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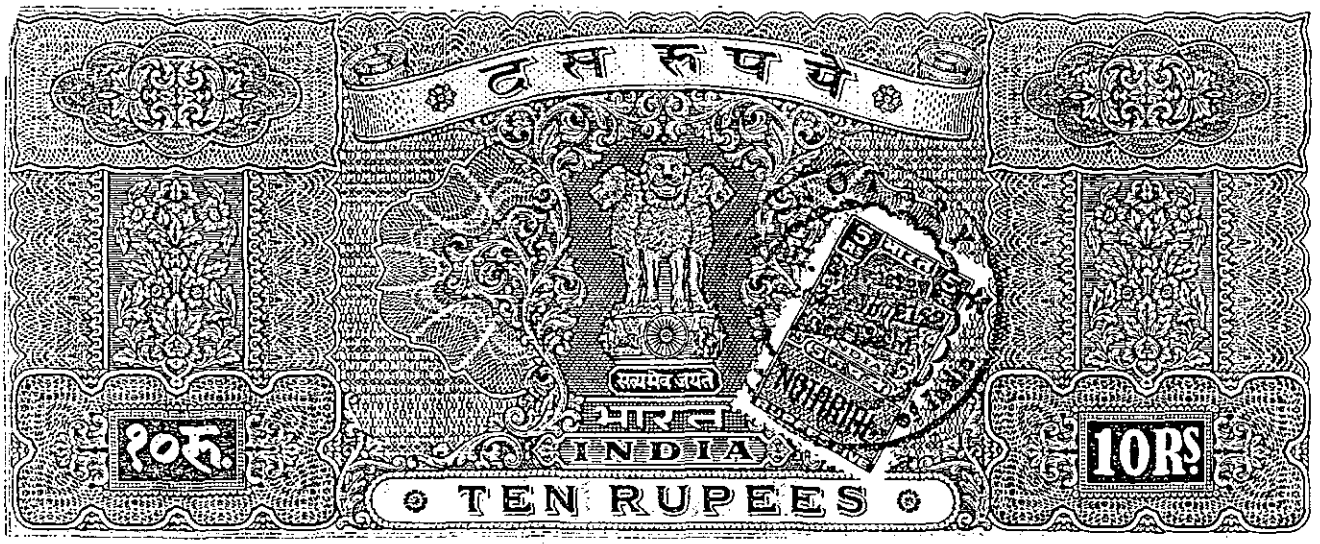

POWER OF ATTORNEY

We, M/s. Ranbaxy Laboratories Limited, a Company incorporated under the Companies Act, 1956, having its Registered Office at A-11, Sahibzada Ajit Singh Nagar-160055, District. Ropar (Punjab) and Head Office at 12th Floor, Devika Tower, 6, Nehru Place, New Delhi-110 019, ("**Appointer**") do hereby authorise M/s. Varadachari Lakshmikumaran, Varadachari Sridharan, Anil Misra, R. Parthasarathy, T. Srinivasan, J Suresh, Sumitha Vibhu, S. Sridharan Advocates/Patent Agents of **Lakshmi Kumaran & Sridharan, at B-6/10, Safdarjung Enclave, New Delhi** – 110 029 and branch offices at Chennai, Banglaore, Bombay and Hyderabd ("Attorney"), to do and perform jointly and severally all or any of the following acts, deeds, matters or things namely:

1. To oppose the grant of patents and/or to take up proceedings for the revocation of patents and exclusive marketing rights before any Court, Tribunal, Board or Authority of appropriate jurisdiction in India.

2. To intervene in or be impleaded in any proceedings as aforementioned.

3. To prefer any appeal, revision or review from the judgment or order in any proceedings as aforementioned and to defend and oppose any appeal, revision or review filed or to be filed by any opposite parties in any proceedings as aforementioned.

4. To file, withdraw or receive documents and moneys from the Court, Tribunal, Board or Authority or the opposite party during the course of any proceedings as aforementioned and to sign and deliver on behalf of the Appointer proper receipt and discharge for the same.

