazolyl, oxazolyl, isoxazolyl or isothiazolyl ring is unsubstituted or substituted with loweralkyl; X is hydrogen and Y is -OH or X is -OH and Y is hydrogen, with the proviso that X is hydrogen and Y is -OH when Z is -N(Rβ)- and R7 is unsubstituted and with the proviso that X is hydrogen and Y is -OH when R3 is methyl and R7 is unsubstituted; and Z is absent, -0-, -S-, -CH2- or -N(Rs)- wherein Re is loweralkyl, cycloalkyl, -OH or -NHR_{8a} wherein R_{8a} is hydrogen, loweralkyl or an N-protecting group; or a pharmaceutically acceptable salt, ester or prodrug thereof. 2. A compound of the formula: wherein Ri is monosubstituted thiazolyl, monosubstituted oxazolyl, monosubstituted isoxazolyl or monosubstituted isothiazolyl wherein the substituent is selected from (i) loweralkyl, (ii) loweralkenyl, (iii) cycloalkyl, (iv) cycloalkylalkyl, (v) cycloalkenyl, (vi)cycloalkenylalkyl, (vii) heterocyclic wherein the heterocyclic is selected from aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, pyridinyl, pyrimidinyl, pyridazinyl and pyrazinyl and wherein the heterocyclic is unsubstituted or substituted with a substituent selected from halo, loweralkyl, hydroxy, alkoxy and thioalkoxy, (viii) (heterocyclic)alkyl wherein heterocyclic is defined as above, (ix) alkoxyalkyl, (x) thioalkoxyalkyl, (xi) alkylamino, (xii) dialkylamino, (xiii) phenyl wherein the phenyl ring is unsubstituted or substituted with a substituent selected from halo, loweralkyl, hydroxy, alkoxy and thioalkoxy, (xiv) phenylalkyl wherein the phenyl ring is unsubstituted or substituted as defined above, (xv) dialkylaminoalkyl, (xvi) alkoxy and (xvii) thioalkoxy; n is 1 , 2 or 3; R2 is hydrogen or loweralkyl; R3 is loweralkyl; R4 is phenyl, thiazolyl or oxazolyl wherein the phenyl, thiazolyl or oxazolyl ring is unsubstituted or substituted with a substituent selected from (i) halo, (ii) loweralkyl, (iii) hydroxy, (iv) alkoxy and (v) thioalkoxy; R5 is hydrogen, halo, loweralkyl, hydroxy, alkoxy or thioalkoxy; Rβ is hydrogen or loweralkyl; R7 is thiazolyl, oxazolyl, isoxazolyl or isothiazolyl wherein the thiazolyl, oxazolyl, isoxazolyl or isothiazolyl ring is unsubstituted or substituted with loweralkyl; X is hydrogen and Y is -OH or X is -OH and Y is hydrogen, with the proviso that X is hydrogen and Y is -OH when Z is -N(Rβ)- and R7 is unsubstituted and with the proviso that X is hydrogen and Y is -OH when R3 is methyl and R7 is unsubstituted; Z is absent, -0-, -S-, -CH2- or -N(Rs)- wherein Re is loweralkyl, cycloalkyl, -OH or -NHR_{8a} wherein R_{8a} is hydrogen, loweralkyl or an N-protecting group; or a pharmaceutically acceptable salt, ester or prodrug thereof. 3. The compound of Claim 2 wherein Ri is monosubstituted thiazolyl or monosubstituted oxazolyl wherein the substituent is selected from (i) loweralkyl, (ii) loweralkenyl, (iii) cycloalkyl, (iv) cycloalkylalkyl, (v) cycloalkenyl, (vi)cycloalkenylalkyl, (vii) heterocyclic wherein the heterocyclic is selected from aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, pyridinyl, pyrimidinyl, pyridazinyl and pyrazinyl and wherein the heterocyclic is unsubstituted or substituted with a substituent selected from halo, loweralkyl, hydroxy, alkoxy and thioalkoxy, (viii) (heterocyclic)alkyl wherein heterocyclic is defined as above, (ix) alkoxyalkyl, (x) thioalkoxyalkyl, (xi) alkylamino, (xii) dialkylamino, (xiii) phenyl wherein the phenyl ring is unsubstituted or substituted with a substituent selected from halo, loweralkyl, hydroxy, alkoxy and thioalkoxy, (xiv) phenylalkyl wherein the phenyl ring is unsubstituted or substituted as defined above, (xv) dialkylaminoalkyl, (xvi) alkoxy and (xvii) thioalkoxy; n is 1 ; R2 is hydrogen; R4 is phenyl or thiazolyl; R5 is hydrogen; RQ is hydrogen and R7 is thiazolyl, oxazolyl, isothiazolyl or isoxazolyl. 4. The compound of Claim 2 wherein Ri is 2-monosubstituted-4- thiazolyl or 2-monosubstituted-4-oxazolyl wherein the substituent is selected from (i) loweralkyl, (ii) loweralkenyl, (iii) cycloalkyl, (iv)

ANNEXURE-V

1st Patent : Annexure-V

US005541206A

United States Patent [19]

Kempf et al.

[11] Patent Number: 5,541,206

[45] Date of Patent: Jul. 30, 1996

[54] **RETROVIRAL PROTEASE INHIBITING COMPOUNDS**

[75] Inventors: **Dale J. Kempf**, Libertyville; **Daniel W. Norbeck**, Crystal Lake; **Hing Leung Sham**; **Chen Zhao**, both of Gurnee, all of Ill.

[73] Assignee: **Abbott Laboratories**, Abbott Park, Ill.

[21] Appl. No.: 423,387

[22] Filed: Apr. 25, 1995

Related U.S. Application Data

[63] Continuation of Ser. No. 158,587, Dec. 2, 1993, abandoned, which is a continuation-in-part of Ser. No. 998,114, Dec. 29, 1992, abandoned, which is a continuation-in-part of Ser. No. 777,626, Oct. 23, 1991, abandoned, which is a continuation-in-part of Ser. No. 746,020, Aug. 15, 1991, abandoned, which is a continuation-in-part of Ser. No. 616,170, Nov. 20, 1990, abandoned, which is a continuation-in-part of Ser. No. 518,730, May 9, 1990, Pat. No. 5,142,056, which is a continuation-in-part of Ser. No. 456,124, Dec. 22, 1989, abandoned, which is a continuation-in-part of Ser. No. 405,604, Sep. 8, 1989, abandoned, which is a continuation-in-part of Ser. No. 355,945, May 23, 1989, abandoned.

[51] Int. Cl.[6] A61K 31/425; C07D 413/12; C07D 417/12

[52] U.S. Cl. 514/365; 548/204; 548/194; 548/187; 548/235; 548/227; 548/228; 548/229; 514/374; 514/369; 514/370; 514/376; 514/377

[58] Field of Search 514/365, 374, 514/369, 370, 376, 377; 548/204, 194, 187, 235, 227, 228, 229

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Zeffren et al. The Study of Enzyme Mechanism. p. 87. 1974.

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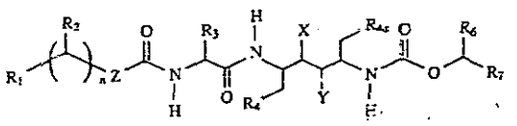
Primary Examiner—Jane Fan

Attorney, Agent, or Firm—Steven R. Crowley

[57] **ABSTRACT**

A retroviral protease inhibiting compound of the formula:



is disclosed.

19 Claims, No Drawings

ANNEXURE-VI

Annexure-VI

THE PATENTS ACT, 1970

SECTION 25(1)

In the matter of an application for patent No. 1602/MAS/98 filed on 17 July, 1998.

And

In the matter of a representation under section 25(1) of the Patents Act, 1970 as amended by the Patents (Amendment) Act, 2005.

And

In the matter of rule 55 of the Patents Rules,2003 as amended by the Patents (Amendment) Rules,2005.

M/s. Novartis AG, Switzerland ..... The Applicant

M/s. CIPLA Ltd., India ..... The Opponent

HEARING HELD ON October 14, 2005

Present :

M/s. Nalini Chidambaram,
Mr. Sanjay Kumar,
Mr. Gladis Daniel,
Ms. Nitin Sen } Agents for the Applicant

Dr. Gopakumar G. Nair
Mr. Ramesh Kumar } Agents for the Opponent

DECISION

An application for patent claiming Switzerland priority date of July 18,1997 was filed by M/s. Novartis AG on July 17, 1998 for an invention titled "Crystal Modification of A N-Phenyl-2-Pyrimidineamine derivative, processes for its manufacture and its use" and the same was allotted the application no. 1602/MAS/1998.

1/1

A representation by way of opposition under section 25(1) of the Patents Act, 1970 as amended by the Patents (Amendment) Act, 2005 was filed by M/s. Gopakumar Nair Associates, Mumbai on behalf of M/s. CIPLA Ltd., Mumbai on July 5, 2005 with a request for hearing under rule 55 of the Patents Rules, 2003 as amended by Patents (Amendment) Rules, 2005.

The Applicant through their agents M/s. Remfry & Sagar, New Delhi filed reply statement along with evidence by way of affidavit affirmed by Dr. Paul William Manley of Switzerland on August 5,2005. In their reply statement, the Applicant had requested for a hearing under rule 55 of the Patents Rules, 2003. They filed another affidavit affirmed by Giorgio Pietro Massimini of Switzerland on September 22, 2005.

Before discussing the grounds of opposition, it is pertinent to briefly mention here the background of the application. The present application claims β-crystal form of methanesulphonic acid salt of 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-[4-pyridin-3-yl)pyrimidin-2-ylamino)phenyl]-benzamide commercially called as imatinib mesylate. Invention of the base compound, 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-[4-pyridin-3-yl)pyrimidin-2-ylamino}phenyl]-benzamide called as imatinib had already been disclosed in the European Patent publication no.EP-A-056409, published on October 6, 1993, and its equivalent US Patent no.5521184, etc.

Not an invention:

Initiating the arguments, Dr. Gopakumar G. Nair, Agent for the Opponent, said imatinib mesylate is known from the US Patent no: 5521184, hereinafter called the 1993 Patent. The Opponent cited two other prior publications, viz., Nature Medicine(May5,1996)and Blood(November 1, 1997) wherein imatinib mesylate has been disclosed. He further said that there is no ingenuity or human intervention in the preparation of the β-crystal salts. This invention claims only a new form of known substance i.e. the β–crystal salts which are inherently disclosed in the 1993 Patent. Hence, the alleged invention is not an invention under section 2(1)(j) of the Patents Act as the alleged product and the process are not novel and devoid of any inventive step.

Agent for the Applicant argued that compared to the disclosure made in the 1993 patent, the present invention involves two fold improvement over the prior art -(i) the imatinib free base has been chemically changed into a salt form (ii) a particular crystal form of the salt has been made through human intervention.

Further the Applicant said that the 1993 Patent does not disclose imatinib mesylate but merely the corresponding free base and it may be correct to say that the claims of the 1993 patent embrace imatinib mesylate. There is neither an example for the preparation of imatinib mesylate in the 1993 Patent nor any claim therefor.

I do not agree with the contention of the Applicant that the 1993 Patent discloses only the free base. The 1993 patent discloses methanesulphonic acid as one of the salt forming groups and also the 1993 patent specification states that the required acid additions salts are obtained in a customary manner. Further, claims 6 to 23 of the 1993 patent claim a pharmaceutically acceptable salt of the base compound. The patent term extension certificate for the 1993 patent issued by the US Patent Office specifically mentions imatinib mesylate (Gleevec®) as the product. All these points clearly prove that imatinib mesylate is already known from the prior art publications.

Section 3(d):

The Opponent said that the application claims only a polymorphic form of the known substance, imatinib mesylate. There is no enhancement of known efficacy as required under section 3(d) of the Patents Act. Moreover the present specification states that all the inhibitory and pharmacological effects are also found with the free base, or other salts thereof.

Countering the arguments of the Opponent, the Applicant said that the β-crystal form of imatinib mesylate is an invention and not a more discovery. They further said that a discovery graduating into a patentable invention solely on the basis of efficiency defies logic and therefore section 3(d) may be unable to stand legal scrutiny. The

Appicant submitted that this aspect of section 3(d) is against the tenets of our patents act and well established principles of jurisprudence and therefore, the said section cannot be used against the subject application.

I do not agree wih the contention of the Appicant that this application claims a new substance. It is only a new form of a known substance. As regards efficacy, the specification itself states that wherever β-crystals are used the imatinib free base or other salts can be used. Even the affidavit submitted by the Applicant states that "the proviso to the section 3(d) is unique to India and there is no analogous provision in the law of any other country of the world". As per the affidavit the technical expert has conducted studies to compare the relative bioavailability of the free base with that of β-crystal form of imatinib mesylate and has said that the difference in bioavailability is only 30% and also the difference in bioavailability may be due to the difference in their solubility in water. The present patent specification does not bring out any improvement in the efficacy of the β-crystal form over the known subtances rather it states the base can be used equally in the treatment of diseases or in the preparation of pharmacological agents wherever the β-crystal is used. Even the affidavit submitted on behalf of the Applicant does not prove any significant enhancement of known efficacy.It is found that this patent application claims only a new form of a known substance without having any significant improvement in efficacy. Hence I conclude that the subject matter of this application is not patentable under section 3(d) of the Patents Act, 1970 as amended by the Patents (Amendment)Act, 2005.

Priority:

The opponent said this appication was filed in India on July 17, 1998 as a convention application claiming Swiss priority whereas Switzerland was not a convention country on that date. Hence this application is legally and technically disqualified and deserves to be rejected.

The Applicant said that priority date is only a facility provided to the Applicant to avoid anticipation by publication of the invention between priority date and the filing date in India. It is the discretion of the Applicant to claim priority. I agree with the contention of the Opponent that this application wrongly claims priority.

In view of the above findings and all the circumstances of the case, I hereby refuse to proceed with the application for Patent No.1602/MAS/1998.

Dated this the 25th day of January, 2006.

V. RENGASAMY
Asst. Controller of Patents & Designs

o/c

Copy to: 014855

1) M/s. Remfry & Sagar,
Remfry House at the Millennium Plaza,
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Between Gundecha & Growel,
Akurli Road, Kandivli, Mumbai – 400 101.

25/1/06
DESPATCHED.
PATENT OFFICE.
CHENNAI 600 032.

I/5

THE PATENTS ACT, 1970

SECTION - 25(1)

In the matter of an application for patent No. 1602/MAS/98 filed on July 17, 1998.

And

In the matter of a representation under section 25(1) of the Patents Act, 1970 as amended by the Patents (Amendment) Act, 2005.

And

In the matter of rule 55 of the Patents Rules,2003 as amended by the Patents (Amendment) Rules,2005.

M/s. Novartis AG, Switzerland ..... The Applicant

M/s. Natco Pharma Ltd., India ..... The Opponent

HEARING HELD ON October 14, 2005

Present :

M/s. Nalini Chidambaram,
Mr. Sanjay Kumar,
Mr. Gladis Daniel,
Ms. Nitin Sen } Agents for the Applicant

Mr. D. Calab Gabriel } Agent for the Opponent

DECISION

An application for patent claiming Switzerland priority date of July 18,1997 was filed by M/s. Novartis AG on July 17, 1998 for an invention titled "Crystal Modification of A N-Phenyl-2-Pyrimidineamine derivative, processes for its manufacture and its use" and the same was allotted the application no. 1602/MAS/1998.

A representation by way of opposition under section 25(1) of the Patents Act, 1970 as amended by the Patents (Amendment) Act, 2005 was filed by M/s. Natco Pharma Ltd., India, on May 26, 2005 with a request for hearing under rule 55 of the Patents Rules, 2003 as amended by Patents (Amendment) Rules, 2005.

The Applicant through their agents M/s. Remfry & Sagar, New Delhi filed reply statement along with evidence by way of affidavit affirmed by Dr. Paul William Manley of Switzerland onJuly 25,2005. In their reply statement, the Applicant had requested for a hearing under rule 55 of the Patents Rules, 2003. They filed another affidavit affirmed by Giorgio Pietro Massimini of Switzerland on September 22, 2005.

Before discussing the grounds of opposition, it is pertinent to briefly mention here the background of the application. The present application claims β-crystal form of methanesulphonic acid salt of 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-[4-pyridin-3-yl)pyrimidin-2-ylamino)phenyl]-benzamide commercially called as imatinib mesylate. Invention of the base compound, 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-[4-pyridin-3-yl)pyrimidin-2-ylamino)phenyl]-benzamide called as imatinib had already been disclosed in the European Patent publication no.EP-A-056409, published on October 6, 1993, and its equivalent US Patent no.5521184, etc.

Anticipation by Prior publication:

The Opponent argued that imatinib mesylate is known from the US Patent no: 5521184, hereinafter called the 1993 Patent. And cited another prior publication, Nature Medicine(May5,1996) whose publication date is prior to the priority date of July 17, 1997 of the present application wherein imatinib mesylate has been disclosed. The patent term extension certificate granted by US Patent Office for the 1993 Patent explicitly mentions imatinib mesylate (Glveevec®)as the product. The Opponent further argued that imatinib mesylate salt inherently existed in the β-crystelline form which is the most stable form of the salt and further said that even the affidavit submited by the Applicant states that the β–form is thermodynamically more stable. In order to confirm the crystalline form in which the salt existed, the Applicant has submitted reports based on the studies done by two reputed government institutions namely Indian Institute of

Chemical Technology, Hyderabad and Indian Institute of Technology, Delhi. From their studies they have found that the salt exists in the β-crystalline form. They have performed the experiments not once but atleast ten times and at all times the crystals were found to exist in the β-form. Hence the claims of the present application stand anticipated by prior publication.

The Applicant argued that compared to the disclosure made in the 1993 patent, the present invention involves two fold improvement over the prior art -(i) the imatinib free base has been chemically changed into a salt form (ii) a particular crystal form of the salt has been made through human intervention. Further the Applicant said that the 1993 Patent does not disclose imatinib mesylate but merely the corresponding free base and it may be correct to say that the claims of the 1993 patent embrace imatinib mesylate. There is neither an example for the preparation of imatinib mesylate in the 1993 Patent nor any claim therefor.

I do not agree with the contention of the Applicant that the 1993 Patent discloses only the free base. The 1993 patent discloses methanesulphonic acid as one of the salt forming groups and also the 1993 patent specification states that the required acid addition salts are obtained in a customary manner. Further, claims 6 to 23 of the 1993 patent claim a pharmaceutically acceptable salt of the base compound. The patent term extension certificate for the 1993 patent issued by the US Patent Office specifically mentions imatinib mesylate (Gleevec®) as the product. All these points clearly prove that imatinib mesylate is already known from the prior art publications and the Opponent has satisfactorily proved that the salt normally exists in the β-form which is the most thermodynamically stable product. Hence I conclude that the Opponent has succeeded in proving that this invention is anticipated by prior publication.

Obviousness :

The Opponent submitted that all the averments made in the above ground are reiterated. The Opponent further said that once the free base is disclosed by the 1993

Patent, it is obvious for a person skilled in the art to prepare corresponding pharmaceutically acceptable salts especially in view of the disclosure provided in column 3 of the 1993 Patent specification. Further, the reports of the Indian Institute of Technology, and Indian Institute of Chemical Technology clearly demonstrate that the salt prepared using instructions of the 1993 Patent inherently exists in β-form. Hence the product claims are obvious over the aforesaid disclosures.

The Appicant replied that the β-crystals are not inherently formed when the 1993 Patent is practised. Moreover, the 1993 Patent discloses only the free base, not any salt of imatinib and hence not obvious to a person skilled in the art.

I do not agree with the contentions of the Applicant that the 1993 Patent discloses only the free base for the reasons stated in the grounds of previous publication and I conclude that the Opponent has reasonably succeeded in establishing this ground of opposition too.

Section 3(d):

The Opponent said that the application claims only a polymorphic form of imatinib mesylate. As per section 3(d) of the Patents Act, any salt, polymorph or derivative of known substance is not patentable unless such salt, polymorph or other substance shows enhanced efficay of the substance. As regards efficacy, the specification itself states that where'er β-crystals are used the imatinib free base or other salts can be used. Even the affidavit submitted by the Applicant states that "the proviso to the section 3(d) is unique to India and there is no analogous provision in the law of any other country of the world". As per the affidavit the technical expert has conducted studies to compare the relative bioavailability of the free base with that of β-crystal form of imatinib mesylate and has said that the difference in bioavailability is only 30% and also the difference in bioavailability may be due to the difference in their solubility in water. The present patent specification does not bring out any improvement in the efficacy of the β-crystal form over the known subtances rather it states the base can be used equaliy in the treatment of diseases or in the preparation of pharmacological agents wherever the β-crystal is used. Even the affidavit submitted on behalf of the Applicant does not prove any significant enhancement of known efficacy.

Countering the arguments of the Opponent, the Applicant said that the case does not come under the exclusion provided under section 3(d). It is denied that it is a mere discovery of a new form of a known substance. The β-crystalline form of imatinib mesylate is a new product because the crystal form is not an inherent property of imatinib acid addition salt exhibiting polymorphism and human intervention was necessary in order to produce the subject compound. As regards efficacy, the Applicant relied on the affidavit by Mr. Massimini submitted on September 22, 2005, wherein he has conducted a study on the relative bioavailability of the free base and and imatinib mesylate in the β-crystalline form.

I do not agree with the contention of the Applicant that this application claims a new substance. It is only a new form of a known substance. It is found that this patent application claims only a new form of a known substance without having any significant improvement in efficacy. Even the affidavit submitted on behalf of the Applicant fails to prove enhanced efficacy of the β-isomer over the known substance. Hence I conclude that the subject matter of this application is not patentable under section 3(d) of the Patents Act, 1970 as amended by the Patents (Amendment)Act, 2005.

Priority:

The Opponent said this application was filed in India on July 17, 1998 as a convention application claiming Swiss priority date of July 18, 1997 whereas Switzerland was not a convention country on that date. Further, section 133 did not have and does not have any retrospective effect. The Opponent cited a decision of the High Court of Calcutta in the case of Danieli AC Officine Meccaniche SPA, Italy in support of his argument. In the present case also, Switzerland became convention country only in September, 1998. Hence no priority may be claimed from Swiss application.

The Applicant said that priority date is only a facility provided to the Applicant to avoid anticipation by publication of the invention between priority date and the filing date in India. It is the discretion of the Applicant to claim priority. I agree with the contention of the Opponent that this application wrongly claims priority.

In view of the above findings and all the circumstances of the case, I hereby refuse to proceed with the application for Patent No.1602/MAS/1998.

Dated this the 25th day of January, 2006.

V. RENGASAMY
Asst. Controller of Patents & Designs

Copy to:

1) M/s. Remfry & Sagar,
Remfry House at the Millenium Plaza, 014857
Sector – 27, Gurgaon – 122 002

2) M/s. Natco Pharma Ltd.,
'Natco House', Road No.2, Banjara Hills 014858
Hyderabad - 500 033.

THE PATENTS ACT, 1970

SECTION - 25(1)

In the matter of an application for patent No. 1602/MAS/98 filed on 17 July, 1998.

And

In the matter of a representation under section 25(1) of the Patents Act, 1970 as amended by the Patents (Amendment) Act, 2005.

And

In the matter of rule 55 of the Patents Rules,2003 as amended by the Patents (Amendment) Rules,2005.

M/s. Novartis AG, Switzerland ..... The Applicant

M/s. Ranbaxy Laboratories Ltd., India ..... The Opponent

HEARING HELD ON October 14, 2005

Present :

M/s. Nalini Chidambaram,
Mr. Sanjay Kumar,
Mr. Gladis Daniel,
Ms. Nitin Sen } Agents for the Applicant

Mr. Lakshmi Kumaran
Mr. Anil Misra } Agents for the Opponent

DECISION

An application for patent claiming Switzerland priority date of July 18,1997 was filed by M/s. Novartis AG on July 17, 1998 for an invention titled "Crystal Modification of A N-Phenyl-2-Pyrimidineamine derivative, processes for its manufacture and its use" and the same was allotted the application no. 1602/MAS/1998.

III/1

A representation by way of opposition under section 25(1) of the Patents Act, 1970 as amended by the Patents (Amendment) Act, 2005 was filed by M/s. Lakshmi Kumaran & Sridharan, New Delhi on behalf of M/s. Ranbaxy Laboratories Ltd., India on May 26, 2005 with a request for hearing under rule 55 of the Patents Rules, 2003 as amended by Patents (Amendment) Rules, 2005.

The Applicant through their agents M/s. Remfry & Sagar, New Delhi filed reply statement along with evidence by way of affidavit affirmed by Dr. Paul William Mainley of Switzerland on July 27,2005. In their reply statement, the Applicant had requested for a hearing under rule 55 of the Patents Rules, 2003. They filed another affidavit affirmed by Giorgio Pietro Massimini of Switzerland.

Before discussing the grounds of opposition, it is pertinent to briefly mention here the background of the application. The present application claims β-crystal form of methanesulphonic acid salt of 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-[4-pyridin-3-yl)pyrimidin-2-ylamino)phenyl]-benzamide commercially called as imatinib mesylate. Invention of the base compound, 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-[4-pyridin-3-yl)pyrimidin-2-ylamino)phenyl]-benzamide called as imatinib had already been disclosed in the European Patent publication no.EP-A-056409, published on October 6, 1993, and its equivalent US Patent no.5521184, etc.

Priority:

The Opponent argued that the application claims convention priority from an earlier Swiss application. Switzerland was not a convention country on the date of the filing of the application. Despite full knowledge of the above fact, the Applicant has chosen not to amend the application to represent the correct position. No patent can be granted on the basis of false and misleading submissions. The application should therefore be rejected.

The Applicant said that priority date is only a facility provided to the Applicant to avoid anticipation by publication of the invention between priority date and the filing date in India. It is the discretion of the Applicant to claim priority. I agree with the contention of the Opponent that this application wrongly claims priority.

Anticipation:

The Opponent said that imatinib mesylate is known from the US Patent no: 5521184, hereinafter called the 1993 Patent. The Opponent cited other prior publications; viz., Nature Medicine(May5,1996), Cancer Research (Vol. 56, Issue 1, 1996 and Blood(November 1, 1997) wherein imatinib mesylate has been disclosed. He further said that there is no ingenuity or human intervention in the preparation of the β-crystal salts. Imatinib mesylate can exist only in a single form namely the β–crystalline form. It therefore follows that the subject matter of the application is anticipated by the 1993 Patent namely the US Patent No.5521184 and its equivalent patents.