5. In connection with any of the proceedings aforementioned to make, sign, execute, verify, affirm and file caveats, plaints, complaints, affidavits, applications, petitions, or written statements, replies, objections, appeals, cross-appeals, warrants of attorney, tabular statements, or any other documents and papers expedient or necessary in the opinion of the Attorney to be made, signed, executed, verified, presented or filed.

20-5-2005

NOTARY
K. Srivastava
Regd. No. 2129
Area Delhi
Govt. of India

10 Rs.

6. To delegate all or any of the powers, authorities and liberties hereunder vested and to appoint any substitute or substitutes or agent hereunder, limited to any one or more purpose or purposes as may be desired from time to time in that behalf and upon such terms as may be fit or proper.

AND GENERALLY to act as the Attorney of the Appointer in relation to the proceedings aforesaid in connection therewith and on their behalf to do, execute and perform all instruments, acts, deeds, matters and things as fully and effectually as the Appointer could itself do notwithstanding no special power of authority in that particular behalf is contained in these presents

AND THE APPOINTER does ratify and confirm all previous acts, if any, done by the Attorney prior to the execution hereof in respect of the matters aforesaid and the Appointer agrees to ratify and confirm and hereby ratifies and confirms all acts done by the Attorney pursuant to these presents.

Dated this 20th day of May, 2005.

WITNESSES:

S.K. PATAWARI
COMPANY SECRETARY
RANBAXY LABORATORIES LTD.,
12TH FLOOR, DEVIKA TOWER,
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For and on behalf of
RANBAXY LABORATORIES LTD.

(RAM S. RAMASUNDAR)
EXECUTIVE VICE PRESIDENT-
FINANCE AND CFO

To
The Controller of Patents
The Patent Office

NOTARY
K. Srivastava
Regd. No. 2122
Area Delhi
Govt. of India

ATTESTED
Notary Public Delhi
20 MAY 2005

Pregrant Oppsition (Ranbaxy) -(1)

REPRESENTATION BY WAY OF OPPOSITION

IN ACCORDANCE WITH SECTION 25(1) OF THE PATENTS ACT, 1970

NAME, ADDRESS & NATIONALITY

1.1 We, Ranbaxy Laboratories Limited, A-11, Sahibzada Ajit Singh Nagar-160055, District, Ropar (Punjab) and Head Office at 12th floor, Devika Tower, 6, Nehru Place, New Delhi-110019 being a company registered under the Companies Act, 1956 **(Opponent)** hereby give notice of opposition to the Patent Application No. IN/PCT/2001/0018/MUM dated 03.01.2001 (**Application, Annexure 1**) made by **ABBOT LABORATORIES,** Abbott Park, IL 60064-6050, United States Of America (**Applicant**), in accordance with section 25(1) of the Patents Act (**Act**) on the grounds hereinafter indicated.

GROUNDS & BRIEF FACTS

Brief Facts

2.1 We are manufacturers and traders in drug and pharmaceutical substances and products and we would be seriously prejudiced in case a patent is granted on the basis of the above Application.

2.2 The Application is titled *"Polymorph of a Pharmaceutical"*.

2.3 The Application has a total of 30 (thirty) claims of which 4 (four) (claims 1 to 4) are product claims for the polymorphic crystalline Form II (**Form II**) of the compound *(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* **(Product),** 2 (two) (claims 5 and 6) are product claims for the amorphous form **(Form A)** of the Product and 24 (twenty four) (claims 7 to 30) are process claims for the preparation of the Form II and Form A .

2.4 We shall in this Representation refer to Form II and Form A collectively as **Forms**.

2.5 The Application acknowledges that the Product is also known as Ritonavir and has been previously disclosed. The Application lists patents and applications dealing with the Product. The Application also discloses that the Product inhibits HIV infection and such use of the product was disclosed in previous patents and patent applications.