The Applicant replied that compared to the disclosure made in the 1993 patent, the present invention involves two fold improvement over the prior art -(i) the imatinib free base has been chemically changed into a salt form (ii) a particular crystal form of the salt has been made through human intervention. Further the Applicant said that the 1993 Patent does not disclose imatinib mesylate but merely the corresponding free base and it may be correct to say that the claims of the 1993 patent embrace imatinib mesylate. There is neither an example for the preparation of imatinib mesylate in the 1993 Patent nor any claim therefor.

I do not agree with the contention of the Applicant that the 1993 Patent discloses only the free base. The 1993 patent discloses methanesulphonic acid as one of the salt forming groups and also the 1993 patent specification states that the required acid additions salts are obtained in a customary manner. Further, claims 6 to 23 of the 1993 patent claim a pharmaceutically acceptable salt of the base compound. The patent term extension certificate for the 1993 patent issued by the US Patent Office specifically mentions imatinib mesylate (Gleevec®) as the product. All these points clearly prove that this invention is anticipated by prior publications.

Section 3(d)

The Opponent said that he is reiterating the submissions made under the ground of anticipation and further said that the application claims only a polymorphic form of imatinib mesylate. As per section 3(d) of the Patents Act, any salt, polymorph or derivative of known substance is not patentable unless such salt, polymorph or other substance shows enhanced efficay of the substance. As regards efficacy, the specification itself states that where'er β-crystals are used the imatinib free base or other salts can be used. Even the affidavit submitted by the Applicant states that "the proviso to the section 3(d) is unique to India and there is no analogous provision in the law of any other country of the world". As per the affidavit the technical expert has conducted studies to compare the relative bioavailability of the free base with that of β-crystal form of imatinib mesylate and has said that the difference in bioavailability is only 30% and also the difference in bioavailability may be due to the difference in their solubility in water. The present patent specification does not bring out any improvement in the efficacy of the β-crystal form over the known subtances rather it states the base can be used equally in the treatment of diseases or in the preparation of pharmacological agents wherever the β-crystal is used. Even the affidavit submitted on behalf of the Applicant does not prove any significant enhancement of known efficacy.

Countering the arguments of the Opponent, the Applicant said that the β-crystal form of imatinib mesylate is an invention and not a more discovery.They further said that a discovery graduating into a patentable invention solely on the basis of efficiency defies logic and therefore section 3(d) may be unable to stand legal scrutiny. The Appicant submitted that this aspect of section 3(d) is against the tenets of our patents act and well established principles of jurisprudence and therefore, the said section cannot be used against the subject application.

I do not agree with the contention of the Appicant that this application claims a new substance. It is only a new form of a known substance. As regards efficacy, the specification itself states that where'er β-crystals are used the imatinib free base or

other salts can be used. The present patent specification does not bring out any improvement in the efficacy of the β-crystal form over the known subtances rather it states the base can be used equally in the treatment of diseases or in the preparation of pharmacological agents wherever the β-crystal is used. Even the affidavit submitted on behalf of the Applicant does not prove any significant enhancement of known efficacy. It is found that the patent application claims only a new form of a known substance without having any significant improvement in efficacy. Hence I conclude that the subject matter of this application is not patentable under section 3(d) of the Patents Act, 1970 as amended by the Patents (Amendment)Act, 2005.

In view of the above findings and all the circumstances of the case, I hereby refuse to proceed with the application for Patent No.1602/MAS/1998.

Dated this the 25th day of January, 2006.

V. RENGASAMY
Asst. Controller of Patents & Designs

Copy to:

1) M/s. Remfry & Sagar.
Remfry House at the Millenium Plaza, 014859
Sector – 27, Gurgaon – 122 002

2) Mr. Laksmi Kumaran & Sridharan
B-6/10 Safdarjung Enclave,
New Delhi – 110 029 014860

THE PATENTS ACT, 1970

SECTION - 25(1)

In the matter of an application for patent No. 1602/MAS/98 filed on July 17, 1998.

And

In the matter of a representation under section 25(1) of the Patents Act, 1970 as amended by the Patents (Amendment) Act, 2005.

And

In the matter of rule 55 of the Patents Rules,2003 as amended by the Patents (Amendment) Rules,2005.

M/s. Novartis AG, Switzerland ..... The Applicant

M/s. Hetero Drugs Limited, India ..... The Opponent

HEARING HELD ON December 15, 2005

Present :

Mr. Sanjay Kumar,
Mr. Habubullah Badsha,
Ms. Nitin Sen
Mr. Saibal Mukherjee } Agents for the Applicant

Mr. Anil Misra } Agent for the Opponent

DECISION

An application for patent claiming Switzerland priority date of July 18,1997 was filed by M/s. Novartis AG on July 17, 1998 for an invention titled "Crystal Modification of A N-Phenyl-2-Pyrimidineamine derivative, processes for its manufacture and its use" and the same was allotted the application no. 1602/MAS/1998.

IV/1

A representation by way of opposition under section 25(1) of the Patents Act, 1970 as amended by the Patents (Amendment) Act, 2005 was filed by M/s. Hetero Drugs Ltd., India, on August 22, 2005 with a request for hearing under rule 55 of the Patents Rules, 2003 as amended by Patents (Amendment) Rules, 2005.

The Applicant through their agents M/s. Remfry & Sagar, New Delhi filed reply statement along with evidence by way of affidavit affirmed by Dr. Paul William Manley of Switzerland November 14,2005. In their reply statement, the Applicant had requested for a hearing under rule 55 of the Patents Rules, 2003. They filed another affidavit affirmed by Giorgio Pietro Massimini of Switzerland.

Before discussing the grounds of opposition, it is pertinent to briefly mention here the background of the application. The present application claims β-crystal form of methanesulphonic acid salt of 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-[4-pyridin-3-yl)pyrimidin-2-ylamino)phenyl]-benzamide commercially called as imatinib mesylate. Invention of the base compound, 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-[4-pyridin-3-yl)pyrimidin-2-ylamino)phenyl]-benzamide called as imatinib had already been disclosed in the European Patent publication no.EP-A-0564409, published on October 6, 1993, and its equivalent US Patent no.5521184, etc.

Priority:

The Opponent argued that the application claims convention priority from an earlier Swiss application. Switzerland was not a convention country on the date of the filing of the application. Despite full knowledge of the above fact, the Applicant has chosen not to amend the application to represent the correct position. No patent can be granted on the basis of false and misleading submissions. The application should therefore be rejected.

The Applicant said that priority date is only a facility provided to the Applicant to avoid anticipation by publication of the invention between priority date and the filing

date in India. It is the discretion of the Applicant to claim priority. I agree with the contention of the Opponent that this application wrongly claims priority.

Anticipation:

The Opponent said that imatinib mesylate is known from the US Patent no: 5521184; hereinafter called the 1993 Patent. The Opponent cited other prior publications, viz., Nature Medicine(May5,1996), Cancer Research (Vol. 56, Issue I, 1996) and Blood(November 1, 1997) wherein imatinib mesylate has been disclosed. He further said that there is no ingenuity or human intervention in the preparation of the β-crystal salts. Imatinib mesylate can exist only in a single form namely the β–crystalline form. It therefore follows that the subject matter of the application is anticipated by the 1993 Patent namely the US Patent No.5521184 and its equivalent patents.

The Applicant replied that compared to the disclosure made in the 1993 patent, the present invention involves two fold improvement over the prior art -(i) the imatinib free base has been chemically changed into a salt form (ii) a particular crystal form of the salt has been made through human intervention. Further the Applicant said that the 1993 Patent does not disclose imatinib mesylate but merely the corresponding free base and it may be correct to say that the claims of the 1993 patent embrace imatinib mesylate. There is neither an example for the preparation of imatinib mesylate in the 1993 Patent nor any claim therefor.

I do not agree with the contention of the Applicant that the 1993 Patent discloses only the free base. The 1993 patent discloses methanesulphonic acid as one of the salt forming groups and also the 1993 patent specification states that the required acid additions salts are obtained in a customary manner. Further, claims 6 to 23 of the 1993 patent claim a pharmaceutically acceptable salt of the base compound. The patent term extension certificate for the 1993 patent issued by the US Patent Office specifically mentions imatinib mesylate (Gleevec®) as the product. All these points clearly prove that this invention is anticipated by prior publications.

Section 3(d):

The Opponent said that he is reiterating the submissions made under the ground of anticipation and further said that the application claims only a polymorphic form of imatinib mesylate. As per section 3(d) of the Patents Act, any salt, polymorph or derivative of known substance is not patentable unless such salt, polymorph or other substance shows enhanced efficay of the substance. As regards efficacy, the specification itself states that where'er β-crystals are used the imatinib free base or other salts can be used. Even the affidavit submitted by the Applicant states that "the proviso to the section 3(d) is unique to India and there is no analogous provision in the law of any other country of the world". As per the affidavit the technical expert has conducted studies to compare the relative bioavailability of the free base with that of β-crystal form of imatinib mesylate and has said that the difference in bioavailability is only 30% and also the difference in bioavailability may be due to the difference in their solubility in water. The present patent specification does not bring out any improvement in the efficacy of the β-crystal form over the known subtances rather it states the base can be used equally in the treatment of diseases or in the preparation of pharmacological agents wherever the β-crystal is used. Even the affidavit submitted on behalf of the Applicant does not prove any significant enhancement of known efficacy.

Countering the arguments of the Opponent, the Applicant said that the β-crystal form of imatinib mesylate is an invention and not a mere discovery. They further said that a discovery graduating into a patentable invention solely on the basis of efficiency defies logic and therefore section 3(d) may be unable to stand legal scrutiny. The Applicant submitted that this aspect of section 3(d) is against the tenets of our patents act and well established principles of jurisprudence and therefore, the said section cannot be used against the subject application.

I do not agree with the contention of the Applicant that this application claims a new substance. It is only a new form of a known substance. As regards efficacy, the specification itself states that where'er β-crystals are used the imatinib free base or other salts can be used. The present patent specification does not bring out any

improvement in the efficacy of the β-crystal form over the known subtances rather it states the base can be used equally in the treatment of diseases or in the preparation of pharmacological agents wherever the β-crystal is used. Even the affidavit submitted on behalf of the Applicant does not prove any significant enhancement of known efficacy. It is found that this patent application claims only a new form of a known substance without having any significant improvement in efficacy. Hence I conclude that the subject matter of this application is not patentable under section 3(d) of the Patents Act, 1970 as amended by the Patents (Amendment)Act, 2005.

In view of the above findings and all the circumstances of the case, I hereby refuse to proceed with the application for Patent No.1602/MAS/1998.

Dated this the 25th day of January, 2006.

V. RENGASAMY
Asst. Controller of Patents & Designs

Copy to:

1) M/s. Remfry & Sagar,
Remfry House at the Millenium Plaza, 014861
Sector – 27, Gurgaon – 122 002

2) Mr. Lakshmi Kumaran & Sridharan
B-6/10 Safdarjung Enclave,
New Delhi – 110 029 014862

V. RENGASAMY
Asst. Controller of Patents & Designs
DESPATCHER,
PATENT OFFICE,
CHENNAI 600 032.

THE PATENTS ACT, 1970

SECTION - 25(1)

In the matter of an application for patent No. 1602/MAS/98 filed on July 17, 1998.

And

In the matter of a representation under section 25(1) of the Patents Act, 1970 as amended by the Patents (Amendment) Act, 2005.

And

In the matter of rule 55 of the Patents Rules,2003 as amended by the Patents (Amendment) Rules,2005.

M/s. Novartis AG, Switzerland ..... The Applicant

M/s. Cancer Patients Aid Association, India ..... The Opponent

HEARING HELD ON December 15, 2005

Present :

Mr. Sanjay Kumar,
Mr. Habibullah Badsha,
Ms. Nitin Sen
Mr. Saibal Mukherjee } Agents for the Applicant

Mr. Anand Grover } Agent for the Opponent

DECISION

An application for patent claiming Switzerland priority date of July 18,1997 was filed by M/s. Novartis AG on July 17, 1998 for an invention titled "Crystal Modification of A N-Phenyl-2-Pyrimidineamine derivative, processes for its manufacture and its use" and the same was allotted the application no. 1602/MAS/1998.

A representation by way of opposition under section 25(1) of the Patents Act, 1970 as amended by the Patents (Amendment) Act, 2005 was filed by M/s. Cancer Patients Aid Association., India, on September 26, 2005 with a request for hearing under rule 55 of the Patents Rules, 2003 as amended by Patents (Amendment) Rules, 2005.

The Applicant through their agents M/s. Remfry & Sagar, New Delhi filed reply statement along with evidence by way of affidavit affirmed by Dr. Paul William Manley of Switzerland October 31,2005. In their reply statement, the Applicant had requested for a hearing under rule 55 of the Patents Rules, 2003. They filed another affidavit affirmed by Giorgio Pietro Massimini of Switzerland.

Before discussing the grounds of opposition, it is pertinent to briefly mention here the background of the application. The present application claims β-crystal form of methanesulphonic acid salt of 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-[4-pyridin-3-yl)pyrimidin-2-ylamino)phenyl]-benzamide commercially called as imatinib mesylate. Invention of the base compound, 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-[4-pyridin-3-yl)pyrimidin-2-ylamino)phenyl]-benzamide called as imatinib had already been disclosed in the European Patent publication no EP-A-056409; published on October 6, 1993, and its equivalent US Patent no.5521184, etc.

Prior publication:

The Opponent argued that imatinib mesylate is known from the US Patent no: 5521184, hereinafter called the 1993 Patent. The patent term extension certificate granted by US Patent Office for the 1993 Patent explicitly mentions imatinib mesylate (Glyveevec) as the product. The Opponent further argued that imatinib mesylate salt inherently existed in the β-crystelline form which is the most stable form of the salt and further said that even the affidavit submited by the Applicant states that the β-form is thermodynamically more stable. Hence the claims of the present application stand anticipated by prior publication.

The Applicant argued that compared to the disclosure made in the 1993 patent, the present invention involves two fold improvement over the prior art -(i) the imatinib free base has been chemically changed into a salt form (ii) a particular crystal form of the salt has been made through human intervention. Further the Applicant said that the 1993 Patent does not disclose imatinib mesylate but merely the corresponding free base and it may be correct to say that the claims of the 1993 patent encrace imatinib mesylate. There is neither an example for the preparation of imatinib mesylate in the 1993 Patent nor any claim therefor.

I do not agree with the contention of the Applicant that the 1993 Patent discloses only the free base. The 1993 patent discloses methanesulphonic acid as one of the salt forming groups and also the 1993 patent specification states that the required acid additions salts are obtained in a customary manner. Further, claims 6 to 23 of the 1993 patent claim a pharmaceutically acceptable salt of the base compound. The patent term extension certificate for the 1993 patent issued by the US Patent Office specifically mentions imatinib mesylate (Gleevec) as the product. All these points clearly prove that imatinib mesylate is already known from the prior art publications and the Opponent has satisfactorily proved that the salt normally exists in the β-form which is the most thermodynamically stable product. Hence I conclude that the Opponent has succeeded in proving that this invention is anticipated by prior publication.

Obviousness :

The Opponent submitted that all the arguments made in the above ground are reiterated. The Opponent further said that once the free base is disclosed by the 1993 Patent, it is obvious for a person skilled in the art to prepare corresponding pharmaceutically acceptable salts in view of the disclosure provided in the 1993 Patent specification. The β-form being the most thermodynamically stable form, imatinib mesylate inherently existed in that form. Hence the product claims are obvious.

The Appicant replied that the β-crystals are not inherently formed when the 1993 Patent is practised. Moreover, the 1993 Patent discloses only the free base, not any salt of imatinib and hence not obvious to a person skilled in the art.

I do not agree with the contentions of the Applicant that the 1993 Patent discloses only the free base for the reasons stated in the grounds of previous publication and I conclude that the Opponent has reasonably succeeded in establishing this ground of opposition too.

Section 3(d):

The Opponent said that the application claims only a polymorphic form of imatinib mesylate. As per section 3(d) of the Patents Act, any salt, polymorph or derivative of known substance is not patentable unless such salt, polymorph or other substance shows enhanced efficacy of the substance. As regards efficacy, the specification itself states that where'er β-crystals are used the imatinib free base or other salts can be used. Even the affidavit submitted by the Applicant states that "the proviso to the section 3(d) is unique to India and there is no analogous provision in the law of any other country of the world". As per the affidavit the technical expert has conducted studies to compare the relative bioavailability of the free base with that of β-crystal form of imatinib mesylate and has said that the difference in bioavailability is only 30% and also the difference in bioavailability may be due to the difference in their solubility in water. The present patent specification does not bring out any improvement in the efficacy of the β-crystal form over the known subtances rather it states the base can be used equally in the treatment of diseases or in the preparation of pharmacological agents wherever the β-crystal is used. Even the affidavit submitted on behalf of the Applicant does not prove any significant enhancement of known efficacy.

Countering the arguments of the Opponent, the Applicant said that the case does not come under the exclusion provided under section 3(d). It is denied that it is a mere discovery of a new form of a known substance. The β-crystalline form of imatinib mesylate is a new product because the crystal form is not an inherent property of imatinib acid addition salt exhibiting polymorphism and human intervention was

necessary in order to produce the subject compound. As regards efficacy, the Applicant relied on the affidavit by Mr. Massimini submitted on September 22, 2005, wherein he has conducted a study on the relative bioavailability of the free base and and imatinib mesylate in the β-crystalline form.

I do not agree with the contention of the Applicant that this application claims a new substance. It is only a new form of a known substance. It is found that this patent application claims only a new form of a known substance without having any significant improvement in efficacy. Even the affidavit submitted on behalf of the Applicant fails to prove enhanced efficacy of the β-isomer over the known substance. Hence I conclude that the subject matter of this application is not patentable under section 3(d) of the Patents Act, 1970 as amended by the Patents (Amendment)Act, 2005.

The Opponent said this application was filed in India on July 17, 1998 as a convention application claiming Swiss priority date of July 18, 1997 whereas Switzerland was not a convention country on that date. In the present case, Switzerland became convention country only in September, 1998. Hence no priority may be claimed from Swiss application.

The Applicant said that priority date is only a facility provided to the Applicant to avoid anticipation by publication of the invention between priority date and the filing date in India. It is the discretion of the Applicant to claim priority. I agree with the contention of the Opponent that this application wrongly claims priority.

In view of the above findings and all the circumstances of the case, I hereby refuse to proceed with the application for Patent No.1602/MAS/1998.

Dated this the 25th day of January, 2006.

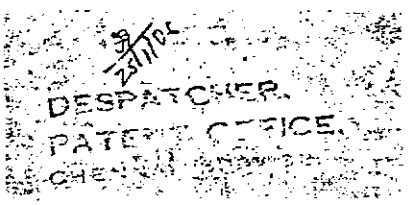
V. RENGASAMY
Asst. Controller of Patents & Designs

dk

Copy to:

1) M/s. Remfry & Sagar,
Remfry House at the Millenium Plaza, 014863
Sector – 27, Gurgaon – 122 002

2) M/s. Cancer Patients Aid Association,
No.5, Malhotra House, Opp. G.P.O,
Mumbai – 400 001. 014864



ANNEXURE-VII

23 JUL 2008

Annexure - VII

IN THE HIGH COURT OF JUDICATURE AT MADRAS

DATED: 06.08.2007

CORAM

THE HON'BLE MR.JUSTICE R.BALASUBRAMANIAN

and

THE HON'BLE MRS.JUSTICE PRABHA SRIDEVAN

W.P. Nos.24759 and 24760 of 2006

Novartis AG
Schwarzwaldalle 215
4058 Basel and Licinstrasse 35
4002 Basel,
Switzerland
represented by it's
Power of Attorney
Ranjna Mehta Dutt .....Petitioner in W.P.24759/06

Novartis India Ltd.
Sandoz House
Dr.Annie Besant Road
Worli,
Mumbai 400 018
represented by it's
Power of Attorney
Saibal Mukherjee .....Petitioner in W.P.24760/06

Vs.

1. Union of India
   through the Secretary
   Department of Industry
   Ministry of Industry and Commerce
   Udyog Bhavan.
   New Delhi

2. The Controller General of
   Patents & Designs
   through the Patent Office
   Intellectual Property Rights
   Building
   G.S.T.Road,
   Guindy,
   Chennai 600 032

3. Natco Pharma Ltd.
"Natco House"
Road No.2,
Banjara Hills
Hyderabad 500 033.

4. M/s.Cipla Ltd., India
289, Bellasis Road
Opp.Hotel Sahil,
Mumbai Central (E)
Mumbai 400 008.

5. M/s.Hetro Drugs Ltd., India
H No.8-3-168/7/1,
Erragada
Hyderabad 500 018.

6. M/s.Cancer Patient Aid
Association, India
No.5, Malhotra House.
Opp. G.P.O.
Mumbai 400 001

7. M/s.Ranbaxy
Laboratories Ltd., India
12th Floor, Deviks Tower
No.6, Nehru Place.
New Delhi 110 019

8. Indian Pharmaceutical Alliance
represented by it's
Secretary General
C/o.Vision Consulting Group
No.201, Darvesh Chambers
Khar,
Mumbai - 00 052

9. M/s. Sun Pharmaceutical
Industries Limited
Acme Plaza, Opp.Sangam Cinema
Andheri - Kurla Road
Andheri (E),
Mumbai 400 059

(R8 and R9 impleaded
as per order dated
29.01.2007 passed in
MP.Nos.3 and 5 of 2006
in W.P. No.24759/2006)

.....Respondents in W.P.24759/06

1. Union of India
   through the Secretary
   Department of Industry
   Ministry of Industry and Commerce
   Udyog Bhavan,
   New Delhi

2. The Controller General of
   Patents & Designs
   through the Patent Office
   Intellectual Property Rights
   Building
   G.S.T.Road,
   Guindy,
   Chennai 600 032

3. Natco Pharma Ltd.
   "Natco House"
   Road No.2,
   Banjara Hills
   Hyderabad 500 033.

4. M/s.Cipla Ltd., India
   289, Bellasis Road
   Opp.Hotel Sahil,
   Mumbai Central (E)
   Mumbai 400 008.

5. M/s.Hetro Drugs Ltd., India
   H No.8-3-168/7/1,
   Erragada
   Hyderabad 500 018.

6. M/s.Cancer Patient Aid
   Association, India
   No.5, Malhotra House.
   Opp. G.P.O.
   Mumbai 400 001

7. M/s.Ranbaxy
   Laboratories Ltd., India
   12th Floor, Devkis Tower
   No.6, Nehru Place,
   New Delhi 110 019 .....Respondents in W.P.24760/06

Prayer in W.P.No.24759/2006: Writ petition under Article 226 of the Constitution of India praying to issue a writ of declaration declaring that section 3(d) of the Patents

Act, 1970 as substituted by the Patents (Amendment) Act, 2005 (Act 15/2005) is non-complaint with the TRIPS Agreement and / or is unconstitutional being vague, arbitrary and violative of Article 14 of the Constitution of India and consequentially to direct the second respondent to allow the Patent Application bearing No.1602/MAS/98 filed by the petitioner.

Prayer in W.P.No.24760/2006: Writ petition under Article 226 of the Constitution of India praying to issue a writ of declaration declaring that section 3(d) of the Patents Act, 1970 as substituted by the Patents (Amendment) Act, 2005 (Act 15/2005) is non-complaint with the TRIPS Agreement and / or is unconstitutional being vague, arbitrary and violative of Article 14 of the Constitution of India.

For Petitioner in both W.Ps : Mr.Habuibulla Badsha, SC,
: Mr.Soli Sorabjee, SC and
: Mr.Shanthi Bhushan, SC for
: Mr.C.Daniel

For R1 and R2 : Mr.V.T.Gopalan, SC for
: Mr.P.Wilson, Asst.Sol.General

For Respondent No.3 : Mr.P.S.Raman, AAG for
Mr.A.A.Mohan

For R4, R8 and R9 : Mr.P.Aravind Datar, SC
: Mr.R.Thiagarajan, SC &
: Mr.K.M.Vijayan, SC for
: Mr.A.Ramesh Kumar

For Respondent No.5 & 7 : Mr.Lakshmi Kumaran

For Respondent No.6 : Mr.Anand Grover for
: Ms.R.Vaigai

COMMON ORDER

(Order of the court was delivered by

Justice R.Balasubramanian)

The writ petitioner in both the writ petitions is one and the same. In the first writ petition, Novartis – a foreign company represented by it's Indian Power of Attorney holder, is the writ petitioner. In the second writ petition, Novartis India represented by it's power agent is the writ petitioner. The respondents in both the writ petitions are one and the same. The prayer in both the writ petitions is one and the same namely, for a declaration that section 3(d) of the Patents Act, 1970, amended by Patents(Amendment) Act 15/2005, is unconstitutional. However, in the first writ petition there was an additional prayer in addition to the relief asked for. The additional prayer was to direct the second respondent in that writ petition namely, the Controller General of Patents and Designs, to allow the patent application bearing No.1602/NAS/98 filed by the petitioner seeking patent. However at a later stage, during the pendency of the writ petitions, M.P.No.1/2007 came to be filed in that writ petition seeking to delete the prayer for a direction to the Patent Controller to allow the application and it was accordingly ordered. Therefore as on date in the two writ petitions, the Constitutional validity of section 3(d) alone is in challenge, both on the ground that it violates not only Article 14 of the Constitution of India but also on the ground that it is not in compliance to "TRIPS". Both the writ petitions along with the connected miscellaneous petitions were admitted by a learned Judge of this court and before the very same learned Judge, at a later stage, all the miscellaneous petitions came up for disposal. We are informed that elaborate arguments were advanced by the learned senior counsels on either side at that stage and on 25.09.2006 learned Judge, who heard these writ petitions with the connected miscellaneous petitions, came to the conclusion that the writ petitions require the attention of a Division Bench of this court, as according to the learned single Judge, the writ petitions involve substantial questions of law. Therefore learned single Judge passed an order directing the Registry to place the entire material papers before the Hon'ble Chief Justice for disposal by a Division Bench. Subsequently, by orders of the Hon'ble Chief Justice, these writ petitions are listed before us. Heard Mr.Soli Sorabji, Mr.Shanthi Bhushan and Mr.Habibulla Badsha, learned senior counsels appearing for the petitioners; Mr.V.T.Gopalan, learned Additional Solicitor General for the Government of India

and the Controller of Patents and Designs; Mr.Anand Grover, learned counsel; Mr.P.S.Raman learned senior counsel Mr.Aravind P Datar learned senior counsel; Mr.K.M.Vijayan learned senior counsel and Mr.Lakshmi Kumaran, learned counsel *appearing for the various respondents.*

2. In this judgment, for convenience sake, we will hereinafter refer the Patents Act as the "Principal Act"; Ordinance 7/2004 introducing an amendment to section 3(d) of the Act as the "Ordinance"; Amending Act of 2005 amending section 3(d) of the Act as the "Amending Act"; section 3(d) as the amended section and the Act after the amendment as the "Amended Act". The challenge to the amended section is mainly on two grounds namely.

(a) it is not compatible to the agreement on Trade Related aspects of Intellectual Property Rights, hereinafter referred to as "TRIPS" for convenience sake; and

(b) it is arbitrary, illogical, vague and offends Article 14 of the Constitution of India. For a better understanding of the attack to the *amended section, we feel that it is* desirable to extract hereunder section 3(d) of the Principal Act; the nature of amendment to that section sought to be brought in by the Ordinance and the amended section itself:

"Unamended section 3(d): The mere discovery of any new property or new use of a known substance or of the mere use of a known process, machine or apparatus unless such known process results in a new product or employs atleast one new reactant.

Amendment to section 3(d) under Ordinance 7/2004: The mere *discovery of any new property or mere new use of a known substance or of the mere* use of a known process, machine or apparatus unless such known process results in a new product or employs atleast one new reactant.

Section 3(d) as amended by the Patents (Amendment) Act, 2005 with effect from 01.01.2005: The mere discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of that substance or the mere discovery of any new property or new use for a known substance or of the mere

use of a known process, machine or apparatus unless such known process results in a new product or employs atleast one new reactant.

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

3. Learned senior counsels appearing for the petitioners took us through the various covenants/clauses in "TRIPS" to argue that the amended section, as it stands today, runs contra to the various articles found incorporated in "TRIPS". The main thrust is with reference to article 27 of "TRIPS". It is contended that article 1(1) of the "TRIPS" mandates every member country to give effect to the provisions of the "TRIPS" and India being a member country, in implementing the various provisions of "TRIPS" brought in the amended section violating their obligations under "TRIPS". It is argued by learned senior counsels that the proposed amendment brought in under the Ordinance is compatible to "TRIPS". However, without any rhyme or reason, the proposed amendment sought to be introduced by the Ordinance had been completely given up and instead, the offending amended section was brought. The sum and substance of the argument advanced by learned senior counsels for the petitioner company is, by bringing in the amended section and the Explanation attached to it, the Union of India had infact not carried out it's obligations arising out of "TRIPS" and instead, by the amended section making that the discovery of a new form of a known substance, which does not result in the enhancement of the known efficacy of that substance as not patentable, the right to have an invention patented guaranteed under section 27 of the "TRIPS" is taken away. As far as the attack to the section on the ground of arbitrariness and vagueness thereby offending Article 14 of the Constitution of India, it is argued by Mr.Soli Sorabji, learned senior counsel that the amended section as it stands today is unworkable. Section 3 of the Act enumerates what are not inventions. Under Article 27 of "TRIPS", all inventions, subject to paragraphs 2 and 3 of that Article, are patentable. Reading Article 27 as a whole, it is argued that the drug invented in the case on hand is patentable. Under the amended section, the patent applicant is required to show that the invention has enhanced efficacy of the known substance. Though the efficacy of a known substance may be well known, yet, unless

there are some guidelines in the amended section itself to understand the expression "enhancement of the known efficacy" namely, what would be treated as "enhanced efficacy", an uncontrolled discretion is given to the Patent Controller to apply his own standards, which may not be uniform, in deciding whether there is enhancement of the known efficacy of that substance. Such wide discretion vested with a Statutory Authority without any guidelines to follow, would result in arbitrary exercise of power. In other words, the Patent Controller may be in a position to decide any case, based on his whims and fancies namely, whether there is enhancement in the known efficacy or not. On this short ground, the section must be held to be violative of Article 14 of the Constitution of India. Likewise, in the Explanation attached to the amended section also, there is vagueness. The Explanation declares that all derivatives of a known substance shall be considered to be the same substance unless they "differ significantly in properties with regard to efficacy". Derivatives need not be the same substance in all cases. Unless the Explanation contains guidelines as to when a derivative can be held to differ significantly in properties with regard to efficacy, the Patent Controller will have an unguided power to decide the issue, which once again would result in arbitrariness. It is argued by learned senior counsels that though efficacy of a known substance could be clinically found, any discovery of a new form of the said substance or it's derivatives, though by themselves are inventions as defined in the Act, are denied patent based on the amended section containing specified offending clauses namely, it should show enhancement of the known efficacy and that the derivatives should differ significantly in properties with regard to efficacy.

4. Learned senior counsels on the opposite side would vehemently contend that the amended section is definitely compatible to "TRIPS". Even assuming that it is not so, the remedy to have the "TRIPS" agreement complied with in letter and spirit available to the member countries does not lie before the Indian courts but only before the Dispute Settlement Board, hereinafter referred to as "DSB" created under "TRIPS" itself. According to them, even assuming if "TRIPS" confers rights on any citizen/legal entity of a member country, then such person should also approach "DSB" only. "DSB" had been constituted to address all disputes that may arise between member countries and their citizens/legal entity in implementing or not implementing "TRIPS" and that is the exclusive authority to go into those

controversies. Therefore, the challenge to the validity of the amended section on the ground that it is not compatible to "TRIPS", cannot be legally sustained before Indian courts. It is contended by learned senior counsels and the other counsels on the opposite side that in discharging their obligations under "TRIPS", Government of India had brought in several amendments to the Parent Act and the amended section is one such provision. Every member country is given enough elbow room to bring in a local law in discharging their obligation under "TRIPS" having regard to the various needs of their citizens. India is a welfare country and it's first obligation under the Constitution is to provide good health care to it's citizens. When that is it's priority commitment under the Constitution of India, the Union of India has every right to bring in any local law in discharging their obligations under "TRIPS" to suit to the needs and welfare of it's citizens. On the attack to the amended section that it is vague, arbitrary and therefore unconstitutional, it is argued by learned senior counsels and the other counsels in the opposite camp that the amended section as it stands is workable. The Patent Controllers are all experts having undergone considerable training abroad in this field. The petitioner is not a novice to the field but on the other hand it is one of the pharmaceutical giants in the world. The efficacy of a known substance is well-known and it is definitely known to everyone in the pharmaceutical field. When the efficacy of that substance would stand enhanced could also be clinically found by those in the field. The petitioner is not a common man but it is having the expertise behind it. When does the properties in a derivative differ significantly with regard to efficacy could also be scientifically established by the people in the field. Therefore when everyone in the pharmaceutical field understands what is meant by enhancement in the known efficacy of a substance or when it can be said that the derivatives differ significantly in properties with regard to efficacy and the Patent Controller also understands it, the amended section cannot be struck down on the ground of arbitrariness and vagueness. If the Patent Controller, exercising his Statutory power, wrongly rejects the patent application on the ground that the drug is excluded under the amended section, then such a decision could always be corrected by the Appellate Authority and then by the higher forums. In other words, a wrong decision arrived at by the Patent Controller based on wrong application of the amended section cannot be a ground to strike down the said amended section which is otherwise in order. Case law was cited at the Bar by learned counsel Mr. Lakshmikumaran appearing for the opposite party that Indian courts have no

jurisdiction to test the validity of a municipal law on the ground that it is in violation of an International Treaty, assuming it is so. It is argued by Mr. Lakshmikumaran, learned counsel, by citing an English Court decision, that a member has a right to make a Law of it's own by breaking an International Treaty, if making such a Law is warranted, to meet the welfare of it's citizens. Responding to the arguments advanced by the learned senior counsels and the other counsels for the opposite party that Indian courts cannot test the validity of the amended section on the ground that it is in violation of an International Treaty, learned senior counsels appearing for the petitioner in each case contended, by showing a precedent, that Indian courts do have the power. It is also argued by them that even assuming for a moment without conceding that an Indian Law cannot be struck down on the ground that it is in violation of an International Treaty, yet, there is no bar, either express or implied, disabling Indian courts to give a declaration that the amended section is in violation of the international Treaty. After broadly stating their respective contentions, R3, R4, R5 & R7, R6, R8 and R9 filed their respective written submissions.

5. On the submissions made by the learned senior counsels on either side, we are of the considered opinion that the following issues arise for consideration in these two writ petitions:

(a) Assuming that the amended section is in clear breach of Article 27 of "TRIPS" and thereby suffers the wise of irrationality and arbitrariness violating Article 14 of the Constitution of India, could the courts in India have jurisdiction to test the validity of the amended section in the back drop of such alleged violation of "TRIPS"? OR Even if the amended section cannot be struck down by this court for the reasons stated above, cannot this court grant a declaratory relief that the amended section is not in compliance of Article 27 of "TRIPS"?.

(b) If it is held that courts in India have jurisdiction to go into the above referred to issue, then is the amended section compatible or non-compatible to Article 27 of "TRIPS"?

(c) Dehors issues (a) and (b) referred to above, could the amended section be held to be violative of Article 14 of the Constitution of India on the ground of

vagueness, arbitrariness and conferring un-canalised powers on the Statutory Authority?

6. Let us take the first issue.

(a) Assuming that the amended section is in clear breach of Article 27 of "TRIPS" and thereby suffers the vice of irrationality and arbitrariness violating Article 14 of the Constitution of India, could the courts in India have jurisdiction to test the validity of the amended section in the back drop of such alleged violation of "TRIPS" (OR) Even if the amended section cannot be struck down by this court for the reasons stated above, cannot this court grant a declaratory relief that the amended section is not in compliance of Article 27 of "TRIPS"?: In support of the arguments that Indian courts have jurisdiction to decide the issue under consideration, learned senior counsels appearing for the petitioners relied upon the decision of the House of Lords in the case reported in Equal Opportunities Commission & Another Vs. Secretary of State for Employment [(1994) 1 All ER Pg.910]. Employment Protection (Consolidation) Act, 1978 was under consideration in that judgment in the context of discrimination against women alleged. Under that Act, full time workers, who worked for 16 or more hours a week had to be in continuous employment for two years to qualify for Statutory rights under the Act whereas, part-time workers, who worked between 8 and 16 hours in a week had to be in continuous employment for five years to qualify for the Statutory rights under that Act. That judgment noted that a great majority of full-time employers in the United Kingdom were men while the great majority of part-time workers were women. Equal Opportunities Commission took the view that such discrimination conflicted with the obligations of the United Kingdom under EEC Law namely, Article 119 of EEC Treaty and Council Directives 75/117 (the Equal Pay Directive) and 76/207 (the Equal Treatment Directive). The Secretary of the State declined to accept that the United Kingdom was in breach of it's obligations under Community Law while providing less favourable treatment in the conditions of employment of full-time workers and part-time workers. Therefore, the Equal Opportunities Commission applied for judicial review of the Secretary of State's decision and sought a declaration that the Secretary of State and United Kingdom were in breach of Community Law obligations and an order of mandamus requiring the Secretary of State to introduce Legislation to provide the right for men

and women to receive equal pay for equal work. Further reliefs were also asked for. The Secretary of State raised two objections namely, the claim of an individual applicant is a private law claim, which ought not to have been brought against the Secretary of State by way of judicial review and that the Commission had no locus standi to bring the proceedings as it's case did not involve any decision on justiciable issue susceptible of judicial review. It was further contended by the Secretary of State that the court had no jurisdiction to declare that United Kingdom or the Secretary of State was in breach of any obligations under the Community Law and that the Divisional Court was not the appropriate forum to determine the substantive issue raised by the applicant. The Divisional Court, among other things, held that the court only had jurisdiction to declare rights and obligations enforceable under the existing state of the Law and had no jurisdiction to order mandamus requiring the Secretary of State to introduce Legislation to amend the 1978 Act or to declare that he was under a duty to do so. The Commission as well as the individual applicant appealed to the Court of Appeal, which dismissed the individual applicant's appeal on the ground that her application was essentially a private law claim, which should have been brought against her employer in an Industrial Tribunal and dismissed the Commission's appeal on the ground that the Secretary of State had not made any "decision". The Court of Appeal also held that there was no justiciable issue suitable for consideration by way of judicial review. The Commission and the individual appealed to the House of Lords. The House of Lords raised various questions to be addressed by it in that appeal and in our respectful opinion, the decision of the House of Lords on one of the questions raised by it to be addressed, would be relevant for the purpose of the case on hand. We extract that question hereunder:

"The question is, whether judicial review is available for the purpose of securing a declaration that certain United Kingdom primary Legislation is incompatible with Community Law?"

In deciding that issue, the House of Lords referred to Article 119 of the EEC Treaty, which provides for the following:

"Equal pay for equal work to men and women; Council Directive (EEC) 75/117 (the equal pay directive); and Article 2(1) of Council Directive (EEC) 76/207 (the equal treatment directive)".

Section 2 of the European Communities Act, 1972 was also brought to the attention of the House of Lords. It being the telling provision in deciding the issue before us, we extract it hereunder:

"(1) All such rights, powers, liabilities, obligations and restrictions from time to time created or arising by or under the Treaties and all such remedies and procedures from time to time provided for by or under the Treaties, as in accordance with the Treaties are without further enactment to be given legal effect or used in the United Kingdom shall be recognised and available in law, and be enforced, allowed and followed accordingly; and the expression "enforceable Community right" and similar expressions shall be read as referring to one to which this subsection applies."

The House of Lords dismissed the appeal of the individual claimant agreeing with the decision of the earlier courts that it was only her private law claim. But however, in deciding the appeal of Equal Opportunities Commission, the House of Lords gave a declaration that Employment Protection (Consolidation) Act, 1978 is incompatible with Article 119 of the EEC Treaty and Council Directive (EEC) 75/117 and Council Directive (EEC) 76/207. Therefore learned senior counsels Mr. Soli Sorabji and Mr. Shanthi Bhushan, relying upon this judgment, argued, as they have done earlier, that there is no legal bar for this court to give a simplicitor declaratory relief that the amended section is incompatible with Article 27 of "TRIPS". It is also argued by the learned senior counsels that this court can go into the validity of the amended section, as being not in compliance with Article 27 of "TRIPS", under Article 226 of the Constitution of India, since there is neither express nr implied bar in the Article itself.

7. Learned counsels, in particular, Mr. Anand Grover and Mr. Lakshmikumaran, argued with tremendous ease - as they are shown to possess - stating that the judgment referred to above and relied upon by the learned senior counsels could not be applied to the case on hand on facts. By taking us through the very same judgment, it is argued by them that under section 2(1) of the European Communities Act, 1972,

Article 119 of the EEC Treaty with the two Council Directives referred to earlier have been domesticated as a domestic Law in England. When the relevant provision of the EEC Treaty and the Councils Directives stand domesticated by an Act of the State, then it becomes Law of that State enforceable in letter and spirit by the citizens of that State. It is their argument that "TRIPS" do not become Law in India on it's own force without any domestic Law legislated by the Indian Government. Only in discharging their obligations under "TRIPS", several amendments, including the amended section, were brought into the Statute book namely, Patents Act, by the Government. Therefore they argued that when Equal Opportunities Commission case can be distinguished on facts, it would be inappropriate to rely upon the same to hold that a declaratory relief can be granted by this court. As the learned counsels were making their submissions on the above point, Mr.Shanthi Bhushan, learned senior counsel appearing for the petitioner in one of the writ petitions, very fairly conceded and stated that Equal Opportunities Commission's case can be distinguished on facts. We do find, on going through the judgment in Equal Opportunities Commission's case, that the provisions of EEC Treaty and the Councils Directives by an Act of the State was domesticated and therefore all the rights flowing out of the said Treaty and the Directives were available as Law in the United Kingdom, which can be enforceable. Only in that context, we state with respect that the House of Lords has given a declaration as prayed for. Learned counsels appearing for the contesting parties did not rest with the laurel of making us accept and Mr. Shanthi Bhushan to concede that Equal Opportunities Commission case is distinguishable on facts but spared no efforts in advancing arguments in their own way, supported by case laws, that Indian Courts have no jurisdiction either to test the validity of a State Act as being incompatible to an International Treaty namely, Article 27 or even to give a declaration simplicitor that such State Act is not compatible to an International Treaty. We will be failing in our duty if we do not mention that Mr.V.T.Gopalan, learned Additional Solicitor General was leading from the forefront the entire band of lawyers in the opposite camp by contending that this court has no jurisdiction at all to go into the issue referred to above; in any event the amended section is in compliance with Article 27 of "TRIPS" and that there is no violation of Article 14 of the Constitution of India. Mr.Lakshmikumaran, learned counsel appearing for R5 and R7 relied upon a judgment reported in 1966-3-All England Law Reports Pg.871 (Salomn Vs. Commissioner of Customs) to contend that if any domestic court is approached

challenging a municipal law on the ground that it violates International Law, then, the remedy for that lies in a forum other than the domestic court. In that judgment, the Court of Appeal through LORD DIPLOCK held as hereunder:

"If the terms of the legislation are clear and unambiguous, they must be given effect to whether omot they carry our Her Majesty's treaty obligations, for the sovereign power of the Queen in Parliament extends to breaking treaties [(see Ellerman Lines, Ltd. Vs. Murray (4)], and any remedy for such a breach of an international obligation lies in a forum other than Her Majesty's own courts."

The above extracted passage refers to an earlier English decision. The learned English Judge, in the latter portion of his judgment, had reiterated that Ellerman Lines Limited's case is the authority for the proposition that when a domestic law is challenged on the ground of it being in violation of an International Treaty, domestic courts would have no jurisdiction. In our considered opinion, this is the direct judgment on the point. We have already noted that the judgment in Equal Opportunities Commission case is distinguishable on facts.

8. Even otherwise, we are of the considered view that in whichever manner one may name it namely, International Covenant, International Treaty, International Agreement and so on and so forth, yet, such documents are essentially in the nature of a contract. In Head Money cases namely, the judgment of the Supreme Court of the United States reported in 112 U.S. 580, it is held as follows:

"A treaty is primarily a compact between independent Nations, and depends for the enforcement of its provisions on the honor and the interest of the governments which are parties to it."

Therefore there cannot be any difficulty at all in examining such treaties on principles applied in examining contracts. Under these circumstances, when a dispute is brought before a court arising out of an International Treaty, courts would not be committing any error in deciding the said dispute on principles applicable to contracts. In other words, the court has to analyse the terms of such international Treaty: the enforceability of the same; by whom and against whom; and if there is violation, is

there a mechanism for solving that dispute under the treaty itself? Based on such construction of the International Treaty namely, "TRIPS", it is argued very strenuously by the learned counsels appearing for the contesting parties that there is a settlement mechanism under the Treaty itself and therefore even assuming without conceding that the petitioner has the right to enforce the terms of the said Treaty, yet, he must go only before the Dispute Settlement Body provided under the "TRIPS" itself. Article 64 of "TRIPS" is pressed into service to sustain this point. It is contended by Mr. Anand Grover learned counsel that the settlement mechanism provided under Article 64 of "TRIPS" is governed by the procedure as understood by the World Trade Organization. Mr. Anand Grover learned counsel took us through the said Dispute Settlement Understanding. Article 1 of the Dispute Settlement Understanding; defines the areas covered under that Rule. Article 1 declares that the agreements listed in Appendix 1 to the said Rule would be covered by the procedure. "TRIPS" is mentioned as one of the agreements in Appendix 1 (B) - Annexure 1C. We have been taken through the above referred to Rules and Procedures governing the settlement of disputes and we find that it contains comprehensive provisions for resolving the disputes arising out of any agreements enumerated in Appendix 1 to that Rules. Under the Rules there is a Dispute Settlement Body. The manner of it's constitution is also provided therein. Various steps to sort out the problem arising out of an agreement are provided therein. Article 17 of the Rules referred to above provides an appellate review against the order passed by the panel. Therefore we have no difficulty at all that Article 64 of "TRIPS" read with World Trade Organization's understanding on Rules and Procedures governing the settlement of disputes provides a comprehensive settlement mechanism of any dispute arising under the agreement. Article 3 of the Rules declares that the dispute settlement system of the World Trade Organization is to provide security and predictability to the multilateral trading system. When such a comprehensive dispute settlement mechanism is provided as indicated above and when it cannot be disputed that it is binding on the member States, we see no reason at all as to why the petitioner, which itself is a part of that member State, should not be directed to have the dispute resolved under the dispute settlement mechanism referred to above. Several nations in the world are parties to "TRIPS" as well as the "WTO" agreement. The agreements are discussed, finalized and entered into at the higher level of the nations participating in such meeting. Therefore it is binding on them. When such participating nations, having

regard to the terms of the agreement and the complex problems that may arise out of the agreement between nation to nation, decide that every participating nation shall have a Common Dispute Settlement Mechanism, we see no reason at all as to why we must disregard it. As we began saying that any International Agreement possesses the basic nature of an ordinary contract and when courts respect the choice of jurisdiction fixed under such ordinary contract, we see no compelling reasons to deviate from such judicial approach when we consider the choice of forum arrived at in International Treaties. Since we have held that this court has no jurisdiction to decide the validity of the amended section, being in violation of Article 27 of "TRIPS", we are not going into the question whether any individual is conferred with an enforceable right under "TRIPS" or not. For the same reason, we also hold that we are not deciding issue No. (b) namely, whether the amended section is compatible to Article 27 of "TRIPS" or not.

9. We also carefully applied our mind as to whether we can give a declaratory relief in exercise of the power under Article 226 of the Constitution of India? We have already found that the judgment in Equal Opportunities Commission case is not a precedent for giving such a declaration. In the judgment reported in AIR 1951 SC Pg.41 (Charanjit Lal Vs. Union of India) and the judgment reported in AIR 1959 SC Pg.725 (K.K.Kochunni Vs. State of Madras) the Supreme Court was considering the power of the court under Article 32 of the Constitution of India to give a declaratory relief. Both the judgments were rendered by two Constitution Benches of the Supreme Court. The Chief Justice of India presided the Constitution Bench in the latter judgment and the said Hon'ble Judge also constituted the coram in the earlier judgment. We extract the relevant portion in paragraph No.45 of the earlier judgment of the Supreme Court:

"As regards the other point, it would appear from the language of Article as of the Constitution that the sole object of the article is the enforcement of fundamental rights guaranteed by the Constitution. A proceeding under this Article cannot really have any affinity to what is known as a declaratory suit."

"Any way, Article 32 of the Constitution gives us very wide discretion in the matter of framing our writs to suit the exigencies of particular cases, and the

application, of the petitioner cannot be thrown out simply on the ground that the proper writ or direction has not been prayed for."

In the latter case, the power of the court to grant declaratory relief came up for consideration. The Constitutionality of Madras Act 32/55 was challenged as infringing fundamental rights under Article 19(1)(f) and Article 31(1). The point that appears to have been argued in favour of granting a declaratory decree, as noted therein, is extracted hereunder:

"The next argument in support of the objection as to the maintainability of these petitions is thus formulated: The impugned Act is merely a piece of a declaratory legislation and does not contemplate or require any action to be taken by the State or any other person and, therefore, none of the well known prerogative writs can afford an adequate or appropriate remedy to a person whose fundamental right has been infringed by the mere passing of the Act. If such a person challenges the validity of such an enactment, he must file a regular suit in a court of competent jurisdiction for getting a declaration that the law is void and, therefore, cannot and does not affect his right. In such a suit he can also seek consequential reliefs by way of injunction or the like, but he cannot avail himself of the remedy under Article 32. In short, the argument is that the proceeding under Article 32 cannot be converted into or equated with a declaratory suit under section 42 of the Specific Relief Act."

The Hon'ble Judges of the Supreme Court in that case referred to the earlier judgment of the Supreme Court referred to above as well as the judgments reported in AIR 1950 SC 163 (Rashid Ahmed Vs. Municipal Board, Kairana); AIR 1954 SC 440 (Basappa Vs. T. Nagappa); AIR 1954 SC 229 (Ebrahim Vadir Mavat Vs. State of Bombay) and held as hereunder:

"But on a consideration of the authorities it appears to be well established that this Court's powers under Article 32 are wide enough to make even a declaratory order where that is the proper relief to be given to the aggrieved party. The present case appears to us precisely to be an appropriate case, if the impugned Act has taken away or abridged the petitioners' right under Article 19(1)(f) by its own terms and without anything more being done and such infraction cannot be justified. If

therefore, the contentions of the petitioners be well founded, as to which we say nothing at present, a declaration as to the invalidity of the impugned Act together with the consequential relief by way of injunction restraining the respondents and in particular respondents 2 to 17 from asserting any rights under the enactment so declared void will be the only appropriate reliefs which the petitioners will be entitled to get. Under Article 32 we must, in appropriate cases, exercise our discretion and frame our writ or order to suit the exigencies of this case brought about by the alleged nature of the enactment we are considering."

Therefore it is clear that when an enactment infringes the fundamental rights and a challenge is made to that on that ground, the Hon'ble Supreme Court of India had said that it should not hesitate to grant a declaratory relief under Article 32 of the Constitution of India. In AIR 1975 SC 1810 (S.G.Films Exchange Vs. Brijnath Singhji) and AIR 1976 SC 888 (Vaish Degree College Vs. Lakshmi Narain), the Supreme Court held that the relief of declaration under the provisions of the Specific *Relief Act is purely discretionary. In the latter judgment, the Supreme Court went on* to hold that while exercising it's discretionary powers, the court must keep in mind the well settled principles of justice and fair play and should exercise the discretion only if the ends of justice require it, for justice is not an object which can be administered in vacuum. As rightly contended by Mr. P. S. Raman learned senior counsel, we have to decide in this case whether the amended section is bad in law for lack of legislative competency or it violates Part-III of the Constitution of India or any other provisions in the Constitution. We also thought whether ends of justice require giving a helping legal hand to the petitioner. The amended section does not take away in toto the right of the petitioner to carry on the trade. It is contended by Mr.P. S. Raman learned senior counsel that the petitioner gets only a proprietary right over the patent lasting for a fixed tenure and beyond that it does not get anything else. We agree with him on this point. We also find that ends of justice, on the facts of this case, is not in favour of the petitioner, which would disable us from exercising our discretionary jurisdiction. It has been held by the Supreme Court in an unreported judgment in Katakis Vs. Union of India (W.P.No.54/68 dated 28.10.1968) that no declaration would be given where it would serve no useful purpose to the petitioner. We thought what will happen if a declaratory relief is given as asked for. Assuming for a moment that we have the jurisdiction. It is a settled position in law that nobody can compel the

Parliament to enact a Law. If that is the position, then, assuming that we give a declaration as prayed for namely, the amended provision is not in the discharge of India's obligation under Article 27 of "TRIPS", even then, we fail to see for what use the petitioner can put it. Even if a consequential relief is not asked for, courts have held, depending upon the facts available in each case, that a declaratory relief could be granted, provided, it is shown that such a declaratory relief would be a stepping stone to claim relief at some other stage. Having that in our mind, when we again thought aloud as to what use to which such a declaratory relief, if granted to the petitioner, could be put to and we find that there is no scope at all to put in use the declaratory relief, if granted, at a later point of time. In other words, the declaratory relief, even if granted, would be only on paper, on the basis of which, the petitioner cannot claim any further relief in the Indian courts. Only in this context, we extract hereunder the relevant portion in the unreported judgment of the Supreme Court in Katakis case referred to above, which was rendered by a Constitution Bench consisting of Hon'ble Judges Sikri, Bachawat, Mitter, Hegde and Grover, JJ:

"It is not even stated that the petitioner did not apply because of the canalisation scheme. The Supreme Court in appropriate circumstances can give a declaration that a particular order or scheme violates the provisions of the constitution but the Supreme Court will not give such a declaration unless it is certain that the declaration will serve some useful purpose to the petitioners. Even if the declaration is given the petitioners may possibly not apply for a licence; if they do apply, the conditions of import and export may change drastically by the time the application is filed, or the policy of the Government may change. But if the petitioners had applied for the licence on the basis that the canalisation scheme was invalid, their application would have been processed by the authorities apart from the canalization scheme but in accordance with law. The Court declined to go into the question of the validity of the canalisation scheme."

Therefore, for the reasons stated above, we find that the petitioner in each writ petition is not entitled to even the declaratory relief.

10. Let us now take the last issue for consideration.

"(c) Dehors issues (a) and (b) referred to above, could the amended section be held to be violative of Article 14 of the Constitution of India on the ground of vagueness, arbitrariness and conferring un-canalised powers on the Statutory Authority?"

The main grounds of attack to the validity of the amended section are that, it is vague, arbitrary and confers uncanalised powers on the Statutory Authority. The Statutory Authority in this case is the Patent controller. There is no doubt that he is exercising a quasi-judicial function namely, considers the patent claim application in the context of the objections received; hears parties on both sides and then passes an order, either granting the patent or rejecting the patent application, by giving reasons. Prior to the amended section was brought into the Statute book by the Patent (Amendment) Act, 2005 (Act 15/2005) with effect from 01.01.2005; it was preceded by Ordinance 7/2004 containing the proposed amendment to be made to section 3(d). In the earlier portion of this judgment, we have extracted section 3(d) as it originally stood; section 3(d) as sought to be brought in by Ordinance 7/2004 and the amended section itself. India is a founder member of the World Trade Organisation, in short, "WTO" and as such a signatory of "TRIPS", which itself is an Annexure to the "WTO" agreement. There is no dispute that under "TRIPS" agreement, India has to permit product patent in all fields of technology, including medicines and drugs, with effect from 01.01.2005. Pending bringing in comprehensive provisions, the Union Government of India made some temporary provisions in the Act itself, which temporary provisions came to an end on and with effect from the coming into force of Act 15/2005. Prior to Amending Act 15/2005, there were Amending Acts 17/1999 and 38/2002. In the affidavits filed in support of both the writ petitions, Parliamentary Debates on Ordinance 7/2004, in the context of the amendment to section 3(d) are extensively extracted. A speech from the Member of the Parliament from Kottayam in that regard and the reply in regard thereto from the Hon'ble Minister of Commerce are found so extracted. The Parliamentarians appear to have been opposing the amendment to section 3(d) on the ground that, if the amendment as indicated in the Ordinance is allowed to be brought in, then, there is a fear of the common man being denied access to life saving medicines and it would encourage evergreening. The reply by the Hon'ble Minister shows that he was aware of the impending problem namely, 'evergreening" and the action which the Hon'ble Minister intend to take. Admittedly,

the amended section is not the amendment sought to be introduced by Ordinance 7/2004. It is argued byleamed senior counsels appearing for the petitioners that had the amendment proposed unde. Ordinance 7/2004 been brought into the Act in the form in which it was shown, then, it would have been in strict compliance to "TRIPS". But instead, the amended section has been brought into the Statute book. It is clear that the amended section appears to have been drafted in a great hurry without realizing that it is likely to be struck down on the ground that it is incompatible with "TRIPS" (we have already held that we cannot go into that question) and also being in violation of Article 14 of the Constitution of India (the later point alone survives now). Since the ground of attack based on vagueness and arbitrariness and conferring uncanalised power to the Statutory Authority over-lap each other and therefore our points of discussion are also likely to over-lap each other. So we have decided to take up all the three individual grounds raised for decision in a consolidated manner.

11. According to the learned senior counsels, the amended section is bad for the following reasons:

Under Ordinance 7/2004 mere discovery of a new property is not treated as an invention. But however, in the amended section, a further clause is added to the effect that the discovery of a new form of a known substance should result in the enhancement of the known efficacy of that substance and if it does not, then, it is not an invention. Therefore the argument goes on the validity of the amended section that in the absence of any guideline in the amended section or the Act itself as to how to find out, when there is enhancement of the known efficacy of the substance from which the discoveries are made, then, an unguided discretion is vested with the Statutory Authority and therefore the amended section is bad in law. They would then argue that to make the matter worse, to the amended section, an Explanation is added. by which, a deeming fiction is created to the effect that all salts, esters, etc., etc., if derived from a known substance, then, such derivatives are also considered to be the same substance, unless the derivatives are shown to differ significantly in properties with regard to efficacy. It is argued that all derivatives need not necessarily be the same substance and therefore the deeming fiction created by the Explanation is bereft of any guidelines and is bad in Law. It is argued that there must be some guidance or guideline in the Act itself as to when a derivative shall be held to be differing

significantly in properties with regard to efficacy. In other words, the submission is that, both the amended section as well as the Explanation to the amended section must prescribe in clear terms for the Authority constituted under the Act, the guidelines to decide in what circumstances it can be held that the discovery of a new form of a known substance had resulted in the enhancement of the known efficacy of that substance and when the derivatives are found to differ significantly in properties with regard to efficacy. Though the expression "efficacy" has a definite meaning, yet, no definite meaning could be attributed to the expression "enhancement of the known efficacy" and "differ significantly in properties with regard to efficacy". These expressions are ambiguous. Therefore it is argued by learned senior counsels that when it is possible for the Legislature to explain what is meant by "enhancement of a known efficacy" and "differing significantly in properties with regard to efficacy", the Legislature is duty bound to clear the ambiguity. According to them, if this ambiguity is not cleared, then, there is every chance for the Statutory Authority to exercise it's power to it's whims and fancies. Therefore the amended section is also irrational. Opposing these arguments, learned Additional Solicitor General of India and the other learned senior counsels and learned counsels for the contesting parties would submit that having regard to the field in which the amended section is to operate; the technological and scientific research oriented advances already made and likely to be made in the coming future and which may be a continuing process for all time to come, the Legislature thought it fit to use only general expressions in the Act, leaving it for the Statutory Authority to apply it's mind to the various facts that are brought to it's notice and then find out whether the invented drug is within the mischief of the amended section or outside it. Therefore it would be unwise to fix any specific formula to be applied, as a matter of static measure, to find out whether the new form of a known substance resulted in the enhancement of the known efficacy or the derivatives differ significantly in properties with regard to efficacy. Having regard to the inventions that are made and are likely to be made in the time to come, it is humanly impossible to prescribe a fixed formula to decide the issue as indicated above and if it is so done without even knowing what would be the new discoveries, then, the hands of the Statutory Authority would be completely tied to a fixed and definite situation, from which it cannot even wriggle out. Discoveries that are likely to be made in the future may not be alike and they may vary from each other in their therapeutic effect and properties. Learned Additional Solicitor General of India and

other learned senior counsels appearing for the pharmaceutical companies would argue that in the given situation, the amended section as it stands today is a classic Legislation by itself thereby giving enough room in the joints for the Statutory Authority to evaluate the materials placed before him in a case to case basis; analyse the comparative details that are likely to be placed before him and then arrive at a decision to say whether the discovery / derivative is an invention or not. Therefore the Statutory Authority has been given a discretion, which he has to exercise based on the details to be placed before him. In exercising such a discretionary power vested in the Statutory Authority, if it is found that he has exercised that discretionary power wrongly or abused it, then, such an error can always be corrected by higher forums, which is provided for in the Act itself and thereafter, by the courts of law. In other words, a provision of law cannot be struck down on the ground that the Authority exercising the power under that provision is likely to misuse it, unless it is shown that the said provision itself ex-facie is violative of Article 14 of the Constitution of India, which is not the case here. When there would be enhancement of the known efficacy and when it would be found that the derivatives differ significantly in properties with regard to efficacy, would vary from discovery to discovery. It is then argued that the Explanation to the amended section does not create any additional criteria but it only explains the amended section itself. Debates in Parliament could not be the basis for interpreting the Statute, is their last submission.

12. In the light of the arguments advanced by the learned senior counsels all-round, we went through the entire records. We do find that section 3(d) as shown in Ordinance 7/2004 had not been reproduced in the form in which it was shown in the Act. Therefore the amended section definitely differs from the form in which it was put in the Ordinance. The amended section is not confined only to drugs as it deals with machines and apparatuses as well. But however, we are clear in our mind that the portions of the amended section and the Explanation under attack is definitely referable only to the pharmacology field namely, drugs. Since Parliamentary debates have been relied upon by the learned senior counsels for the petitioners to argue that since the amended section appears to be a hurriedly brought out Legislation, the Parliamentary debates can be looked into to find out whether the amended section is ex-facie violative of Article 14 of the Constitution of India. We went through the case laws brought to our notice by Mr. V. T. Gopalan, learned Additional Solicitor General

of India: Mr. P. S. Raman learned senior counsel and Mr. Anand Grover. Mr. Shanthi Bhushan, learned senior counsel relied upon one or two judgments so brought to our notice. We also tried to find out as to whether the "statement of objects and reasons" of an Act would help the court to analyse the provision which the writ petitioner alleges is violating Article 14 of the Constitution of India. The earliest judgment of the Indian court brought to our notice in this context by Mr. P. S. Raman learned senior counsel, is the judgment of the Supreme Court reported in AIR 1952 SC Pg.369 (Aswini Kumar Vs. Arabinda Bose), in which the law on the subject is laid down as hereunder:

"The speeches made by the members of the House in the course of the debate are not admissible as extrinsic aids to the interpretation of statutory provisions: AIR 1952 SC 366."

"The Statement of Objects and Reasons, seeks only to explain what reasons induced the mover to introduce the bill in the House and what objects he sought to achieve. But those objects and reasons may or may not correspond to the objective which the majority of members had in view when they passed it into law. The Bill may have undergone radical changes during its passage through the House or Houses, and there is no guarantee that the reasons which led to the introduction and the objects thereby sought to be achieved have remained the same throughout till the Bill emerges from the House as an Act of the Legislature. for they do not form part of the Bill and are not voted upon by the members. The Statement of Objects and Reasons appended to the Bill should be ruled out as an aid to the construction of a statute."

Therefore from the above pronouncement, it is clear that when the Bill is debated, new things are likely to emerge and the emerging new things may be taken into account while a final shape is given to the Bill before it was brought into an Act. The statement of objects and reasons also stands excluded as extrinsic aid to the construction of a Statute. The next in line is the judgment of the Supreme Court reported in (1986) 2 SCC Pg.257 (Girdhari Lal & Sons Vs. Balbir Nath Mathur) wherein, on the subject of interpretation of Statutes, the Supreme Court had laid down the law as hereunder:

"7. Parliamentary intention may be gathered from several sources. First, of course, it must be gathered from the statute itself, next from the preamble to the statute, next from the Statement of Objects and Reasons, thereafter from parliamentary debates, reports of committees and commissions which preceded the legislation and finally from all legitimate and admissible sources from where there may be light. Regard must be had to legislative history too."

"8. Once parliamentary intention is ascertained and the object and purpose of the legislation is known, it then becomes the duty of the court to give the statute a purposeful or a functional interpretation. This is what is meant when, for example, it is said that measures aimed at social amelioration should receive liberal or beneficent construction. Again, the words of a statute may not be designed to meet the several uncontemplated forensic situations that may arise. The draftsman may have designed his words to meet what Lord Simon of Glaisdale calls the "primary situation". It will then become necessary for the court to impute an intention to Parliament in regard to "secondary situations". Such "secondary intention" may be imputed in relation to a secondary situation so as to best serve the same purpose as the primary statutory intention does in relation to a primary situation."

Mr. Anand Grover, learned counsel appearing for one of the pharmaceutical companies brought to our notice the judgment of the Supreme Court in the case reported in (1994) 5 SCC Pg.593 (K. S. Paripoorman Vs. State of Kerala), wherein, the Supreme Court had held on the Law of Interpretation of Statutes as hereunder:

"As regards the Statement of Objects and Reasons appended to the Bill the law is well settled that the same cannot be used except for the limited purpose of understanding the background and the state of affairs leading to the legislation but it cannot be used as an aid to the construction of the statute. (See Aswini Kumar Ghosh Vs. Arabinda Bose; State of West Bengal Vs. Subodh Gopal Bose per Das, J; State of West Bengal Vs. Union of India). Similarly, with regard to speeches made by the members in the House at the time of consideration of the Bill it has been held that they are not admissible as extrinsic aids to the interpretation of the statutory provisions though the speech of the mover of the Bill may be referred to for the

purpose of finding out the object intended to be achieved by the Bill. (See State of Travancore, Cochin Vs. Bombay Co. Ltd. And Aswini Kumar Vs. Arabinda Bose)."

Learned senior counsels on either side also relied upon a judgment of the Supreme Court reported in (1998) 4 SCC Pg.626 (P.S.Narasimha Rao Vs. State (CBI/SPE), wherein, it has been held as follows:

"It would thus be seen that as per the decisions of this court the statement of the Minister who had moved the Bill in Parliament can be looked at to ascertain the mischief sought to be remedied by the legislation and the object and purpose for which the legislation is enacted. The statement of the Minister who had moved the Bill in Parliament is not taken into account for the purpose of interpreting the provisions of the enactment. The decision in Pepper Vs. Hari permits reference to the statement of the Minister or other promoter of the Bill as an aid to construction of legislation which is ambiguous or obscure or the literal meaning of which leads to an absurdity provided the statement relied upon clearly discloses the mischief aimed at or the legislative intention lying behind the ambiguous or obscure words and that such a statement of the Minister must be clear and unambiguous."

In Narasimha Rao's case referred to supra, the Supreme Court had held that the statement of the Minister, who makes the Bill in Parliament, can be looked at, to ascertain the mischief sought to be remedied by the Legislation. We now go back to Girdhari Lal's case referred to supra, wherein, the Supreme Court had held as follows:

"Our own court has generally taken the view that ascertainment of legislative intent is a basic rule of statutory construction and that a rule of construction should be preferred which advances the purpose and object of a legislation and that though a construction, according to plain language, should ordinarily be adopted, such a construction should not be adopted where it leads to anomalies, injustices or absurdities, vide K.P.Varghese Vs. ITO; State Bank of Travancore Vs. Mohd. M.Khan; Som Prakash Rekhi Vs. Union of India; Ravula Subba Rao Vs. CIT; Govindlal Vs. Agricultural Produce Market Committee and Bahaji Kondaji Vs. Nasik Merchants Co-op. Bank Ltd."

If we read the Parliamentary debate on Ordinance 7/2004, it appears that there was a wide spread fear in the mind of the members of the House that if section 3(d) as shown in Ordinance 7/2004 is brought into existence, then, a common man would be denied access to life saving drugs and that there is every possibility of "evergreening". The reply by the Hon'ble Minister for Commerce shows that the Hon'ble Minister was sure that Ordinance 7/2004 would prevent "evergreening". The Parliamentary debates also show that the Hon'ble Minister was concerned with the other issues as well. Therefore it is clear to our mind that section 3(d) brought by Amending Act 15/2005 is as a result of debates on Ordinance 7/2004 in the Parliament and due to debates change in the form is unavoidable and permissible, it is not possible to sustain the arguments advanced by the learned senior counsels that having shown section 3(d) in particular form in Ordinance 7/2004 and bringing it in a totally different form in Amending Act 15/2005, the amending section ex-facie stands in violation of Article 4 of the Constitution of India.

13. Let us now test the argument advanced before this court by learned Senior Counsels on the validity of the amended section on the touchstone of Article 14 of the Constitution of India. As we understand the amended section, it only declares that the very discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of that substance, will not be treated as an invention. The position therefore is, if the discovery of a new form of a known substance must be treated as an invention, then the Patent applicant should show that the substance so discovered has a better therapeutic effect. Darland's Medical Dictionary defines the expression "efficacy" in the field of Pharmacology as "the ability of a drug to produce the desired therapeutic effect" and "efficacy" is independent of potency of the drug.Dictionary meaning of "Therapeutic", is healing of disease - having a good effect on the body." Going by the meaning for the word "efficacy" and "therapeutic" extracted above, what the patent applicant is expected to show is, how effective the new discovery made would be in healing a disease / having a good effect on the body? In other words, the patent applicant is definitely aware as to what is the "therapeutic effect" of the drug for which he had already got a patent and what is the difference between the therapeutic effect of the patented drug and the drug in respect of which patent is asked for. Therefore it is a simple exercise of though preceded by research, - we state - for any Patent applicant to place on record

what is the therapeutic effect / efficacy of a known substance and what is the enhancement in that known efficacy. The amended section not only covers the field of pharmacology but also the other fields. As we could see from the amended section, it is made applicable to even machine, apparatus or known process with a rider that mere use of a known process is not an invention unless such a known process results in a new product or employs atleast one new reactant. Therefore the amended Section is a comprehensive provision covering all fields of technology, including the field of pharmacology. In our opinion, the explanation would come in aid only to understand what is meant by the expression "resulting in the enhancement of a known efficacy" in the amended section and therefore we have no doubt at all that the Explanation would operate only when discovery is made in the pharmacology field. In 1989 (4) SCC Pg.378 (Aphali Pharma. Ltd. Vs. State of Maharashtra), in laying down the law on "Explanation", the Supreme Court held as hereunder:

"33. An Explanation, as was found in Bihta Marketing Union Vs. Bank of Bihar, may only explain and may not expand or add to the scope of the original section. In State of Bombay Vs. United Motors, it was found that an Explanation could introduce a fiction or settle a matter of controversy. Explanation may not be made to operate as "exception" or "proviso". The construction of an Explanation, as was held in Collector of Customs Vs. G.Dass & Co., must depend upon its terms and no theory of its purpose can be entertained unless it is to be inferred from the language used. It was said in Burmah Shell Oil Ltd. Vs. CTO, that the Explanation was meant to explain the article and must be interpreted according to its own tenor and it was an error to explain the Explanation with the aid of the article to which it was annexed. We have to remember what was held in Dattatraya Govind Mahajan Vs. State of Maharashtra, that mere description of a certain provision, such as "Explanation" is not decisive of its true meaning. It is true that the orthodox function of an Explanation is to explain the meaning and effect of the main provision to which it is an explanation and to clear up any doubt or ambiguity in it, but ultimately it is the intention of legislature which is paramount and mere use of a label cannot control or deflect such intention. State of Bombay Vs. United Motors laid down that the interpretation must obviously depend upon the words used therein, but this must be borne in mind that when the provision is capable of two interpretations, that should be adopted which fits the description. An Explanation is different in nature from a

Proviso for a Proviso excepts, excludes or restricts while an Explanation explains or clarifies. Such explanation or clarification may be in respect of matters whose meaning is implicit and not explicit in the main section itself. In Hiralal Ratanlan Vs. State of U.P it was ruled that if on a true reading of an Explanation it appears that it has widened the scope of the main section, effect be given to legislative intent notwithstanding the fact that the legislature named that provision as an Explanation. In all these matters courts have to find out the true intention of the legislature. In D.G.Mahajan Vs. State of Maharashtra, this court said that legislature has different ways of expressing itself and in the last analysis the words used alone are repository of legislative intent and that if necessary an Explanation must be construed according to its plain language and not on any a priori consideration."

In 2006 (8) SCC 613 ((Hardev Motor Transport Vs. State of M.P.), on the role of "Explanation", the Supreme Court held as hereunder:

"31. The role of an Explanation of a statute is well known. By inserting an Explanation in the Schedule of the Act, the main provisions of the Act cannot be defeated. By reason of an Explanation, even otherwise, the scope and effect of a provision cannot be enlarged. It was so held in S.Sundaram Pillai Vs. V.R.Pattabiraman in the following terms: (SCC p.613, para 53:

"53. Thus, from a conspectus of the authorities referred to above, it is manifest that the object of an Explanation to a statutory provision is

(a) to explain the meaning and intendment of the Act itself,

(b) where there is any obscurity or vagueness in the main enactment, to clarify the same so as to make it consistent with the dominant object which it seems to subserve,

(c) to provide an additional support to the dominant object of the Act in order to make it meaningful and purposeful.

(d) an Explanation cannot in any way interfere with or change the enactment or any part thereof but where some gap is left which is relevant for the purpose of the Explanation, in order to suppress the mischief and advance the object of the Act it can help or assist the court in interpreting the true purport and intendment of the enactment, .

(See also Swedish Match AB Vs. Securities & Exchange Board of India)

In this case we find that the Explanation creates a deeming fiction of derivatives of a known substance are deemed to be the same substance unless they differ significantly in properties with regard to efficacy. Therefore it is clear from the amended section and the Explanation that in the pharmacology field, if a discovery is made from a known substance, a duty is cast upon the patent applicant to show that the discovery had resulted in the enhancement of a known efficacy of that substance and in deciding whether to grant a Patent or not on such new discovery, the Explanation creates a deeming fiction that all derivatives of a known substance would be deemed to be the same substance unless it differ significantly in properties with regard to efficacy. In *our opinion, the amended section and Explanation give importance to efficacy.* We have already referred to the meaning of "efficacy" as given in Dorland's Medical Dictionary. Scientifically it is possible to show with certainty what are the properties of a "substance". Therefore when the Explanation to the amended section says that any derivatives must differ significantly in properties with regard to efficacy, it only means that the derivatives should contain such properties which are significantly different with regard to efficacy to the substance from which the derivative is made. Therefore in sum and substance what the amended section with the Explanation prescribes is the test to decide whether the discovery is an invention or not is that the Patent applicant should show the discovery has resulted in the enhancement of the known efficacy of that substance and if the discovery is nothing other than the derivative of a known substance, then it must be shown that the properties in the derivatives differ significantly with regard to efficacy. As we stated earlier, due to the advanced technology in all fields of science, it is possible to show by giving necessary comparative details based on such science that the discovery of a new form a of known substance had resulted in the enhancement of the known efficacy of the original substance and the derivative so derived will not be the same substance. since

the properties of the derivatives differ significantly with regard to efficacy. As rightly contended by learned Additional Solicitor General India and the leaned Senior Counsels and learned counsels for the Pharmaceutical Company opposing the Writ that the writ petitioner is not a novice to the pharmacology field but it, being pharmaceutical giant in the whole of the world, cannot plead that they do not know what is meant by enhancement of a known efficacy and they cannot snow that the *derivatives differ significantly in properties with regard to efficacy. Mr.P.S.Raman* learned senior counsel argued that the Legislature, while enacting a Law, is entitled to create a deeming fiction and for that purpose, brought to our notice a judgment of the Supreme Court reported in AIR 1988 SC 191 (M/s.J.K.Cotton Spinning and Weaving Mills Ltd. Vs. Union of India) where, in paragraph 40, the Supreme Court had said that "the Legislature is quite competent to enact a deeming provision for the purpose of assuming the existence of a fact which does not really exist." It is also stated in the very same paragraph that "it is well settled that a deeming provision is an admission of the non-existence of the fact deemed."

14. It is argued by learned Senior Counsels for the writ petitioners that it is possible for the Parliament to define in the Act itself what is meant by enhancement of a known efficacy and what is meant by differing significantly in properties with regard to efficacy. The above expressions are vague and ambiguous by themselves and therefore the meaning of such expressions ought to have been given in the Act or the amended section. Therefore when the meaning is not so given, then the vagueness and ambiguity in the provision would result in arbitrary exercise of power by the statutory authority. Oppos ng this argument, learned Additional Solicitor General of India would contend hat Parliament is not an expert; it cannot foresee the future contingencies which may arise, when they enact an Act; therefore the Parliament always thinks it wise to use only general expressions in the Statute leaving it to the Court to interpret it depending upon the context in which it is used and the facts that are made available in each case. For this purpose, learned Additional Solicitor General brought to our notice the judgment of the Supreme Court reported in 1995 Supp. (1) SCC 235 (Benilal Vs. State of Maharashtra) and 1980 (1) SCC 340 (Registrar of Co-op. Societies Vs. K.Kunjabmu). Mr.P.S.Raman, learned senior counsel in supporting the argument of learned Additional Solicitor General that the Parliament cannot foresee things that may arise in the future, brought to our notice the

judgment of the English Court reported in (1949) 2 All England Law Reports 155 (Seaford Court Estates Vs. Asher), to understand and realise whether it would be possible at all to foresee things that may arise in the future when a Statute comes up for consideration before the Houses and what would be the duty of the Judge before whom interpretation of such a Statute arise for consideration. The Court of Appeal in that judgment had laid down the Law in that context as hereunder:

"Whenever a statute comes up for consideration, it must be remembered that it is not within human powers to foresee the manifold sets of facts which may arise, and, even if it were, it is not possible to provide for them in terms free from all ambiguity. The English language is not an instrument of mathematical precision. Our literature would be much the poorer if it were. This is where the draftsmen of Acts of Parliament have often been unfairly criticised. A Judge, believing himself to be fettered by the supposed rule that he must look to the language and nothing else, laments that the draftsmen have not provided for this or that, or have been guilty of some or other ambiguity. It would certainly save the judges trouble if Acts of Parliament were drafted with divine prescience and perfect clarity. In the absence of it, when a defect appears a judge cannot simply fold his hands and blame the draftsman. He must set to work on the constructive task of finding the intention of Parliament, and he must do this not only from the language of the statute, but also from a consideration of the social conditions which gave rise to it and of the mischief which it was passed to remedy, and then he must supplement the written word so as to give "force and life" to the intention of the legislature. That was clearly laid down (3 Co. Rep. 7b) by the resolution of the judgdes (SIR ROGER MANWOOD, C.B., and the other barons of the Exchequer) in Hey lon's case (4), and it is the safest guide to-day. Good practical advice on the subject was given about the same time by FLOWDEN in his note (2 Plowd. 465) to Eyston Vs. Studd (5). Put into homely metaphor it is this: A judge should ask himself the question how, if the makers of the Act had themselves come across this ruck in the texture of it, they would have straightened it out? He must then do as they would have done. A judge must not alter the material of which the Act is woven, but he can and should iron out the creases."

In 1980 (1) SCC 340 referred to supra the Supreme Court had held as hereunder:

"(1) Parliament and the State Legislatures function best when they concern themselves with general principles, broad objectives and fundamental issues, instead of technical or situational intricacies which are better left to better equipped full time expert executive bodies and specialist public servants. Parliament and the State Legislatures have neither the time nor expertise to be involved in detail or circumstance, nor can visualise and provide for new strange unforeseen or unpredictable situations. That is the raison d'etre for delegated legislation. The power to legislate carries with it the power to delegate. But excessive delegation may amount to abdication. Delegation unlimited may invite despotism uninhibited. So the theory has been evolved that the legislature cannot delegate its essential legislative function. Legislate it must, by laying down policy and principle and delegate it may to fill in detail and carry out policy. The legislature may guide the delegate by speaking through the express provision empowering delegation or the other provisions of the statute such as the preamble, the scheme or even the very subject-matter of the statute. If guidance there is, wherever it may be found, the delegation is valid. A good deal of latitude has been held to be permissible in the case of taxing statutes and on the same principle generous degree of latitude must be permissible in the case of welfare legislation, particularly those statutes which are designed to further the Directive Principles of State Policy."

In 1995 Supp. (1) SCC 235 referred to supra, the Supreme Court had held as hereunder:

"It is well settled that the legislative scheme may employ words of generality conveying its policy and intention to achieve the object set out therein. Every word need not be defined. It may be a matter of judicial construction of such words or phrases. Mere fact that a particular word or phrase has not been defined is not a ground to declare the provisions of the Act itself or the order as unconstitutional. The word "habitual" cannot be put in a straitjacket formula. It is a matter of judicial *construction and always depends upon the given facts and circumstances in each case.* As to when an inference that a tenant is habitually in arrears disentitling him to the protection of the Order could be drawn is a question of fact in each case. But on that ground or circumstance itself, the provision of the Act cannot be declared to be ultra vires."

The commentary on canons - interpretation of broad terms in Bennion - Statutory Interpretation contains the following passage:

"For the sake of brevity, or because the enactment has to deal with a multiplicity of circumstances, the draftsman often uses a broad term. This has the effect of delegating legislative power to the courts and officials who are called upon to apply the enactment. The governing legal maxim is generalia verba sunt generaliter intelligenda (general words are to be understood generally). {3 Co Inst 76.See Examples 78.5, 80.5 and 83.1} It is not to be supposed that the draftsman could have had in mind every possible combination of circumstances which may chance to fall within the literal meaning of general words. {For a detailed discussion of the concept of the broad term see Bennion Statute Law (2nd edn. 1983) Chap. 13}

The broad term which is a substantive has been called a nomen generale. {Hunter Vs. Bowyer (1850) 15.LTOS 281.} Other judicial descriptions of the broad term include 'open-ended expression' {Express Newspapers Ltd Vs. McShane [1980] 2 WLR 89, at p 94.}, 'word of the most loose and flexible description' {Green v Marsden (1853) 1 Drew 646.} and 'somewhat comprehensive and somewhat indeterminate term'. {Campbell v Adair [1945] JC 29.}

The broadest terms, such as 'reasonable' or 'just', virtually give the court or official an unlimited delegated authority, subject to the remedies available on judicial review or appeal. {As to these see s 24 of this Code (judicial review) and s 23 (appeal)}"

In Girdhari Lal's case referred to supra, the Supreme Court held as hereunder:

"Again, the words of a statute may not be designed to meet the several uncontemplated forensic situations that may arise. The draftsman may have designed his words to meet what Lord Simon of Glaisdale calls the "primary situation". It will then become necessary for the court to impute an intention to Parliament in regard to "secondary situations". Such "secondary intention" may be imputed in relation to a secondary situation so as to best serve the same purpose as the primary statutory intention does in relation to a primary situation."

Therefore it is clear from the case laws referred to above that Parliamentarians expresses its object and purpose in general terms when enacting a Statute and does not foresee the minute details that are likely to arise in the future and provide a solution for the same at the time when the Act itself is enacted. On the other hand, they would be acting wiser if they make only general expressions, leaving it to the experts / Statutory Authorities and then courts, to understand the general expressions used in the Statute in the context in which they are used in a case to case basis depending upon the facts available in each case. Using general expressions in a Statute, leaving the court to understand it's meaning, would not be a ground to declare a section or an Act ultra vires, is the law laid down by the Supreme Court in Benilal's case referred to supra. Interpretation of a Statute must be to advance the object which the Act wants to achieve

15. Now, we went through the statements of objects and reasons of Amending Act 15/2005. As rightly emphasized by Mr.Soli Sorabji learned senior counsel for the petitioners, the statement of objects and reasons for Amending Act 15/2005 emphasises in more than one place that the amendment is in the discharge of India's obligation to "TRIPS", which forms part of the "WTO" agreement. Therefore a need has arisen for us to look into the relevant Articles of "TRIPS" for the limited purpose of what obligations are created under "TRIPS", which, India was attempting to discharge by bringing in Amending Act 15/2005. Article 7 of "TRIPS" provides enough elbow room to a member country in complying with "TRIPS" obligations by bringing a law in a manner conducive to social and economic welfare and to a balance of rights and obligations. Article 1 of "TRIPS" enables a member country free to determine the appropriate method of implementing the provisions of this agreement within their own legal system and practice. But however, any protection which a member country provides, which is more extensive in nature than is required under "TRIPS", shall not contravene "TRIPS". Article 27 speaks about patentability. Lengthy arguments have been advanced by learned Additional Solicitor General appearing for the Government of India, learned senior counsels and learned counsels appearing for the pharmaceutical companies that India, being a welfare and a developing country, which is pre-dominantly occupied by people below poverty line, it has a constitutional duty to provide good health care to it's citizens by giving them easy access to life saving drugs. In so doing, the Union of India would be right. It is

argued, to take into account the various factual aspects prevailing in this big country and prevent evergreening by allowing generic medicine to be available in the market. As rightly contended by the learned Additional Solicitor General of India, the Parliamentary debates show that welfare of the people of the country was in the mind of the Parliamentarians when Ordinance 7/2004 was in the House. They also had in mind the International obligations of India arising under "TRIPS" and under "WTO" agreement. Therefore the validity of the amended section on the touchstone of Article 14 of the Constitution of India must be decided having regard to the object which Amending Act 15/2005 wanted to achieve.

16. It is argued by the learned senior counsels for the petitioners that since the amended section uses only general expressions, leaving it to the Statutory Authority to understand what it means, the Statutory Authority is likely to act arbitrarily in exercising it's discretion, since it has no guidelines. We have already held that the amended section cannot be said to be vague or ambiguous. We reiterate here at this stage that the amended section with it's Explanation is capable of being understood and worked out in a normal manner not only by the Patent applicant but also by the Patent controller. In other words, the patent controller would be guided by various relevant details which every patent applicant is expected to produce before him showing that the new discovery had resulted in the enhancement of the known efficacy; the derivatives differ significantly in properties with regard to efficacy and therefore it cannot be said that the patent controller had an uncanalised power to exercise, leading to arbitrariness. The argument that the amended section must be held to be bad in Law since for want of guidelines it gives scope to the Statutory Authority to exercise it's power arbitrarily, has to be necessarily rejected since, we find that there are inbuilt materials in the amended section and the Explanation itself, which would control / guide the discretion to be exercised by the Statutory Authority. In other words, the Statutory Authority would be definitely guided by the materials to be placed before it for arriving at a decision. Mr.P.S.Raman learned senior counsel brought to our notice two judgments of the Supreme Court reported in AIR 1957 SC 397 (M/s.Pannalal Binjraj Vs. Union of India) and (1974) 1 SCC 549 (State of Punjab Vs. Khan Chand) to highlight the types of discretions, if exercised, affecting various rights and the outcome of such exercise of discretion. We extract paragraph 34 of the judgment reported in AIR 1957 SC 397 hereunder:

"34. There is a broad distinction between discretion which has to be exercised with regard to a fundamental right guaranteed by the Constitution and some other right whichis given by the statute. If the statute deals with a right which is not fundamental in character the statute can take it away but a fundamental right the statute cannot take away. Where for example, discretion is given in the matter of issuing licences for carrying on trade, profession or business or where restrictions are imposed on freedom of speech etc., by the imposition of censorship, the discretion must be controlled by clear rules so as to come within the category of reasonable restrictions. Discretion of that nature must be differentiated from discretion in respect of matters not involving fundamental rights such as transfers of cases. As inconvenience resulting from a change of place or venue occurs when any case is transferred from one place to another but it is not open to a party to say that a fundamental right has been infringed by such transfer. In other words, the discretion vested has to be looked at from two points of view, viz., (1) does it admit of the possibility of any real and substantial discrimination, and (2) does it impinge on a fundamental right guaranteed by the Constitution? Article 14 can be invoked only when both these conditions are satisfied. Applying this test, it is clear that the discretion which is vested in the Commissioner of Income - Tax or the Central Board of Revenue, as the case may be, under s.5 (7-A) is not at all discriminatory."

From the above extracted portion, it is clear that Article 14 can be invoked only when it is shown that in the exercise of a discretionary power there is a possibility of a real and substantial discrimination and such exercise interferes with the fundamental right guaranteed by the Constitution. This judgment is by a Constitution Bench. The latter judgment [(1974) 1 SCC 549] is also by a Constitution Bench, which also quotes with approval the above extracted passage, in paragraph No.10 of that judgment. It is not shown by the learned senior counsels appearing for the petitioners before us that in the exercise of the discretionary power by the Patent controller, any of the petitioner's fundamental rights are violated namely, to carry on the trade or the petitioner stand singularly discriminated. We find that the amended section by itself does not discriminate nor does it prohibit the trade being carried on.

17. It is argued by the learned senior counsels for the petitioners that the Statutory Authority is likely to misuse the discretion vested in it by throwing out the patent application as "not an invention", by relying upon the amended section, when the amended section itself does not contain any guidelines. We have already found that the amended section has in-built protection enabling each of the patent applicant to establish before the patent controller that his discovery had resulted in the enhancement of the known efficacy of that substance and the derivatives are significantly differing in properties with regard to efficacy. Therefore it boils down to only one question namely, could an arbitrary exercise of a discretionary power invalidate an Act? We have a direct answer for this point in favour of the State from a judgment of the Supreme Court reported in 2006 (8) SCC 212 (M.Nagaraj Vs. Union of India), where, in paragraph No.106, the Supreme Court had held as hereunder:

"Every discretionary power is not necessarily discriminatory. According to the Constitutional Law of India, by H.M.Seervai, 4th Edn., p.546, equality is not violated by mere conferment of discretionary power. It is violated by arbitrary exercise by those on whom it is conferred. This is the theory of "guided power". This theory is based on the assumption that in the event of arbitrary exercise by those on whom the power is conferred, would be corrected by the courts."

In the judgment reported in 2007-1-LW.Pg.724 (Selvi.J.Jayalalitha & Others Vs. The Union of India & Others), rendered by one of us (Justice Prabha Sridevan), in dealing with such a contention namely, an Act must be invalidated because of possible misuse and abuse of the law, it was held as hereunder:

"67. It was also contended that there could be flagrant misuse and abuse of the law. The possibility of flagrant abuse or misuse of law has never been a ground for holding a provision ultra vires. We cannot presume that the authorities will administer the law "with an evil eye and an unequal hand." This has been so held in several cases where the constitutionality of a legal provision was attacked. The observations of the Supreme Court in Krishna Lal's case (supra), where the Kerala Abkari Act was challenged, are squarely applicable to the present case. Merely because the Act requires the assessee to prove that there were circumstances which prevented the

of economic regulation than in other areas where fundamental human rights are involved. Nowhere has this admonition been more felicitously expressed than in Morey Vs. Doud where Frankfurter, J. said in his inimitable style:

"In the utilities, tax and economic regulation cases, there are good reasons for judicial self-restraint if not judicial deference to legislative judgment. The legislature after all has the affirmative responsibility. The courts have only the power to destroy, not to reconstruct. When these are added to the complexity of economic regulation, the uncertainty, the liability to error, the bewildering conflict of the experts, and the number of times the Judges have been overruled by events - self-limitation can be seen to be the path of judicial wisdom and institutional prestige and stability."

The court must always remember that "legislation is directed to practical problems, that the economic mechanism is highly sensitive and complex, that many problems are singular and contingent, that laws are not abstract propositions and do not relate to abstract units and are not to be measured by abstract symmetry" that exact wisdom and nice adaptation of remedy are not always possible and that "judgment is largely a prophecy based on meagre and uninterpreted experience". Every legislation, particularly in economic matters is essentially empiric and it is based on experimentation or what one may call trial and error method and therefore it cannot provide for all possible situations or anticipate all possible abuses. There may be crudities and inequities in complicated experimental economic legislation but on that account alone it cannot be struct down as invalid. The courts cannot, as pointed out by the United States Supreme Court in Secretary of Agriculture Vs. Central Roig Refining Co. be converted into tribunals for relief from such crudities and inequities. There may even be possibilities of abuse, but that too cannot of itself be a ground for *invalidating the legislation, because it is not possible for any legislature to anticipate* as if by some divine prescience, distortions and abuses of its legislation which may be made by those subject to its provisions and to provide against such distortions and abuses. Indeed, howsoever great may be the care bestowed on its framing, it is difficult to conceive of a legislation which isnot capable of being abused by perverted human ingenuity. The court must therefore adjudge the constitutionality of such legislation by the generality of its provisions and not by its crudities or inequities or by the possibilities of abuse come to light, the legislature can always step in and enact

suitable amendatory legislation. That is the essence of pragmatic approach which must guide and inspire the legislature in dealing with complex economic issues."

In fact, we find that the aoove position in law is also spoken to by another Constitution Bench of the Supreme Court in the judgment reported in 2001 (4) SCC 139 (Union of India Vs. Elphinstone Spinning & Weaving Co. Ltd.) (See para 11). It is a settled position in law (See (2001) 4 SCC 139- (at page 158) that "it must be presumed that the Legislature understands and correctly appreciates the need of its own people, that its laws are directed to problems made manifest by experience and that its discriminations are based on adequate grounds." We now went through the Patents Act, 1970 as amended by Act 15/2005. In India there was an Act called Indians Patent & Designs Act enacted in the year 1911. The statement of objects and reasons of the Patents Act, 1970 (Act 39/1970) noticed that since the 1911 enactment, there had been substantial changes in the political and economic conditions of the country and therefore a need has arisen for a comprehensive law so as to ensure more effectively that patent rights are not worked out to the detriment of the consumer or to the prejudice of trade or the industrial development of the country, which was felt as early as 1948 resulting in the Government appointing the Patents Enquiry Committee to review the working of the Patents Law in India. Therefore right from the year 1948 or so, the Parliament was aware about the change in the economic conditions of the country, which made them to change the 1911 enactment to suit to the needs of the economic conditions of the country. Therefore there cannot be any doubt at all that the Patents Act as it stood then and as it stands today, is designed to safeguard the economic interests of this country and if that is so, the amended section must be viewed with greater latitude.

18. In 1996 (3) SCC 709 (State of A.P. Vs. Mc Dowell & Co.) the Supreme Court reiterated the position that "a law made by Parliament or the Legislature can be struck down by courts on two grounds and two grounds alone namely, lack of legislative competence and violation of any of the fundamental rights guaranteed in Part III of the Constitution of India or of any other Constitutional provision." There is no third ground. In the case before us, learned senior counsels, except arguing that the amended section must be struck down on the ground of ambiguity, arbitrariness, leading to exercise of uncanalised powers - with which we have not agreed at all - had

not shown any other legal ground to invalidate the amended section. In the same judgment, the Supreme Court had held as follows:

"No enactment can be struck down by just saying that it is arbitrary or unreasonable. Some or other Constitutional infirmity has to be found before invalidating an Act. An enactment cannot be struck down on the ground that court thinks it unjustified. Parliament and the Legislatures, composed as they are of the representatives of the people, are supposed to know and be aware of the needs of the people and what is good and bad for them. The court cannot sit in judgment over their wisdom."

In (2006) 3 SCC 434 (Bombay Dyeing & Mfg. Co.Ltd. (3) Vs. Bombay Environmental Action Group) (See paragraph 205) it was held by the Supreme court that "arbitrariness on the part of the legislature so as to make the legislation violative of Article 14 of the Constitution should ordinarily be manifest arbitrariness. What would be arbitrary exercise of legislative power would depend upon the provisions of the statute vis-a-vis the purpose and object thereof". In AIR 1961 SC 1602 (Jyoti Persiiad Vs. Union Territory of Delhi) the Supreme Court held as hereunder:

"So long as the Legislature indicates, in the operative provisions of the statute with certainty, the policy and purpose of the enactment, the mere fact that the legislation is skeletal or the fact that a discretion is left to those entrusted with administering the law, affords no basis either for the contention that there has been an excessive delegation of legislative power as to amount to an abdication of its functions, or that the discretion vested is uncanalised and unguided as to amount to a carte blanche to discriminate. If the power or discretion has been conferred in a manner which is legal and constitutional, the fact that Parliament could possibly have made more detailed provisions, could obviously not be a ground for invalidating the law."

As we have already found, the amended section has in-built measures to guide the Statutory Authority in exercising it's power under the Act. We have also found that the amended section does not suffer from the vice of vagueness, ambiguity and arbitrariness. The Statutory Authority would be definitely guided in deciding whether a discovery is an invention or not by the materials to be placed before him by the

Patent applicant. If that is so, then, going by the law laid down by the Supreme Court in M.Nagaraj's case referred to supra, if the Statutory Authority, in exercising his power, mis-directs himself; abuses his power in an arbitrary manner and passes an order, then, the same could be corrected by the hierarchy of forums provided in the Act itself in addition to the further reliefs available before the Courts of Law. When that is the position, then, we have to necessarily state that the amended section cannot be invalidated solely on the ground that there is a possibility of misusing the power.

19. Now we refer to the decisions mainly relied upon by the learned senior counsel for the petitioners. Mr.Soli Sorabji learned senior counsel relied upon the following judgments:

(a) AIR 1960 SC 554 (Hamdard Dawakhana & Anr. Vs. The Union of India & Others);

(b) 1961 Cri.L.J. 442 (The State of Madhya Pradesh & Anr. Vs. Baldeo Prasad);

(c) AIR 1970 SC 1453 (Harakchand Ratanchand Banthia & Others Vs. Union of India); and

(d) AIR 1967 SC 829 (Lala Hari Chand Sarda Vs. Mizo District Council and Another).

We went through the judgments very carefully. In the first case, the Legislation impugned was stated to be in violation of Article 19 - restriction on freedom of speech - of the Constutiton of India. In considering the provisions of the Act challenged, the Supreme Court found that sections 3(d) and 8 of the Act are unconstitutional and arbitrary as they provided uncontrolled power to the executives to do the act. In the second case, the validity of Central Provinces and Berar Goondas Act, 1946 was in challenge. The Apex Court found various infirmities in the operative sections of the Act and upheld the order of the High court invalidating the offending provisions. In the third case, the validity of certain provisions of the Gold Control Act was in challenge. In the last case, there was a challenge to the validity of section 3 of the

LUSHAI HILLS District (Trading by Non- Tribals) Regulation 2. 1963 was in challenge, being in violation of Article 19(1)(g) of the Act. In our respectful opinion, when the validity of an Act is challenged on the touchstone of Article 14 of the Constitution of India, the decision has to depend upon the provisions of the concerned Statute itself, which are in challenge. Of course, law is well settled that when there is vagueness in any provision of law leading to arbitrary exercise of power / uncanalised powers, the Act should be struck down. Therefore whether any provision of law is hit by Article 14 of the Constitution of India on the ground stated above, would depend upon the construction of the provisions in challenge. When a particular Act is found to be suffering the vice of vagueness and arbitrariness, then, it must be held that it was so on the construction of that Statute. It cannot be said that whenever arbitrariness and vagueness are the vices projected as grounds of attack, the court should close its eyes and simply strike down the law without even finding out whether in the Act challenged there are such vices. In fact, that is what the Supreme Court itself had said in the first judgment brought to our notice by Mr.Soli Sorabji learned senior counsel, which in turn quotes with approval an earlier judgment of the Supreme Court reported in 1954 SCR 674 wherein it is stated that "In order to decide whether a particular legislative measure contravenes any of the provisions of Part III of the Constitution of India, it is necessary to examine with some strictness the substance of the legislation in order to decide what the Legislature has really done." We again find in the first judgment that the Supeme Court had held as follows:

"Another principle which has to be borne in mind in examining the Constitutionality of a Statute is that, it must be assumed that the Legislature understands and appreciates the need of the people and the laws it enacts are directed to problems which are made manifest by experience and that the elected representatives assembled in a Legislature enact laws which they consider to be reasonable for the purpose for which they are enacted. Presumption is therefore in favour of the Constitutionality of an enactment."

If we have the above referred to principles of law in mind on Statutory Interpretation, we have to state with great respect that the judgment of the Supreme Court brought to our notice by Mr.Soli Sorabji learned senior counsel, would not stand attracted to the case on hand. The validity of the provisions of law considered in those cases and the

validity of the provision of law in contest before us are not in pari materia. There is definitely a difference in the language and wording of the provisions challenged in those cases and the one before us. The context in which the offending provisions are used in the Act in challenge is also totally different from the context in which the offending provisions in the cases decided by the Supreme Court are used. Of course, in those judgments, the Supreme Court had clearly laid down that vagueness / ambiguity and arbitrariness resulting in uncanalised powers are grounds to invalidate an Act. In other words, with great respect, we state that in all the cases brought to our notice by Mr.Soli Sorabji learned senior counsel, the Supreme Court, analyzing the provisions of the Statute before them in the context of the arguments advanced, found that they are violative. We state that in this case we have already found, analysing the alleged offending provision, that it is not in violation of Article 14 of the Constitution of India. We have borne in mind the object which the Amending Act wanted to achieve namely, to prevent evergreening; to provide easy access to the citizens of this country to life saving drugs and to discharge their Constitutional obligation of providing good health care to its citizens. We have also referred to the case laws brought to our notice by Mr.Habibullah Badsha viz., (1974) 1 SCC Pg.549 (State of Punjab Vs. Khan Chand); (1985) 1 SCC 234 (State of Maharashtra Vs. Kamal S. Durgule); (1988) 2 SCC 415 (B.B.Rajwanshi Vs. State of U.P.); (1989) 4 SCC 683 (A.N.Parasuraman Vs. State of Tamil Nadu); and (2005) 12 SCC 77 (State of Rajasthan Vs. Basant Nahata). On a perusal of the same also, we are in a position to reiterate with respect that our conclusions based on the case laws brought to our notice by Mr.Soli Sorabji learned senior counsel would equally apply to the case laws brought to our notice by Mr.Habibullah Badsha learned senior counsel. For all the reasons stated above, on issue (c) we hold that the amended section is not in violation of Article 14 of the Constitution of India and accordingly, both the writ petitions are dismissed with no order as to costs.

vsl

ANNEXURE-VII

Annexure - VIII

PATENT SPECIFICATION

761,163

Date of Application and filing Complete Specification: April 6, 1954.

No. 10079/54.

Application made in Italy on April 7, 1953.

Complete Specification Published: Nov 14, 1956.

Index at acceptance:—Class 81(1), B12.

COMPLETE SPECIFICATION

Process for Preparing a Substance having Antituberculous Activity.

I, PIETRO MASCHERPA, an Italian Citizen, of Piazza Duca d'Aosta, 8-Pavia, Italy, do hereby declare the invention, for which I pray that a patent may be granted to me, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to a process for preparing a substance having antituberculous activity.

It has been found that from bovine lung tissues and mainly from the lungs of calves it is possible to obtain, by means of a mechanical squeezing that does not damage biochemical structures, a substance which can be ultrafiltered and, therefore, is not proteic, which is thermo-stable, soluble in water, has a peptidic structure and is endowed with bacteriostatic and bactericidal action upon Mycobacterium tuberculosis, capable of preventing the rising of tubercular manifestations in experimentally infected animals, perfectly tolerated in the tuberculous man, provided with scarce toxicity and with an elevated therapeutic coefficient (ratio between therapeutical effect and toxicity), certainly capable of curing and healing pulmonary tuberculosis and perhaps also other forms of tuberculosis. Said substance, which was unknown heretofore, has to be considered a new antituberculous substance of animal origin of which important therapeutic applications are to be expected.

According to the present invention, there is provided a process for the preparation of an antituberculous substance, characterized in that calves' lung is triturated and admixed with an inert granular material, then the mixture thus formed is subject to squeezing in a specially provided apparatus, the juice obtained at pressures between 100 and 500 atmospheres is collected, the proteins and the high molecular weight peptides are removed by ultrafiltration through an acetate collodion membrane or through a Cellophane filter having the porosity of the acetate collodion membrane or by coagulation and subsequent selective ultrafiltration, aminoacids and peptides formed of from 2 to 4 aminoacids are removed by selective adsorption, and finally the pyrogens are removed by adjusting the pH of the solution to 7.8-8.0 and neutralizing.

The starting material to be used is bovine lung (it having been found that in the liver, kidney, prostrate gland and thymus, the substance in question is contained in much smaller quantity than in the lung) preferably taken from calves (it having been found that the lungs of horses, rabbits, pigs, dogs, adult or young, are not practically utilizable) having a weight of about 100 to 120 kgs., normally corresponding to an age of 2-3 months (it having been proved that the lungs of very young calves or of adult livestock contain the substance in question in much smaller quantity).

The lung taken from a freshly killed animal, is subjected to squeezing, preferably fractional squeezing, by applying a pressure higher than 100 atmospheres. The juice obtained between 100 and 500 atmospheres is collected, this being the fraction richest in active substance. It is advisable to exert said pressure upon the lung previously triturated not too finely and admixed with siliceous sand. The homogenate (the homogenized lung) cannot completely replace the press juice. The juice obtained is centrifuged, decanted and then subjected to ultrafiltering; by ultrafiltration, the proteins (anti-bodies, globulins, etc.) are separated.

Deproteinization may also be accomplished by heating the juice to 50°C. and by subsequent coagulation at 80°C.; also in this case, filtering through special membranes (acetate collodion solution or Cellophane) is always necessary to obtain sufficient purification of the antituberculous sub-

stance. The word "Cellophane" is a registered Trade Mark. Rapid coagulation at 80°C. alone entails a considerable loss of activity. The liquid obtained after deproteinization is subjected to selective adsorption, e.g., with Permutit (the word "Permutit" is a registered Trade Mark), which retains amino acids and small chain peptides. Adsorption may also be effected by treating the deproteinized liquid with cationic or anionic resins. The pH of the collected liquid is adjusted to 7.8-8.0 with 0.1N NaOH and, after 20 hours, the liquid is neutralized with 0.1N HCl and it yields by evaporation on water bath an amorphous residue, which is perfectly soluble in distilled water, thermo-stable and with the solution of which there can be prepared phials of hypodermic or intravenous injections, which are sterilizable even in autoclave (e.g., during 20 minutes at a temperature of 120°C.).

As the substance in aqueous solution loses to a great extent its activity after about ten days, it is advisable to carry out lyophilization of the depyrogenized ultra-filtrate.

The lylophilized substance appears white, amorphous or pseudo-crystalline, perfectly soluble in water; the solution so obtained proves active even if prepared with a 5 or 6 months old lyophilized substance.

The residue, obtained by evaporation or by lyophilization of the ultra-filtrate, represents the active part which is of polypeptidic character in that by acid hydrolysis in hot condition it liberates amino acids. The following amino acids have been thus identified by chromatographic analysis: phenyl alanine, tyrosine, lysine, theonine, serine, methionine, aspartic acid, glutamic acid, tryptophan, arginine, histidine, cystine.

It is probable that some of these amino acids are contained in the molecule a number of times or that they are present as an impurity. The amino acids coming from the hydrolysis of the polypeptide, are devoid of any anti-tuberculotic action. The same substance, if treated with pepsin at pH= 2.5 for 24 hours, loses its activity to a great extent; an analogous effect is obtained by the action of a diaminase (e.g., hystaminase) and 24 vol. hydrogen peroxide; an analogous inactivation is caused by adsorption with carbon (ultracarbo Merck.). On the contrary, activity persists after treatment with trypsin at pH 7.6. The action, therefore, is the property of a peptidic structure and is specially due to the bonds of the amino acids forming part of it. The substance in question as purified to maximum extent attained so far proves to have a molecular weight between 1500 and 2000 and has probably the following empirical composition:

$$C_{60}\,H_{98}\,O_{32}\,N_7\,S_4.$$

The molecular weight has been determined by the method of fractional ultrafiltration according to GRABAR. In practice the active substance is not found in substantial amounts in bovine blood and scarcely in intercellular liquids (as proved by the result of fractional pressing); it is part, instead, of the biochemical outfit of cells and it comes probably from the nucleoproteid metabolism. The chemical characteristics as well as the pharmacological characteristics distinguish it from spermin, in which some authors recognized a tuberculostatic action recently.

As a matter of fact, spermin is not a polypeptide, has a much lower molecular weight, does not contain any sulphur, has prevailing localization in the liver, kidney, prostate instead of in the lung; it requires an activator, that must be a protein or the proteic support of a ferment and said activator or promoter is liable to heat (thermo-labile), while the substance according to the present invention does not need any promoter and is, as said, thermo-stable; moreover, it is more active than activated spermin and is far less toxic.

The antituberculous substance according to the present invention is indeed—among other things—soluble in acetone, it has a much lower molecular weight and is much more active upon Mycobacterium Tuberculosis.

As for biological action, the substance present in the lung and extracted by the method described above is important because it possesses surprising special biological properties and in particular a bacteriostatic and bactericidal activity upon various strains of Mycobacterium Tuberculosis, a circumstance not observed by anybody heretofore and suitable for therapeutic applications. The action *in vitro* upon some strains of Mycobacterium Tuberculosis (Myc.bovis. ranae, Minetti, Ascoli H37, ATCC607) bred on solid and liquid media has proved to be higher than or at least equal to that of isonicotinic hydrazide, about 5 times as high than that of streptomycin and about 100 times as high as that of para-aminosalicylic acid.

It has been found by experimental research that the substance extracted from the lung is also active upon streptomycin-resistant strains; it also acts upon strains resistant against isonicotinic hydrazide. On the other hand, none of the strains investigated so far has proved to be resistant against the new substance.

The bacteriostatic power of the new substance appears to a considerable extent to be selective for M. Tuberculosis because upon other germs, such as Staphylococcus pyogenus aureus and Escherichia coli and the bacillus of carbuncle, action is almost nil. The mechanism appears to be anti-

metabolic, since under certain conditions the substance in question exerts an action hindering respiration of the M. Tuberculosis (evaluated with the manometric technique according to WARBURG).

The antituberculotic activity of the substance extracted from the lung has been studied on tuberculous albino mice infected by endonasal introduction of 0.6 mg. of a culture of M. Tuberculosis, bovine B_4, and Ascoli variety.

While the control animals show a tuberculosis localized in the lung and with rapid evolution, the animals treated with the antituberculous substance obtained from the lung with the technique described, do not show any evident lesions or show much smaller lesions both at the macroscopic and histological examination. Analogous research work with analogous results has been carried out on rabbits made tuberculous experimentally. In the rabbit the rate of the antituberculous substance in the blood shows a characteristic curve and the useful values persist during about four hours.

Subcutaneous administration of 0.10 g. a day in man proved to be perfectly tolerable. The daily therapeutic dosage is expected to be equal to 0.06-0.10 g. sub cute. The curing effect has been investigated both in the forms of lobites and in fibro-ulcerative forms of acute as well as of chronic character, feverous, progressive with typical radiological patterns. The effect of the antibiotic injected subcutaneously in the form of a solution obtained extemporaneously from the lyophilized substance, three times a day in individual doses of 0.05 g., was evidenced by the rapid disappearance of infiltrative and exudative phaenomena (infiltrations and exudations), by a substantial change of the radiologic pattern, by the negativity of the expectorate (by the negative expectorate), by the dropping of fever, by important modifications of allergic reactivity. A great number of cases is in course of being investigated and comprises also tubercular meningitis and the treatment with the antituberculous substance by injection round the spinal cord.

The toxicity of the antituberculous substance extracted from the lung is very small in the normal animal. The average lethal dose in the adult mouse is 1500 mg./kg. subcutaneous and 1000 mg./kg. intravenous; the daily dosage of 400 mg./kg. subcutaneous is tolerated even with a treatment lasting 15 days. In the tuberculotic mouse the toxicity appears to be slightly higher. The rabbit tolerates perfectly the substance in question: daily doses of 3 mg./kg. subcutaneous are tolerated for over one month, the acute treatment with 30 mg./kg. endovenous is also tolerated.

In the dog, subcutaneous or intravenous injection of 1 mg./kg. does not cause either cardiocirculatory or any other troubles to the principal organic apparatuses. Hence the toxicity of the antituberculous substance is about 10 times smaller than that of streptomycin, and about 5 times smaller than that of isoniazide.

The following examples are illustrative of the preparation of the substance according to the invention:

EXAMPLE 1

As a starting material, calf lungs of about 120 kg. are used. After rough trituration in a mincer, the material is mixed in the ratio 1:1 by weight with siliceous sand calcined (to destroy the organic substances) and washed (to eliminate the salts and other impurities), constituted by granules passing through a sieve No. 20 of the Official Italian Pharmacopoeia, 6th edition (i.e., 20 meshes per centimeter). Using a micropress made of steel and comprising a press and a pump, a gradual pressure is applied, collecting until complete squeezing that portion of juice that is obtained at from 100 to 500 atmospheres, in a quantity of 25 g. from 100 g. of lung, and which possesses the following characteristics:

Appearance turbid
Colour: reddish grey
Density = 1.07 at 15°C.
Residue at 100° = 3.8%
Ash at 400° = 1.01%
Total N = 0.381%

The juice is centrifuged at 3,500 revolutions per minute and then decanted and ultra-filtered through 10% acetate collodion.

From 100 mg. of lung, there are obtained 22 g. of a liquid having the following characteristics:

Colour straw-yellow
Appearance clear
Density = 1.04 at 15°C.
Average residue at 100° = 0.580%
Organic substances = 0.460%
Ashes at 400° = 0.120%
Total N = 0.079%
Amino N = 0.048%
Polypeptide N—0.027%
pH—7.6
Biuret reaction: positive

The liquid obtained by ultra-filtration is passed through a column of Permutit (50) ($2\,SiO_2.Al_2O_3.Na_2O+6H_2O$ of the Permutite Company prepared according to POLIN).

The collected liquid is deprived of the pyrogens by bringing it to pH = 7.8 with NaOH/10. If necessary, it should be filtered. The liquid obtained about 22 g. has the following characteristics:

Colourless
Appearance: clear
Density = 1.03 at 15°C.
Residue at 100° = 0.310%
Organic substances = 0.295%

Total N=0.037%
Polypeptide N=0.027%
pH=7
Biuret reaction: positive

The depyrogenized liquid gives by evaporation on a water bath, the product in the form of a white residue, amorphous, soluble in water, thermostable.

Yield: 0.700 g. from 1,000 g. of lung.

EXAMPLE 2

The procedure of Example 1 is followed to obtain a lung juice having the characteristics described in the preceding example. Said juice is centrifuged at 3,500 revolutions per minute. It is decanted and heated to 50°C. for 20 minutes and then coagulated at 80°C. on a water bath, while stirring slightly. The mass is allowed to cool down, filtered through paper and is then ultrafiltered through cellophane under a pressure of 15 atmospheres, in an atmosphere of nitrogen, at a temperature of +2°C. 100 g. of lung yielded 19.8 g. of a liquid having the following characteristics:

Colour: straw-yellow
Appearance: clear
Density=1.08 at 15°C.
Average residue at 100°=0.885%
Organic substances=0.763%
Ashes at 400°=0.122%
Total N=0.093%
Amino N=0.051%
Polypeptide N=0.0031%
pH=7.7
Biuret reaction: positive

The liquid obtained is made to pass through columns of Amberlite I R-4 B OH and subsequently through a column of Amberlite I R-120 cycle H, as sold by Rohm & Haas Company, Philadelphia. The word "Amberlite" is a registered Trade Mark. After adsorption, the liquid collected is deprived of pyrogens by bringing it to pH 7.8 with NaOH/10. After 24 hours' rest at 20°C., it is neutralized with N/10 HCl. If necessary, it should be filtered. The liquid obtained (about 20 g.) has the following characteristics:

Colourless
Appearance: clear
Density=1.02 at 5°C.
Residue at 100°=0.409%
Organic substances=0.278%
Ashes at 400°=0.131%
Total N=0.032%
Polypeptide N=0.023%
pH=7.1
Biuret reaction: positive.

The depyrogenized liquid gives, by evaporation on a water bath, or by lyophilization, the product in the shape of a white, amorphous residue soluble in water, thermostable. Lyophilization can be effected at a temperature —55°C. in the condenser, freezing temperature —45°C. and subsequent sizing up to the room temperature for 3½ hours.

CLINICAL-THERAPEUTICAL EXAMPLES

The examples are cited of three sick people treated with the antituberculous substance according to the present invention, in the "Instituto Forlanini," Pavia, and in the "Clinica Tisiologica," Milano.

L. CARLO, 40 year old, right superior ulcerated lobitis, streptomycino- and hydrazido-resistant. Feverish temperature with an average daily maximum of 38.7°C. Sedimentation rate: after 1 hour, 15; after 2 hours, 35; Katz index 16.5. Red blood corpuscles 3,600,000 Hb=75%. White blood corpuscles 4,800; leucocytes differential count: N 76; E 7; B —; L 11; M 6. Expectorate: Koch positive. Weight 58 kg. After one month of treatment with antibiotic, subcutaneous (0.10 g. a day) it was observed at the radiological examination:— the disappearance of infiltrations, a consideration reduction of the cavern. Normal temperature (average daily maximum 37.1°C.). Sedimentation rate: after 1 hour, 5; after 2 hours, 11; Katz index 5.5. Red blood corpuscles, 4,800,000 Hb=95%. White blood corpuscles 8,000; leucocytes differential count: N 75; E 3; B —; L 15; M 7. Expectorate: Koch negative. Weight 61 kg.

D. EUGENIA, 17 years old, left superior lobitis, disseminated seats, never treated. Subfebrile temperature, with daily peaks of 38.2°C. Sedimentation rate: after 1 hour, 16; after 2 hours, 26. Katz index 18.1. Red blood corpuscles 4,250,000 Hb=78%. White blood corpuscles 5,200. Leucocytes differential count: N 70; E 2; B 1; L 19; M 8. Expectorate: Koch positive. Weight 52 kg. After 40 days, treatment with the antituberculous substance, subcutaneous (0.10 g. a day), the radiological examination shows the lung returned to normal transparency. General condition improved. Weight 55 kg. The patient has recovered appetite and is feeling fairly well. Fever has disappeared. Sedimentation rate: after 1 hour, 18; after 2 hours, 29. Katz index 18.2. Red blood corpuscles 4,500,000 Hb =80%. White blood corpuscles 5,300. Leucocytes differential count: N72; E 3; B —; L 17; M 8. Expectorate: Koch negative.

S. CARLO, 51 years old. Chronic fibro-caseous ulcerative tuberculosis of the left superior lobe, in evolving stage and counterlateral bronchiogenic diffusion. No advantage from a previous treatment with streptomycin and isoniazid. Weight 56 kg. Febrile temperature with maxima of 39.0°-39.3°C. Sedimentation rate: after 1 hour, 28; after 2 hours, 50. Katz index 26.5. Red blood corpuscles 4,500,000 Hb=80%. White blood corpuscles 6,800. Leucocytes differen-

tial count: N 69; E 1; B —; L 20; M 10. Expectorate: Koch positive. After 30 days' treatment, subcutaneous (0.11 g. a day), at the radiological treatment a substantial limitation of counter-lateral diffusion is noted. Fever has disappeared. General feeling of ease. Weight 57.5 kg. Sedimentation rate: after 1 hour, 25; after 2 hours, 52. Katz index 25.2. Red blood corpuscles 4,900,000 Hb=91%. White blood corpuscles 6,200. Leucocytes differential count: N 64; E 2; B —; L 23; M 12. Expectorate: Koch negative.

What I claim is:—

1. A process for the preparation of an antituberculous substance, characterised in that calves' lung is triturated and admixed with an inert granular material, then the mixture thus formed is subject to squeezing in a specially provided apparatus, the juice obtained at pressures between 100 and 500 atmospheres is collected, the proteins and the high molecular weight peptides are removed by ultrafiltration through an acetate collodion membrane or through a Cellophane filter having the porosity of the acetate collodion membrane or by coagulation and subsequent selective ultrafiltration, aminoacids and peptides formed of from 2 to 4 aminoacids are removed by selective adsorption, and finally the pyrogens are removed by adjusting the pH of the solution to 7.8-8.0 and neutralizing.

2. A process according to Claim 1, wherein the water is eliminated from the final liquid obtained, and the dry residue is collected.

3. A process according to Claim 1, wherein the final liquid obtained is lyophilized.

4. A process according to Claim 1, wherein the elimination of the proteins from the juice is obtained by means of ultra-filtration.

5. A process according to Claim 1, wherein the elimination of the proteins from the juice is obtained by means of coagulation by heating and subsequent ultra-filtration.

6. A process according to Claim 1, wherein the elimination of the amino acids and of the short chain peptides is obtained by selective adsorption on ion exchange resins.

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ANNEXURE-IX

23 JUL 2008

Annexure - IX

United States Court of Appeals for the Federal Circuit

2006-1261

PFIZER, INC.,

Plaintiff-Appellee,

v.

APOTEX, INC. (formerly known as TorPharm, Inc.)

Defendant-Appellant.

Richard G. Greco, Kay Scholer LLP, of New York, New York, argued for plaintiff-appellee. With him on the brief were Milton Sherman, Betty A. Ryberg, and Regina O. Kent.

Robert B. Breisblatt, Welsh & Katz, Ltd., of Chicago, Illinois, argued for defendant-appellant. With him on the brief were A. Sidney Katz, Steven E. Feldman, and Philip D. Segrest, Jr.

Appealed from: United States District Court for the Northern District of Illinois

Chief Judge James M. Rosenbaum

23 JUL 2008

United States Court of Appeals for the Federal Circuit

2006-1261

PFIZER, INC.,

Plaintiff-Appellee,

v.

APOTEX, INC. (formerly known as TorPharm, Inc.)

Defendant-Appellant.

DECIDED: March 22, 2007

Before MICHEL, Chief Judge, MAYER, and LINN, Circuit Judges.

Opinion for the court filed by Chief Judge MICHEL. Circuit Judge LINN concurs in the result.

MICHEL, Chief Judge.

Pfizer Inc. filed suit against Apotex, Inc. (formerly known as TorPharm, Inc.) in the United States District Court for the Northern District of Illinois on July 30, 2003, alleging that, pursuant to 21 U.S.C. § 355(j)(5)(B)(iii), Apotex's filing with the United States Food and Drug Administration ("FDA") of its Abbreviated New Drug Application ("ANDA") No. 76-719 seeking approval to commercially sell amlodipine besylate tablets (2.5 mg, 5 mg, and 10 mg strengths) before the expiration of the term of U.S. Patent No. 4,879,303 ("the '303 patent") to Pfizer, infringed claims 1-3 of the '303 patent. The ANDA product sought to be approved by Apotex is a generic version of Pfizer's

amlodipine besylate drug product, which is commercially sold in tablet form in the United States under the trademark Norvasc®. Norvasc® is approved by the FDA for treating hypertension and chronic stable and vasospastic angina. The '303 patent, entitled "Pharmaceutically Acceptable Salts," is listed in the FDA's Approved Drug Products with Therapeutic Equivalence Evaluations ("Orange Book") with respect to the Norvasc® drug product in accordance with 21 U.S.C. § 355(b)(1). Apotex certified in ANDA No. 76-719 that it believed the '303 patent was invalid and unenforceable, and sought approval to market and sell its amlodipine besylate tablets before September 25, 2007 (i.e., the expiration date of the '303 patent plus an additional six months of pediatric exclusivity) pursuant to 21 C.F.R. § 314.94(a)(12)(i)(A)(4).

In its answer to Pfizer's complaint, Apotex denied infringement and counterclaimed for declaratory judgments that the claims of the '303 patent are invalid for anticipation and obviousness, and that the '303 patent is unenforceable due to Pfizer's alleged inequitable conduct before the United States Patent and Trademark Office ("USPTO"). Prior to trial, however, Apotex stipulated that its ANDA product contains each limitation of claims 1-3 of the '303 patent, and that if the '303 patent were upheld as valid and enforceable, its ANDA product would literally infringe those claims.

Following a bench trial, the district court entered a final judgment on January 29, 2006 for Pfizer and against Apotex on Apotex's request for declaratory judgments that the claims of the '303 patent are invalid or unenforceable. Based on the stipulation, the trial court found infringement. The district court then ordered that the effective date of any approval of Apotex's ANDA No. 76-719 shall not be earlier than September 25, 2007, and enjoined Apotex from making, using, offering to sell, selling, or importing into

the United States any product comprising amlodipine besylate covered by (or the use of which is covered by) the claims of the '303 patent until September 25, 2007. Pfizer Inc. v. Apotex, Inc., No. 03C 5289 (N.D. Ill. Jan. 29, 2006).

Pfizer dismissed its claim of willful infringement against Apotex by a Stipulation and Order dated January 23, 2006. Apotex now appeals from the district court's final judgment, challenging the rulings as to validity and enforceability. Because the district court erred in holding that the subject matter of claims 1-3 of the '303 patent would not have been obvious, we reverse. We therefore do not address Apotex's assertion that it had proven that Pfizer engaged in inequitable conduct before the USPTO during prosecution of the '303 patent.

I. BACKGROUND

A.

Norvasc® contains amlodipine besylate. The active ingredient found in Norvasc® is 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-3-ethoxycarbonyl-5-methoxycarbonyl-6-methyl-1,4-dihydropyridine, commonly referred to as amlodipine. Amlodipine is a member of a class of compounds referred to as dihydropyridines. Active drug molecules, such as amlodipine, are frequently made into pharmaceutically-acceptable acid addition salts to improve their bioavailability. Amlodipine besylate[1] is an acid addition salt form of amlodipine, formed from the reaction of amlodipine, a weak base, and benzene sulphonic acid.

Pfizer's Discovery Chemistry group, located in Sandwich, England, invented amlodipine and discovered its anti-hypertensive and anti-ischemic pharmacological

[1] Besylate is referred to in the art interchangeably as benzene sulphonate, benzenesulphonate, or benzene sulfonate.

properties prior to 1982. Pfizer filed a patent application in the United Kingdom on March 11, 1982 specifically claiming amlodipine. A U.S. counterpart application claiming priority from the U.K. application issued as U.S. Patent No. 4,572,909 ("the '909 patent") on February 25, 1986.[2] The '909 patent claims certain dihydropyridine compounds and their pharmaceutically-acceptable acid addition salts. The '909 patent discloses that the pharmaceutically-acceptable acid addition salts of amlodipine "are those formed from acids which form non-toxic acid addition salts containing pharmaceutically acceptable anions, such as hydrochloride, hydrobromide, sulphate, phosphate or acid phosphate, acetate, maleate, fumarate, lactate, tartrate, citrate and gluconate salts," and that the preferred salt is maleate.[3] '909 patent col.2 ll.3-10.

Meanwhile, on or about July 14, 1982, the Discovery Chemistry group recommended that amlodipine be developed as a commercial drug product. By this time, Pfizer had made several acid addition salts of amlodipine, including the maleate, fumarate, salicylate, hydrochloride, and methane sulphonate forms. The Discovery Chemistry group designated amlodipine maleate as the drug substance for development.

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[2] The '909 patent was subject to an appeal before this court in Pfizer Inc. v. Dr. Reddy's Labs., Ltd., 359 F.3d 1361 (Fed. Cir. 2004). There, this court held that the term of the '909 patent as extended under the patent term restoration provision of the Hatch-Waxman Act covers amlodipine and any salt or ester as claimed in claims 1, 7, and 8. Id. at 1367.

[3] We recognize that hydrochloride and hydrobromide are not technically anions. However, since the patentee chose to be his own lexicographer, we will refer to these two acids as anions for purposes of this opinion. Phillips v. AWH Corp., 415 F.3d 1303, 1316 (Fed. Cir. 2005) (en banc).

On or about August 11, 1982, the project of formulating a commercial drug product was assigned to Dr. James Wells, a manager in Pfizer's Pharmaceutical Research and Development Department, who was assisted by Mr. Edward Davison, a member of the same group. By April 24, 1984, Dr. Wells identified a formulation for amlodipine maleate that produced "excellent capsules." In attempting to produce a direct compression tablet product of an amlodipine maleate formulation, however, Dr. Wells encountered two problems: (1) chemical instability of the amlodipine maleate, and (2) stickiness of the tablet blend of amlodipine maleate. Chemical stability refers to the resistance of a drug compound to chemical breakdown, while stickiness refers to the adherence of the drug substance, in formulation, to manufacturing equipment, such as the punch faces of a tablet-making press.

To solve the problems of the tablet form of amlodipine maleate, Dr. Wells suggested that other amlodipine salts be made and tested. In a memo dated April 24, 1984, Dr. Wells acknowledged the difficulty in stickiness and stability he was experiencing in attempting to make a tablet formulation of amlodipine maleate and stated that, by changing from the maleate salt to the free base of amlodipine or another acid addition salt, "many of the stability problems would disappear." Dr. Wells identified six alternative anions, i.e., hydrochloride, methane sulphonate, benzene sulphonate, lactate, succinate, and acetate, as potential anions with which to create acid addition salt forms of amlodipine. He also eventually added the tosylate anion to this group. Dr. Wells testified at trial that he selected these candidates based on their differing structures and properties, but could not explain why three of the seven alternative anions were members of the same class of sulphonic acids.

Mr. Davison testified at trial that he tested these amlodipine acid addition salt forms as well as amlodipine maleate and the free base for solubility, pH, hygroscopicity, and stickiness. Another researcher, Dr. Robin Platt, an analytical chemist at Sandwich, was brought in to test the stability of the amlodipine acid addition salts. Dr. Platt subjected the maleate, acetate, succinate, besylate, mesylate, and eventually the tosylate, salicylate, and hydrochloride salt forms of amlodipine to thin-layer chromatography to determine the number and amount of degradants found in the various amlodipine salts, and compiled a ranking thereof based upon the stability of each salt formulation.

Dr. Platt's findings were communicated to Dr. Wells via memorandum on or about October 9, 1984, wherein Dr. Platt reported that the besylate salt "showed a much improved stability profile over the maleate in all cases." On October 11, 1984, Dr. Wells recommended via memorandum to Dr. J.R. Davidson, a deputy of Pfizer's Pharmaceutical Research and Development Department, that the amlodipine maleate salt be replaced with amlodipine besylate for the commercial amlodipine tablet product based on Dr. Platt's memo and Mr. Davison's test results.

By April 30, 1985, both amlodipine maleate and amlodipine besylate were undergoing human testing in clinical trials. Pfizer scientists predicted that the capsule form of amlodipine maleate would have a shelf life of three years, but that "poor stability of amlodipine maleate tablet formulations" precluded commercialization. On the other hand, the scientists noted that amlodipine besylate tablet formulations exhibited "clear superiority" in their processing characteristics, particularly non-stickiness, and in stability. Capsule formulations of amlodipine besylate had not yet been produced, but

work on this project was "expected to be straightforward."

On April 4, 1986, Pfizer filed a patent application to amlodipine besylate in the U.K., which eventually issued as U.K. Patent No. 160833. On May 5, 1986, Pfizer submitted a supplement to the FDA stating that the dosage form anticipated for commercial use would be a tablet of amlodipine besylate and that all future clinical trials with amlodipine would use this new formulation. In the supplement, Pfizer stated, "We feel that the change in salt form is justified since benzenesulfonate is a commercially acceptable salt, as exemplified by the tranquilizer mesoridazine (Serentil)." In support of the use of the besylate salt form of amlodipine, Pfizer submitted a summary of the acute oral toxicity of amlodipine besylate and amlodipine maleate in rats and a comparison of the effects of both the besylate and maleate forms on blood pressure and heart rate of dogs. Pfizer stated that the results showed that there was no quantitative difference in efficacy between equivalent doses of amlodipine besylate tablets or capsules and amlodipine maleate capsules. In addition, Pfizer submitted a pharmacokinetic report and interim clinical summary showing that amlodipine besylate tablets and amlodipine maleate capsules were bioequivalent and had comparable safety and toleration when administered to healthy human volunteers.

On March 25, 1987, Pfizer filed a U.S. application (serial no. 07/030,658) to amlodipine besylate claiming priority from the U.K. application. During prosecution, the examiner initially rejected all claims of the application as obvious over the '909 patent in view of U.S. Patent 4,032,637 to Spiegel (1977) ("Spiegel") and U.S. Patent 3,816,612 to Schmidt (1974) ("Schmidt"). The examiner noted that Schmidt discloses that aryl sulphonic acid salts, which include besylate, are superior to the preferred maleate of the

'909 patent, while Spiegel provides an example of a pharmaceutical compound wherein the besylate form is specifically identified as the preferred embodiment. In response to the rejection, Pfizer argued that the besylate salt,

> while not the most soluble salt, has many other advantages not possessed by other acid addition salts . . . . [I]n addition to having good solubility, [the besylate salt] is unique in imparting to the product good stability, nonhygroscopicity and good processability. For one salt to have all of these outstanding features is not suggested or taught in the art, and would require extensive experimentation to find.

The examiner, however, maintained the rejection, stating that "these qualities are basic considerations by a person skilled in the art for selecting a suitable pharmaceutical salt" as evidenced by Berge, "Pharmaceutical Salts," J. Pharm. Sci., 66(1):1-19 (Jan. 1977) ("Berge"). Table 1 of Berge shows 53 FDA-approved, commercially marketed anions, including benzene sulphonate, that are useful for making pharmaceutically-acceptable salts, and lists the relative frequency of which each was used as a percentage based on the total number of anions or cations in use through 1974. Berge discloses that benzene sulphonate had a frequency of use of 0.25%.

In response to a final obviousness rejection by the Examiner, Pfizer filed a continuation application (serial no. 07/256,938) and abandoned the original application. Along with the continuation application, Pfizer submitted a preliminary amendment and statement, and a declaration under 37 C.F.R. § 1.132 by Dr. Wells dated October 3, 1988 ("Wells Declaration"). In the statement, Pfizer argued that the Wells Declaration demonstrated that the besylate salt of amlodipine possessed "all the desired characteristics necessary for a medicinal agent" and that it would not have been obvious "that only the besylate salt of amlodipine would have all the necessary properties for a commercial product." Pfizer argued that choosing an appropriate salt is

a very difficult task "since each salt imparts unique properties to the parent compound" and that one skilled in the art would "conclude that the besylate salt of amlodipine is a unique compound and not an obvious one." The Wells Declaration stated that the besylate salt of amlodipine was "found to possess a highly desirable combination of physicochemical properties," including good solubility, stability, non-hygroscopicity, and processability, which properties are "unpredictable both individually and collectively."

The continuation application was allowed and issued as the '303 patent on November 7, 1989. The first three claims of the '303 patent are reproduced here:

> 1. The besylate salt of amlodipine.
>
> 2. A pharmaceutical composition comprising an antihypertensive, antiischaemic or angina-alleviating effective amount of the besylate salt of amlodipine as claimed in claim 1 together with a pharmaceutically-acceptable diluent or carrier.
>
> 3. A tablet formulation comprising an anti-hypertensive, antiischaemic or angina-alleviating effective amount of the besylate salt of amlodipine as claimed in claim 1 in admixture with excipients.

Norvasc® was launched as a commercial product by Pfizer in the U.S. in November 1992.

B.

From January 11, 2006, to January 18, 2006, the district court conducted a bench trial on the issues of (1) whether the claims of the '303 patent were anticipated by the disclosure of the '909 patent, (2) whether the '303 patent was invalid for obviousness, and (3) whether the claims of the '303 patent were unenforceable due to inequitable conduct before the USPTO. On January 18, 2006, the district court stated its findings and conclusions pursuant to Fed. R. Civ. P. 52(a) orally in open court. Bench Order Tr. 1-28, January 18, 2006. The district court concluded that Apotex failed

to meet its burden of proving invalidity or inequitable conduct by clear and convincing evidence.

The district court first addressed the issue of invalidity by anticipation, finding that while the '909 patent claims a genus of pharmaceutically-acceptable salts of amlodipine that encompasses amlodipine besylate, the '909 patent does not as a matter of law disclose it. The district court held that since the '909 patent does not list the species of a salt made from benzene sulphonate, it does not anticipate the claims of the '303 patent.

With regard to obviousness, the district court rejected Apotex's argument that the '909 patent in view of the Berge article (and other prior art) rendered the invention of the claims of the '303 patent obvious. The district court first found that a person of ordinary skill in the art would have a bachelor's degree in pharmaceutical science or analytical chemistry, and some experience in drugs and drug preparation. The district court concluded that the Berge article does not direct the skilled artisan to create the besylate salt of amlodipine because Berge discloses that benzene sulphonate was used only at a frequency of 0.25%, or 1 out of every 400 drugs, prior to 1974. The district court noted that the examiner must have considered the Berge article since it was cited in the '303 patent, yet the examiner ultimately determined that the claims of the '303 patent were not obvious in view of this reference.[4] Further, the district court stated that there would

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[4] The trial transcript reads, "The patent examiner cannot [sic] have been aware of the Berge article as it was specifically noted and cited in the '303 patent itself. As such, the Court could not possibly find by clear and convincing evidence that the article and its teachings could not have been considered by the patent [sic] when ultimately determining whether the '303 patent was obvious . . . ." Bench Order Tr. 22:16-22. We interpret this passage in the only way that makes sense—that the

be no expectation of success in making a besylate salt of amlodipine because, as Berge teaches and expert testimony on both sides accepted, "There is no reliable way of predicting the influence of a particular salt species on the behavior of a parent compound." Bench Order Tr. 23:3-6.

The district court also stated that the besylate salt of amlodipine was unexpectedly superior to the amlodipine salts of the prior art. Specifically, the district court stated that, while amlodipine besylate was not superior to amlodipine maleate "in every category," it nonetheless "clearly and unexpectedly illustrates a superior combination of properties when compared to what was suggested in the preferred preparation"—ostensibly the amlodipine maleate disclosed as the preferred embodiment of the '909 patent. These properties included good solubility, stability, non-hygroscopicity, and processability (non-stickiness). The district court found that amlodipine besylate exhibited at least a solubility exceeding 1.0 mg/ml, which the court stated is the desirable solubility factor for a commercial product, and that the '303 patent listed the besylate salt form of amlodipine as the most stable salt form out of eight salts tested, with the maleate salt form being sixth on the list.

The district court also rejected Apotex's argument that amlodipine besylate is actually hygroscopic rather than non-hygroscopic as disclosed in the '303 patent. Apotex asserted that amlodipine besylate attracts water because it (1) can exist as a hydrate, (2) may have water within its crystalline structure, and (3) can have water on its surface at extended temperatures and humidity. The district court stated that while each of these facts is true, each was entirely unenlightening because hygroscopicity per

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Examiner did consider the Berge reference during prosecution. While oral bench rulings are certainly authorized, they may be ill-advised in a case of this complexity.

se was not a critical factor. Instead, the district court emphasized that the maleate salt of amlodipine underwent a Michael addition reaction when exposed to water, creating at least ten degradation products making amlodipine maleate unsuitable at least in tablet form for medicinal purposes, whereas the amlodipine besylate did not undergo the same reaction. Lastly, the district court found that Pfizer conducted extensive tests for processability of the amlodipine besylate by manufacturing tablets on conventional tablet-making machinery and measuring the amount of product sticking to the punch face after each manufacturing run. The district court concluded that the tests showed that amlodipine besylate was sufficiently non-sticky so as to be commercially processable and less sticky than the maleate form.

Besides evidence of superiority provided in the '303 patent itself, the district court pointed to another "objective consideration" in determining that amlodipine besylate was not obvious over the prior art: "Pfizer would not have changed from the maleate, into which it had invested both time and research dollars, to seek out a very strange and rare besylate salt, absent an extremely good reason." Bench Order Tr. 23:16-21. For all these reasons, the district court held that the claims of the '303 patent were not proven invalid for obviousness.

Next, the district court rejected Apotex's claim that Pfizer engaged in inequitable conduct before the USPTO in violation of its duty of candor and 37 C.F.R § 1.56. Apotex argued that Pfizer made several material misrepresentations to the USPTO during prosecution of the application leading to the '303 patent, including misrepresenting the solubility, stability, and hygroscopicity of amlodipine besylate and misrepresenting the number of tablets tested for processability both in the patent

application and in the Wells Declaration. Specifically, Apotex asserted that Pfizer (1) fraudulently identified the solubility of amlodipine besylate in its application for patent as 4.6 mg/ml where internal Pfizer documents show the solubility to actually be 3.5 mg/ml; (2) fraudulently claimed in the application to have tested over a thousand tablets for stickiness where internal Pfizer documents show varying numbers up to only 150 tablets were actually tested; and (3) fraudulently ranked the respective stabilities of the various salt forms of amlodipine in an ordinal—rather than quantitative—fashion so as to conceal from the USPTO that the stability differences between the besylate, tosylate, *and mesylate salt forms of amlodipine were actually very minor.*

The district court first determined that none of these alleged misrepresentations were either material or false. In this regard, the court stated that whether the solubility of amlodipine besylate is 4.6 mg/ml as identified in the '303 patent or 3.5 mg/ml as identified in internal Pfizer documents was at most a minor discrepancy given that any solubility over the critical 1.0 mg/ml level was sufficient solubility to meet the standards of a drug company seeking to produce a commercial drug. As for stability, the district court found that amlodipine besylate was far more stable than amlodipine maleate, which as described above undergoes the undesirable Michael addition reaction. Second, the district court held that Apotex failed to show intent to deceive by clear and convincing evidence. Indeed, the court found "precious little evidence at all" showing an intent to deceive, stating that "[w]hile it is clear that Pfizer was eager to extend the patent life of its amlodipine compound, such a desire does not rise to the level of fraudulent conduct." Bench Order Tr. 25:24-26:1.

On January 29, 2006, the district court entered a final judgment in favor of Pfizer and against Apotex on Pfizer's claim of infringement as well as on Apotex's counterclaims alleging and seeking declarations of invalidity and unenforceability of the '303 patent. The district court also ordered that, pursuant to 35 U.S.C. § 271(e)(4)(A), the effective date of any approval of Apotex's ANDA No. 76-719 shall not be earlier than September 25, 2007, and pursuant to 35 U.S.C. § 271(e)(4)(B), enjoined Apotex, its officers, agents, servants, employees and attorneys, and those persons in active concert or participation with it, from engaging in the manufacture, use, offer for sale, or sale within the U.S., or importation into the U.S. of any product comprising amlodipine besylate covered by, or the use of which is covered by, the claims of the '303 patent until September 25, 2007. Pfizer Inc. v. Apotex, Inc., No. 03C 5289 (N.D. Ill. Jan. 29, 2006). On February 17, 2006, Apotex filed a timely notice of appeal. We have jurisdiction pursuant to 28 U.S.C. § 1295(a)(1).

II. DISCUSSION

A.

Apotex appeals the district court's final judgment that it failed to prove by clear and convincing evidence that the invention of claims 1-3 of the '303 patent would have been obvious and are therefore invalid, and the district court's finding that Apotex failed to prove Pfizer committed inequitable conduct before the USPTO. Because the district court erred in holding non-obvious the invention of claims 1-3 of the '303 patent, we reverse the district court's judgment. Since we hold that claims 1-3 are invalid for obviousness, we need not and do not address Apotex's assertion that Pfizer engaged in inequitable conduct before the USPTO during prosecution of the '303 patent.

On appeal from a bench trial, this court reviews the trial court's conclusions of law de novo and findings of fact for clear error. Golden Blount, Inc. v. Robert H. Peterson Co., 365 F.3d 1054, 1058 (Fed. Cir. 2004). The ultimate conclusion of whether a claimed invention would have been obvious is a question of law reviewed de novo based on underlying findings of fact reviewed for clear error. Richardson-Vicks Inc. v. Upjohn Co., 122 F.3d 1476, 1479 (Fed. Cir. 1997). A factual finding is clearly erroneous if, despite some supporting evidence, "the reviewing court on the entire evidence is left with the definite and firm conviction that a mistake has been committed." United States v. U.S. Gypsum Co., 333 U.S. 364, 395 (1948).

B.

The district court held that Apotex had established a prima facie case of obviousness because the patent examiner initially rejected the claims to amlodipine besylate for obviousness. Specifically, the district court stated, "The '303 patent's file wrapper shows that the examiner originally rejected the claimed invention because of obviousness. Under these circumstances, of course, the Court must accept that the defendant has made a prima facie showing on this question." Bench Order Tr. 21:20-24. The district court's ruling must be rejected, not only because it is legally incorrect, but also because it may reflect a serious misconception regarding the proper burden of proof each party bears in a patent litigation.

Our case law consistently provides that a court is never bound by an examiner's finding in an ex parte patent application proceeding. Fromson v. Advance Offset Plate, Inc., 755 F.2d 1549, 1555 (Fed. Cir. 1985). Thus, it can never be the case that an examiner's interim finding of prima facie obviousness renders the claims of an issued

patent prima facie obvious. Instead, deference to the decisions of the USPTO takes the form of the presumption of validity under 35 U.S.C. § 282. Purdue Pharma L.P. v. Faulding Inc., 230 F.3d 1320, 1329 (Fed. Cir. 2000). That is, by statute a patent is valid upon issuance, 35 U.S.C. § 282, and included within the presumption of validity is a presumption of non-obviousness. Structural Rubber Prods. Co. v. Park Rubber Co., 749 F.2d 707, 714 (Fed. Cir. 1984). Since we must presume a patent valid, the patent challenger bears the burden of proving the factual elements of invalidity by clear and convincing evidence.[5] That burden of proof never shifts to the patentee to prove validity. Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1375 (Fed. Cir. 1986). "The presumption [of validity] remains intact and [the burden of proof remains] on the challenger throughout the litigation, and the clear and convincing standard does not change." Id.

It is true that once a challenger has presented a prima facie case of invalidity, the patentee has the burden of going forward with rebuttal evidence. See Mas-Hamilton Group v. LaGard, Inc., 156 F.3d 1206, 1216 (Fed. Cir. 1998) (citing Hybritech, 802 F.2d at 1376); Cable Elec. Prods. Inc. v. Genmark, Inc., 770 F.2d 1015, 1022 (Fed. Cir. 1985) ("[I]f evidence is presented establishing a prima facie case of invalidity, the opponent of invalidity must come forward with evidence to counter the prima facie

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[5] The "clear and convincing" standard is an intermediate standard which lies somewhere in between the "beyond a reasonable doubt" and the "preponderance of the evidence" standards of proof. Addington v. Texas, 441 U.S. 418, 425 (1979); see also SSIH Equip. S.A. v. United States Int'l Trade Comm'n, 718 F.2d 365, 380-81 (Fed. Cir. 1983) (Nies, J., additional views). Although an exact definition is elusive, "clear and convincing evidence" has been described as evidence that "place[s] in the ultimate factfinder an abiding conviction that the truth of its factual contentions are highly probable." Colorado v. New Mexico, 467 U.S. 310, 316 (1984) (internal quotations omitted).

challenge to the presumption of section 282."). But, all that means is that even though a patentee never must submit evidence to support a conclusion by a judge or jury that a patent remains valid, once a challenger introduces evidence that might lead to a conclusion of invalidity—what we call a prima facie case—the patentee "would be well advised to introduce evidence sufficient to rebut that of the challenger." Orthokinetics, Inc. v. Safety Travel Chairs, Inc., 806 F.2d 1565, 1570 (Fed. Cir. 1986).

However, this requirement does not "in substance shift the burden of persuasion," Cable Elec., 770 F.2d at 1022, because "the presumption of validity remains intact and the ultimate burden of proving invalidity remains with the challenger throughout the litigation." Mas-Hamilton Group, 156 F.3d at 1216; see also Innovative Scuba Concepts, Inc. v. Feder Indus., Inc., 26 F.3d 1112, 1115 (Fed. Cir. 1994); Ashland Oil, Inc. v. Delta Resins & Refractories, Inc., 776 F.2d 281, 287 (Fed. Cir. 1985). The trial court has the responsibility to determine whether the challenger has met its burden by clear and convincing evidence by considering the totality of the evidence, including any rebuttal evidence presented by the patentee. Stratoflex, Inc. v. Aeroquip Corp., 713 F.2d 1530, 1534 (Fed. Cir. 1983).

The basis (as opposed to the mere existence) of an examiner's initial finding of prima facie obviousness of an issued patent is therefore, at most only one factual consideration that the trial court must consider in context of the totality of the evidence "in determining whether the party asserting invalidity has met its statutory burden by clear and convincing evidence." Fromson, 755 F.2d at 1555. It does not, however, lessen or otherwise affect the burden of proof, nor does it require that unless the patentee introduces evidence of secondary considerations to establish non-

obviousness, the patent challenger will necessarily prevail.

C.

The underlying factual determinations made by the trial court that this court must review for clear error include (1) the scope and content of the prior art, (2) the level of ordinary skill in the art, (3) the differences between the claimed invention and the prior art, and (4) objective indicia of non-obviousness. Graham v. John Deere Co., 383 U.S. 1, 17 (1966). We start by noting that the parties stipulated to many of the facts, but disagree as to the ultimate legal outcome of obviousness based upon those facts. The parties do not dispute that benzene sulphonate was known in the art at the time of the inventions claimed in the '909 and '303 patents. Pfizer admitted that several publications, including the Berge article, were prior art to claims 1-3 of the '303 patent and pertinent to the problem the inventors sought to overcome. Neither party disputes the district court's characterization of the ordinarily skilled artisan.

Further, there is really no dispute as to the scope of the '909 patent and the differences between it and the claimed invention. The '909 patent specifically states that the pharmaceutically-acceptable salts of amlodipine "are those formed from acids which form non-toxic acid addition salts containing pharmaceutically-acceptable anions." '909 patent col.2 ll.3-6. The '909 patent lists a genus of pharmaceutically-acceptable anions "such as the hydrochloride, hydrobromide, sulphate, phosphate or acid phosphate, acetate, maleate, fumarate, lactate, tartrate, citrate and gluconate." '909 patent col.2 ll.6-9. The only examples of acid addition salts of amlodipine are maleates. The '909 patent does not expressly disclose the benzene sulphonate anion nor salts formed from benzene sulphonic acid or a larger class of sulphonic acids in

general. But, while neither the claims nor the written description of the '909 patent expressly disclose amlodipine besylate or the benzene sulphonate anion, neither do they exclude amlodipine besylate or the benzene sulphonate anion. Rather, the only limitations placed on the anion are that it is pharmaceutically-acceptable, and that in salt form, it is able to produce a non-toxic acid addition salt. Thus, as the district court found and the parties agree, the '909 patent claims literally encompass amlodipine besylate.

By statute, a claimed invention is unpatentable if the differences between it and the prior art "are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art." 35 U.S.C. § 103(a). Subsumed within the Graham factors is a subsidiary requirement articulated by this court that where, as here, all claim limitations are found in a number of prior art references, the burden falls on the challenger of the patent to show by clear and convincing evidence that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so. DyStar Textilfarben GmbH v. C.H. Patrick Co., 464 F.3d 1356, 1360 (Fed. Cir. 2006); Velander v. Garner, 348 F.3d 1359, 1363 (Fed. Cir. 2003). Here, the parties vigorously disagree.

A difficulty in the district court's opinion arises because, in assuming a prima facie case of obviousness, the district court did not fully address whether Apotex showed by clear and convincing evidence that a skilled artisan would have been motivated to combine the teachings of the prior art references relied on, especially the '909 patent and Berge, to achieve the claimed invention. However, the district court's omission in this case is harmless error because evidence of record easily satisfies us

that a reasonable fact-finder could only conclude that Apotex has shown by clear and convincing evidence that the skilled artisan would indeed have been so motivated to combine the prior art to produce the besylate salt of amlodipine. The record also satisfies us that, contrary to the district court's finding, a reasonable fact-finder could only conclude that the skilled artisan would have had a reasonable expectation of success with the besylate salt form of amlodipine for the reasons elaborated, post.

Motivation to Combine Prior Art References to Achieve the Claimed Invention

Pfizer does not argue that there was no motivation to combine the prior art references per se. Rather, Pfizer argues that (1) the '909 patent does not suggest or motivate the skilled artisan to make amlodipine besylate because none of the anions listed in the '909 patent have a cyclic structure as does besylate, and (2) even if the '909 patent were combined with Berge, the skilled artisan would not have been motivated to make amlodipine besylate because Berge shows that besylate was actually one of the most rarely used anions in the pharmaceutical industry, as only 0.25% of approved drugs as of 1974 were besylate salts. Finally, Pfizer asserts that other prior art references relied upon by Apotex are not relevant because the examples of besylate salts disclosed in these references are limited to pharmaceuticals unrelated to amlodipine.

We reject Pfizer's first argument, since a suggestion, teaching, or motivation to combine the relevant prior art teachings to achieve the claimed invention does not have to be found explicitly in the prior art references sought to be combined, but rather "may be found in any number of sources, including common knowledge, the prior art as a whole, or the nature of the problem itself." DyStar, 464 F.3d at 1361; see also Ormco

Corp. v. Align Tech., Inc., 463 F.3d 1299, 1307-08 (Fed. Cir. 2006). In other words, it is irrelevant that none of the anions specifically listed in the '909 patent have a cyclic structure, because the motivation to make amlodipine besylate here is gleaned not only from the prior art as a whole rather than the '909 patent alone, but also from the nature of the problems encountered with the amlodipine maleate tablet formulations sought to be solved by the inventors of the '303 patent. In this regard, testimony of record evidences that one skilled in the art would have been motivated to choose an anion having a different structure than that of maleate. The maleate salt ion is acyclic and consists of a double bond between the carbon atoms, whereas the besylate salt ion is cyclic and lacks the same double bond. Early in development, Pfizer discovered that amlodipine maleate was susceptible to degradation from a Michael addition reaction in which the double bond of maleate underwent an addition reaction causing the formation of degradation products. Apotex avers that unrebutted testimony from its expert, which we find compelling, supports an inference that the skilled artisan actually would have been encouraged, rather than discouraged, to choose an anion without the same double bond, such as benzene sulphonate, in order to avoid the Michael addition reaction. Thus, the fact that none of the anions listed in the '909 patent have a cyclic structure is hardly dispositive to the question of whether the skilled artisan would have been motivated to combine the prior art references to achieve amlodipine besylate.

We similarly are not persuaded by Pfizer's second argument as clear and convincing evidence shows that a skilled artisan would have been motivated to combine the '909 patent and Berge to make amlodipine besylate. Pfizer's expert, Dr. Anderson, testified that there were an unlimited number of anions, many of which could be used to

form pharmaceutically-acceptable acid addition salts. Yet a reasonable fact-finder could not accept Dr. Anderson's testimony that the number of acceptable anions was "unlimited." Of course, new salts can always be made or attempted. However, irrefutable evidence shows that a skilled chemist at the time would simply make known pharmaceutically-acceptable salts of whatever active ingredient with which he or she was working at the time. Indeed, Mr. Davison, an inventor of the '303 patent, testified that it "would have been a mistake" to choose a novel anion. Rather, "part and parcel of pharmaceutically accepted[] was to look in pharmacopoeias and compendia" to find an anion having "precedence for use within the pharmaceutical industry." Dr. Anderson similarly admitted in his testimony that it would have been logical to use Berge's list of FDA-approved anions to produce a drug formulation:

> Court: What if I sic my phalanx of zealous scientists on that list and then come up with a product. Would that be a logical thing for me to do?
> The Witness: It would be logical to try that.

This is true especially given the fact that the genus of FDA-approved anions at the time was small, i.e., only 53. That benzene sulphonate was only used in creating 0.25% of FDA-approved drugs is not highly probative, much less dispositive. Indeed, beyond hydrochloride, which was used in approximately 43% of approved drugs, almost all other salts could be characterized as "rarely used." See Berge, Table 1 (showing that 40 out of 53 anions were used in less than 1% of drugs and 23 out of 53 were used in 0.25% or less of drugs).

But the outcome of this case need not rest heavily on the size of the genus of pharmaceutically-acceptable anions disclosed by Berge because clear and convincing evidence establishes that, out of the list of 53 anions, one of ordinary skill in the art would have favorably considered benzene sulphonate because of its known acid

strength, solubility, and other known chemical characteristics as reported in several other publications Pfizer has admitted are prior art. Schmidt discloses that aryl sulphonic acids, such as benzene sulphonic acids, considerably increase the solubility of pharmaceuticals containing one or more basically reacting nitrogen atoms. '612 patent col.2 ll.14-41. Spiegel specifically identifies besylate as the preferred pharmaceutically-acceptable acid addition salt form of a pharmaceutical compound. '637 patent col.2 ll.38-39. Other patents not before the examiner during prosecution of the '303 patent also point to benzene sulphonate. U.S. Patent 3,970,662 to Carabateas (1976) ("Carabateas") discloses an intermediate dihydropyridine compound useful in the form of an acid addition salt derived from benzene sulphonate. '662 patent col.3 ll.35-49 & col.4 ll.20-24. U.S. Patent 4,432,987 to Barth (1984) ("Barth"), assigned to Pfizer, discloses the besylate acid addition salt form of a pharmaceutical composition having excellent pharmacokinetic properties, near-optimal solubility, and improved stability. '987 patent col.2 ll.45-46. Taken together, these references provide ample motivation to narrow the genus of 53 pharmaceutically-acceptable anions disclosed by Berge to a few, including benzene sulphonate.

The district court ignored the significance of these other prior art references suggesting the besylate salt because the pharmaceuticals disclosed in those prior art references were not described as useful to treat hypertension or angina, as is amlodipine. By not considering these references in its obviousness analysis, however, the district court clearly erred. As here, the besylate acid addition salt form was described in these prior art references as useful in promoting stability and solubility, as well as improving other physicochemical characteristics. That none of these references

discloses a medication for treating hypertension or angina like amlodipine is therefore unimportant, if not actually irrelevant. As Pfizer concedes, the besylate part of the acid addition salt has no therapeutic effect, but merely serves as a means to deliver the amlodipine part of the molecule to the body. Prior art disclosing the use of benzene sulphonate for improving the bioavailability of other pharmaceuticals—especially a dihydropyridine as disclosed by Carabateas—is therefore highly relevant in weighing the factors relating to obviousness.

Considering all of the evidence, we hold that a reasonable fact-finder could only conclude that Apotex indeed produced clear and convincing evidence that one skilled in the art, facing the problems including the stickiness of the tablet form of the maleate acid addition salt, would have been motivated to combine the teachings of the '909 patent, Berge, and other prior art, to produce the besylate salt of amlodipine.

Reasonable Expectation of Success

As noted above, the district court found that the skilled artisan would have had no expectation of success in making a besylate salt of amlodipine because there was no reliable way to predict the influence of a particular salt species on the active part of the compound. We cannot reject the district court's finding that in 1986, it was generally unpredictable as to whether a particular salt would form and what its exact properties would be. The problem with the district court's ultimate conclusion of non-obviousness based on that factual finding, however, is that case law is clear that obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success. See In re Corkill, 771 F.2d 1496, 1500 (Fed. Cir. 1985) ("Although [the inventor] declared that it cannot be predicted how any

candidate will work in a detergent composition, but that it must be tested, this does not overcome [the prior art's] teaching that hydrated zeolites will work."); see also Brown & Williamson Tobacco Corp. v. Philip Morris Inc., 229 F.3d 1120, 1125 (Fed. Cir. 2000); Merck & Co., Inc. v. Biocraft Labs., Inc., 874 F.2d 804, 809 (Fed. Cir. 1989); In re Merck & Co., Inc., 800 F.2d 1091, 1097 (Fed. Cir. 1986). Indeed, a rule of law equating unpredictability to patentability, applied in this case, would mean that any new salt—including those specifically listed in the '909 patent itself—would be separately patentable, simply because the formation and properties of each salt must be verified through testing. This cannot be the proper standard since the expectation of success need only be reasonable, not absolute. Merck, 874 F.2d at 809; In re O'Farrell, 853 F.2d 894, 903 (Fed. Cir. 1988).

The evidence would convince a reasonable finder of fact that the skilled artisan would have had that reasonable expectation of success that an acid addition salt of besylate would form and would work for its intended purpose. See In re Rinehart, 531 F.2d 1048, 1053-54 (C.C.P.A. 1976). Specifically, the evidence clearly shows that as soon as tablet processing problems arose with the amlodipine maleate tablet formulations, Dr. Wells readily compiled a list of seven alternative anions—including the besylate—each of which he expected would form an amlodipine acid addition salt:

> Q. And one of the reasons why you chose these various salts [sic], or suggested these various salts [sic], is because you expected that they would be able to make a salt of them, correct?
> A. There was an expectation, but that wasn't guaranteed.

But, once again, only a reasonable expectation of success, not a guarantee, is needed. O'Farrell, 853 F.2d at 903; Brown & Williamson, 229 F.3d at 1125. That reasonable expectation of success is further amply reflected in Dr. Wells' further testimony that he

expected these seven amlodipine acid addition salts would show improved physicochemical characteristics over the maleate salt, including improved stability and non-stickiness:

> Q. And when you chose these salts . . . you believed that if you could, in fact, make an amlodipine salt out of them, these might be a cure for the problems you were having with maleate, correct?
> A. Indeed.

We also note that the '909 patent placed no limitations on the acid addition salt whatsoever, except that it be non-toxic and formed from an acid containing a pharmaceutically-acceptable anion. Accordingly, the '909 patent contained a strong suggestion that any and all pharmaceutically-acceptable anions would form non-toxic acid addition salts and would work for their intended purpose—that is, to improve bioavailability of the active ingredient amlodipine and to improve handling and storage of amlodipine. Indeed, in proceedings before this court in Pfizer v. Dr. Reddy's Laboratories involving the '909 patent, Pfizer downplayed any difference between amlodipine maleate and any other acid addition salt form of amlodipine, including the besylate, prompting this court to observe that the sole active ingredient is amlodipine, and that it acts the same in the human body whether administered as a besylate salt or as a maleate salt. 359 F.3d at 1366.

Finally, there is a suggestion in Pfizer's supplemental filing with the FDA that it was known that the besylate salt of amlodipine would work for its intended purpose: "We feel that the change in salt form [from maleate to besylate] is justified since benzenesulfonate is a commercially acceptable salt, as exemplified by the tranquilizer mesoridazine (Serentil)." Thus, although Dr. Wells testified that it was not guaranteed whether amlodipine besylate would form and what its salient characteristics would be,

"this does not overcome [the prior art's] teaching that [amlodipine besylate] will work." Corkill, 771 F.2d at 1500.

Considering all of the evidence, we conclude that the district court clearly erred in finding that Apotex failed to produce clear and convincing evidence that one skilled in the art would have had a reasonable expectation of success with the besylate salt of amlodipine.

"Obvious-to-Try"

To be sure, "to have a reasonable expectation of success, one must be *motivated to do more than merely to vary all parameters or try each of numerous* possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of *many possible choices is likely to be successful.*" Medichem, S.A. v. Rolabo, S.L., 437 F.3d 1157, 1165 (Fed. Cir. 2006) (internal quotations omitted). Pfizer argues that, if anything, amlodipine in its besylate salt form would at most be "obvious to try," i.e., to vary all parameters or try each of numerous possible choices to see if a successful result was obtained. O'Farrell, 853 F.2d at 903.

Parties before this court often complain that holdings of obviousness were based on the impermissible "obvious to try" standard, and this court has accordingly struggled to strike a balance between the seemingly conflicting truisms that, under 35 U.S.C. § 103, "obvious to try" is not the proper standard by which to evaluate obviousness, In re Antonie, 559 F.2d 618, 620 (C.C.P.A. 1977), but that, under O'Farrell and other precedent, absolute predictability of success is not required. 853 F.2d at 903. Reconciling the two is particularly germane to a situation where, as here, a formulation

must be tested by routine procedures to verify its expected properties. The question becomes then, when the skilled artisan must test, how far does that need for testing go toward supporting a conclusion of non-obviousness?

As we have said before, "[e]very case, particularly those raising the issue of obviousness under section 103, must necessarily be decided upon its own facts." In re Jones, 958 F.2d 347, 350 (Fed. Cir. 1992). Consequently, courts cannot decide the obviousness or non-obviousness of a patent claim by proxy. Undue dependence on mechanical application of a few maxims of law, such as "obvious to try," that have no bearing on the facts certainly invites error as decisions on obviousness must be narrowly tailored to the facts of each individual case. As we stated in DyStar,

> Obviousness is a complicated subject requiring sophisticated analysis, and no single case lays out all facets of the legal test. [There is] danger inherent in focusing on isolated dicta rather than gleaning the law of a particular area from careful reading of the full text of a group of related precedents for all they say that is dispositive and for what they hold. When parties . . . do not engage in such careful, candid, and complete legal analysis, much confusion about the law arises and, through time, can be compounded.

464 F.3d at 1367. On the facts of this case, however, we are satisfied that clear and convincing evidence shows that it would have been not merely obvious to try benzene sulphonate, but would have been indeed obvious to make amlodipine besylate.

First, this is not the case where there are "numerous parameters" to try. Rather, the only parameter to be varied is the anion with which to make the amlodipine acid addition salt. Although we recognize some degree of unpredictability of salt formation, see, e.g., Sanofi-Synthelabo v. Apotex, Inc., 470 F.3d 1368, 1379 (Fed. Cir. 2006), the mere possibility that some salts may not form does not demand a conclusion that those that do are necessarily non-obvious. This is especially true here, where (1) as noted

above, the skilled artisan had a reasonable (although not guaranteed) expectation that amlodipine besylate would form; (2) Pfizer conceded in prior litigation that the type of salt had no effect on the therapeutic effect of the active ingredient, amlodipine, and was practically interchangeable, Pfizer v. Dr. Reddy's Labs., 359 F.3d at 1365-66; and (3) numerous other publications (described above) clearly directed the skilled artisan to a pharmaceutically-acceptable acid addition salt made from benzene sulphonate, including, significantly, the Carabateas patent which taught the besylate acid addition salt form of another dihydropyridine pharmaceutical compound.

Second, this is not the case where the prior art teaches merely to pursue a "general approach that seemed to be a promising field of experimentation" or "gave only general guidance as to the particular form of the claimed invention or how to achieve it." O'Farrell, 853 F.2d at 903; Medichem, 437 F.3d at 1167. Here, as admitted by Mr. Davison, in selecting an acid addition salt formulation, one skilled in the art looked to pharmacopoeias and compendia to find a salt that was previously approved by the FDA and used successfully within the pharmaceutical industry. Berge clearly pointed the skilled artisan to 53 anions that, as of 1974, were pharmaceutically acceptable. As Dr. Wells' testimony and the Carabateas patent demonstrated, one of ordinary skill in the art was capable of further narrowing that list of 53 anions to a much smaller group, including benzene sulphonate, with a reasonable expectation of success.

Finally, Pfizer protests that a conclusion that amlodipine besylate would have been obvious disregards its "discovery" because it was obtained through the use of trial and error procedures. While the pharmaceutical industry may be particularly adversely impacted by application of an "obvious to try" analysis, see, e.g., In re Merck, 800 F.2d

at 1100 (Baldwin, J., dissenting), that Pfizer had to verify through testing the expected traits of each acid addition salt is of no consequence because it does not compel a conclusion of non-obviousness here. In coming to this conclusion, we have not ignored the fact that "[p]atentability shall not be negatived by the manner in which the invention was made." 35 U.S.C. § 103(a). Nor are we ignorant of the fact that reference to "routine testing" or "routine experimentation" is disfavored. See, e.g., In re Yates, 663 F.2d 1054, 1056 n.4 (C.C.P.A. 1981) ("The Solicitor . . . argues that it is 'not unobvious to discover optimum or workable ranges by routine experimentation.' In many instances, this may be true. The problem, however, with such 'rules of patentability' (and the ever-lengthening list of exceptions which they engender) is that they tend to becloud the ultimate legal issue—obviousness—and exalt the formal exercise of squeezing new factual situations into preestablished pigeonholes. Additionally, the emphasis upon routine experimentation is contrary to the last sentence of section 103.") (internal citation omitted); In re Saether, 492 F.2d 849, 854 (C.C.P.A. 1974) ("In his argument that 'mere routine experimentation' was involved in determining the optimized set of characteristics, the solicitor overlooks the last sentence of 35 U.S.C. § 103 . . . . Here we are concerned with the question of whether the claimed invention would have been obvious at the time it was made to a person having ordinary skill in the art—not how it was achieved.") (internal citation omitted); In re Fay, 347 F.2d 597, 602 (C.C.P.A. 1965) ("[W]e do not agree that 'routine experimentation' negatives patentability. The last sentence of section 103 states that 'patentability shall not be negatived by the manner in which the invention was made.' To support the board's decision that 'routine experimentation within the teachings of the art' will defeat patentability requires a

primary determination of whether or not appellants' experimentation comes within the teachings of the art. Whether the subsequent experimentation is termed 'routine' or not is of no consequence.").

However, on the particularized facts of this case, consideration of the "routine testing" performed by Pfizer is appropriate because the prior art provided not only the means of creating acid addition salts but also predicted the results, which Pfizer merely had to verify through routine testing. Merck, 874 F.2d at 809. The evidence shows that, upon making a new acid addition salt, it was routine in the art to verify the expected physicochemical characteristics of each salt, including solubility, pH, stability, hygroscopicity, and stickiness, and Pfizer's scientists used standard techniques to do so. These type of experiments used by Pfizer's scientists to verify the physicochemical characteristics of each salt are not equivalent to the trial and error procedures often employed to discover a new compound where the prior art gave no motivation or suggestion to make the new compound nor a reasonable expectation of success. This is not to say that the length, expense, and difficulty of the techniques used are dispositive since many techniques that require extensive time, money, and effort to carry out may nevertheless be arguably "routine" to one of ordinary skill in the art. Rather, our conclusion here relies on the fact that one skilled in the art would have had a reasonable expectation of success at the time the invention was made, and merely had to verify that expectation. Cf. Velander v. Garner, 348 F.3d 1359, 1368 (Fed. Cir. 2003) (that one skilled in the art would view variability in producing fibrinogen in transgenic mammals as evidence that "expense, time and effort" would be involved did not equate to a conclusion that success was unlikely). Simply put, to conclude that

amlodipine besylate would have been obvious, "the prior art, common knowledge, or the nature of the problem, viewed through the eyes of an ordinary artisan" merely had to suggest reacting amlodipine base with benzene sulphonic acid to form the besylate acid addition salt, and that that acid addition salt form would work for its intended purpose. DyStar, 464 F.3d at 1361. They did. See O'Farrell, 853 F.2d at 904.

We find this case analogous to the optimization of a range or other variable within the claims that flows from the "normal desire of scientists or artisans to improve upon what is already generally known." In re Peterson, 315 F.3d 1325, 1330 (Fed. Cir. 2003) (determining where in a disclosed set of percentage ranges the optimum combination of percentages lies is prima facie obvious). In In re Aller, 220 F.2d 454, 456 (C.C.P.A. 1955), our predecessor court set forth the rule that the discovery of an optimum value of a variable in a known process is usually obvious. See also In re Boesch, 617 F.2d 272, 276 (C.C.P.A. 1980) ("[D]iscovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art."). Similarly, we hold that the optimization of the acid addition salt formulation for an active pharmaceutical ingredient would have been obvious where as here the acid addition salt formulation has no effect on the therapeutic effectiveness of the active ingredient and the prior art heavily suggests the particular anion used to form the salt. Cf. In re Geisler, 116 F.3d 1465, 1470 (Fed. Cir. 1997) ("'[I]t is not inventive to discover the optimum or workable ranges by routine experimentation.'" (quoting Aller, 220 F.2d at 456)); In re Kulling, 897 F.2d 1147, 1149 (Fed. Cir. 1990) (finding no clear error in Board of Patent Appeals and Interferences' conclusion that the amount of eluent to be used in a washing sequence was a matter of routine optimization known in the pertinent

prior art and therefore obvious). Indeed, the logical line of testing was to react benzene sulphonate with amlodipine to confirm the presence of a salt, and then to verify that the physicochemical properties of amlodipine besylate were adequate, particularly the trait of sufficient non-stickiness. The experimentation needed, then, to arrive at the subject matter claimed in the '303 patent was "nothing more than routine" application of a well-known problem-solving strategy, Merck, 874 F.2d at 809, and we conclude, "the work of a skilled [artisan], not of an inventor." DyStar, 464 F.3d at 1371; see also In re Luck, 476 F.2d 650, 652-53 (C.C.P.A. 1973) (use of routine testing to identify optimum amounts of silane to be employed in a lamp coating, without establishing a critical upper limit or demonstrating any unexpected result, lies within the ambit of the ordinary skill in the art); In re Esterhoy, 440 F.2d 1386, 1389 (C.C.P.A. 1971) ("One skilled in the art would thus manifestly operate the Switzer et al. process under conditions most desirable for maximum and efficient concentration of the acid. The conditions recited in the claims appear to us to be only optimum and easily ascertained by routine experimentation."); In re Swentzel, 219 F.2d 216, 219 (C.C.P.A. 1955) ("It may well be that the size represents the largest particles suitable for appellant's purpose, but the determination of that desired size under the present circumstances involves nothing more than routine experimentation and exercise of the judgment of one skilled in the art."); In re Swain, 156 F.2d 246, 247-48 (C.C.P.A. 1946) ("In the absence of a proper showing of an unexpected and superior result over the disclosure of the prior art, no invention is involved in a result obtained by experimentation.").

Thus, while patentability of an invention is not negated by the manner in which it was made, "the converse is equally true: patentability is not imparted where 'the prior

art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success.'" Merck, 874 F.2d at 809 (quoting In re Dow Chem. Co., 837 F.2d 469, 473 (Fed. Cir. 1988)). For these reasons, we hold that Apotex introduced clear and convincing evidence that a skilled artisan would have had a reasonable expectation of success with the besylate salt form of amlodipine at the time the invention was made. Accordingly, we agree with the district court that a prima facie case of obviousness was established with regard to the claims of the '303 patent, albeit for different reasons.

Secondary Considerations

Before we turn to the remaining conflict between the parties—the district court's consideration of the objective indicia of non-obviousness—we must first address the district court's reference in its bench opinion to Pfizer's business decision to switch its commercial product from an amlodipine maleate formulation to an amlodipine besylate formulation, apparently as evidence of non-obvicusness. See Bench Order Tr. at 6:21-7:1 ("Pfizer is a big company, which by this time had a large investment in amlodipine maleate. . . . A decision to switch to some other product, or even to abandon the entire product, is the corporate equivalent of turning the Queen Mary."); Bench Order Tr. at 18:17-21 ("Pfizer would not have changed from the maleate, into which it had invested both time and research dollars, to seek out a very strange and rare besylate salt, absent an extremely good reason."). The district court's reliance on this "objective consideration" seems suspect as there is no evidence in the appellate record to support the implicit finding that Pfizer ever considered abandoning amlodipine or stood to lose significant time and investment dollars. Indeed, we are not ignorant of the fact that

pharmaceutical companies are in the business of research and development. We therefore disregard the district court's findings on this point as clearly erroneous, or in any event insufficiently probative of non-obviousness to overcome the evidence of the prior art teachings.

Evidence of unexpected results can be used to rebut a prima facie case of obviousness. Peterson, 315 F.3d at 1330. The district court found that, while amlodipine besylate was not superior to amlodipine maleate in every category of physicochemical properties, it nonetheless "clearly and unexpectedly illustrates a superior combination of properties when compared to" amlodipine maleate.[6] With regard to solubility, the '303 patent discloses that amlodipine besylate has a solubility of 4.6 mg/ml at pH 6.6, whereas amlodipine maleate has a solubility of 4.5 mg/ml at pH 4.8. The district court stated that any product having a solubility greater than 1.0 mg/ml is acceptable, and that "[t]he rest is sound and fury." Bench Order Tr. at 11:10. We conclude from this statement that the district court did not find that the solubility of amlodipine besylate was materially superior, much less "unexpectedly superior" to the solubility of amlodipine maleate. Similarly, we also conclude that the district court did not rely on non-hygroscopicity as a secondary consideration. Thus, the two allegedly unexpected and superior properties remaining are drug stability and tablet processing.

With respect to stability, the district court found that the '303 patent provided an ordinal listing of several tested salts descending in rank order from the most stable to

[6] We reject Apotex's assertion that the district court erred by giving weight to the commercial success of Norvasc®. The district court relied on the production of billions of amlodipine besylate tablets by Pfizer as evidence of non-stickiness rather than commercial success. Apotex's arguments with regard to an alleged absence of a "nexus" between the claimed features and the sales of Norvasc® are therefore irrelevant.

the least stable, where the besylate salt was the most stable of the eight salts tested, and the maleate salt was the sixth most stable salt. The district court also found that amlodipine besylate was "sufficiently nonsticky to obtain commercial processability." Pfizer asserts that these improvements have significant practical value and are indicative of non-obviousness.

In contrast, Apotex asserts that the district court committed several errors when assessing secondary considerations. Specifically, Apotex asserts that the district court erred by comparing amlodipine besylate only to the maleate preferred embodiment disclosed in the '909 patent rather than the entire genus of amlodipine salts claimed therein. Apotex also asks this court to discount Pfizer's evidence of unexpectedly superior properties because the stability and drug processing properties of amlodipine besylate are neither "unexpected" nor "surprising." Finally, Apotex asserts that even if amlodipine besylate exhibits a better combination of solubility, pH, stability, non-hygroscopicity, and non-stickiness properties than other members of the genus of amlodipine salts, this purported superiority of amlodipine besylate is not significant enough as a matter of law to make it non-obvious. Apotex argues that amlodipine is the active ingredient and the sole source of therapeutic effects of amlodipine besylate, whereas the besylate is merely a means of delivering the amlodipine part of the molecule. Thus, Apotex asserts, any salt need only exhibit adequate physicochemical characteristics in order to serve its purpose of delivering the amlodipine. Apotex contends that the record here demonstrates that the amlodipine maleate tablet also performs these same functions. The issue before us is whether, based upon the evidence as a whole, Pfizer's showing of superior results was sufficiently unexpected so

as to rebut Apotex's showing of a prima facie case of obviousness.

While we agree that the teaching of a prior art patent is not limited to its preferred embodiment, see Merck, 874 F.2d at 807 ("the fact that a specific [embodiment] is taught to be preferred is not controlling, since all disclosures of the prior art, including unpreferred embodiments, must be considered"), the other amlodipine salts of which Apotex complains (i.e., amlodipine tosylate and amlodipine mesylate) were not expressly recited in the '909 patent or elsewhere in the prior art. Thus, the district court's obligation to consider the entire range of prior art compounds would have been satisfied here by its comparison of the closest prior art compound to amlodipine besylate. Kao Corp. v. Unilever United States, Inc., 441 F.3d 963, 970 (Fed. Cir. 2006) ("'[W]hen unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art.'" (quoting In re Baxter Travenol Labs., 952 F.2d 388, 392 (Fed. Cir. 1991)). However, there is precious little (if any) evidence to support any implicit finding by the district court that amlodipine maleate is actually the closest prior art compound to amlodipine besylate. Indeed, the prior art of Schmidt, Spiegel, Carabateas, and Barth, discussed above, evidences that one skilled in the art would expect an acid addition salt made from benzene sulphonate to have good physicochemical properties.

Another defect in the district court's reasoning is its failure to recognize that by definition, any superior property must be unexpected to be considered as evidence of non-obviousness. In re Chupp, 816 F.2d 643, 646 (Fed. Cir. 1987). Thus, in order to properly evaluate whether a superior property was unexpected, the court should have considered what properties were expected. Merck, 874 F.2d at 808. Here, Pfizer's

evidence must fail because the record is devoid of any evidence of what the skilled artisan would have expected. We will not simply presume that the skilled artisan would have expected that amlodipine besylate would have the same characteristics as amlodipine maleate, because as Pfizer asserts, its properties are not absolutely predictable. Further, Dr. Wells' testimony reflects the fact that he believed that amlodipine besylate would solve the problems of amlodipine maleate. Unrebutted testimony from Apotex's expert evidences that, given the range of 53 anions disclosed by Berge, one skilled in the art would expect those anions to provide salts having a range of properties, some of which would be superior, and some of which would be inferior, to amlodipine maleate. Pfizer has simply failed to prove that the results are unexpected. Boesch, 617 F.2d at 278.

Finally, we do not see the trial court's finding that amlodipine besylate had adequate physicochemical characteristics as sufficient to uphold the court's ultimate holding of unexpected superiority. Pfizer rejected amlodipine maleate not because it failed to exhibit an adequate combination of solubility, pH, stability in capsule form, and non-hygroscopicity, but because it could not be easily manufactured because of stickiness and limited stability of amlodipine maleate in the preferred commercial form of a tablet. The district court wrongly relied on the fact that the "besylate salt works" because considerable evidence shows that amlodipine maleate also worked for its intended purpose and even did so in human clinical trials, even though somewhat inferior in ease of tableting and projected shelf-life. At most, then, Pfizer engaged in routine, verification testing to optimize selection of one of several known and clearly suggested pharmaceutically-acceptable salts to ease its commercial manufacturing and

marketing of the tablet form of the therapeutic amlodipine. Creating a "product or process that is more desirable, for example because it is stronger, cheaper, cleaner, faster, lighter, smaller, more durable, or more efficient . . . to enhance commercial opportunities . . . is universal—and even common-sensical." DyStar, 464 F.3d at 1368. Amlodipine besylate is obvious on the facts of this case because the '909 patent suggested—and Dr. Wells expected—that every other potential salt form of amlodipine would be adequate for its intended purpose, i.e., to increase bioavailability of amlodipine, and would solve the stickiness problem of the maleate salt. The fact that amlodipine besylate was the best of the seven acid addition salts actually tested proves nothing more than routine optimization that would have been obvious to one of ordinary skill in the art. See Aller, 220 F.2d at 456 ("[E]ven though applicant's modification results in great improvement and utility over the prior art, it may still not be patentable if the modification was within the capabilities of one skilled in the art."). These facts lead us to conclude that the resulting commercial embodiment claimed in the '303 patent, amlodipine besylate, does not satisfy the standards of patentability.

Alternatively, we hold that even if Pfizer showed that amlodipine besylate exhibits unexpectedly superior results, this secondary consideration does not overcome the strong showing of obviousness in this case. Although secondary considerations must be taken into account, they do not necessarily control the obviousness conclusion. Newell Cos., Inc. v. Kenney Mfg. Co., 864 F.2d 757, 768 (Fed. Cir. 1988). Here, the record establishes such a strong case of obviousness that Pfizer's alleged unexpectedly superior results are ultimately insufficient. Id. at 769.

From our de novo assessment of the determination below on obviousness in *view of all of the evidence and for the reasons articulated above, we conclude that the* district court erred in holding that the claims of the '303 patent would not have been obvious.

III. CONCLUSION

Because we find claims 1-3 of the '303 patent invalid for obviousness, we find it unnecessary to address Apotex's assertion that Pfizer engaged in inequitable conduct during prosecution of the '303 patent and that its patent should therefore be declared unenforceable. For the aforementioned reasons, the district court's judgment is reversed.

REVERSED.

LINN, Circuit Judge, concurs in the result.