2.6 The Application does not assert any specific utility for the Forms.

Grounds

3.1 We assert that no patent can be granted on the basis of the Application for the following reasons:

i. The subject matter of the Application stands anticipated;

ii. No utility is claimed;

iii. The Application could not have been filed under section 5(2) of the previous Act;

iv. No patent can be granted for a new form of a known substance; and

v. The invention is not clearly and sufficiently described;

3.2 The detailed submissions in regard to each of the above points are given below.

The subject matter of the Application stands anticipated

4.1 The subject matter of the Application is not new and there have been in the past, publications, which have disclosed the Form.

4.2 The Act provides that in cases of applications claiming subject matter already disclosed previously in another specification, then no patent can be granted for that application.

4.3 The Product was disclosed for the first time in the US Patent **5,541,206** (**'206 patent, Annexure 2**) at **column 8, line 32**, filed on April 25, 1995 and granted on July 30, 1996. The Application too acknowledges at **page 1 at line 20** that the Product and the salts thereof stood disclosed in '206 patent.

4.4 The '206 patent at **column 1, lines 29 to 35** states that "*The present invention relates to novel compounds and a composition and method for inhibiting retroviral proteases and in particular for inhibiting human immunodeficiency virus (HIV) protease, a composition and method for treating a retroviral infection and in particular an HIV infection, processes for making such compounds and synthetic intermediates employed in these processes .....*".

4.5 Further **US 5,635,523** and **US 5,674,882** disclose the use of the product in the treatment of disease. **US 5,567,823** discloses a process for the preparation of the Product by recrystallization of ritonavir from heptane/ethyl acetate (see column 8, example 4, lines 58-60). The above patents are at **Annexures 3 to 5** respectively.

4.6 It is clear from the above that the Product in all its forms was disclosed in the '206 patent. Further the use of the Product without limitation of form was disclosed in the US 5,635,523 and US 5,674,882 patents. Further the process for making the Product too stands disclosed. Clearly all forms of the Product stand anticipated. The Forms therefore lack novelty.

4.7 No patent can therefore be granted on the basis of the Application.

No utility is claimed in the Application

5.1 It is settled law that an application for patent must in the specifications assert utility. Further the asserted utility must be substantial and verifiable.

5.2 In the instant case there are no assertions as to utility. No patent can be granted to such an application.

5.3 The Application must therefore be rejected.

The Application could not have been filed under section 5(2) of the Act

6.1 The Act prior to its amendment with effect from January 1, 2005 did not permit the grant of product patents in respect of chemicals, medicines or drugs.

6.2 A limited exemption was created under section 5(2) of the Act. Applications for the grant of a patent could be filed in respect of:

> *"a claim for patent of an invention for a substance itself intended for use, or capable of being used , as a medicine or drug, ...*

6.3 It is thus clear that in case a patent has to be granted on the basis of the Application, the subject matter of the invention must conform to the requirements of section 5(2) of the Act.

6.4 The requirements of section 5(2) are:

(i) *The Application must be for an invention;*

(ii) The invention must be for a substance; and

(iii) The above substance must itself be *intended for use*, or capable of being used as a medicine or drug.

6.5 It would be noted that in the instant case, in accordance with para 4 supra, it stands established that there is no invention in the instant case. Assuming however, without conceding, that there is an invention, it would be noted that the Application does not claim any clinical or pharmaceutical utility.

6.6 The Application at best claims certain Forms of a known pharmaceutical substance. The Application does not claim the invention of a pharmaceutical or drug substance. It thus stands established that the Application is not for the *invention* of a substance itself intended for use, or capable of being used, as a medicine or drug.

6.7 An Application that does not claim to be the invention of a medicine or a drug cannot be the subject matter of section 5(2) of the Act. The Application thus

has to be examined with reference to the law as on the priority date of the Application. On such date no patent could be granted for a chemical substance.

6.8 It would thus follow that the Application is not the proper subject matter of an application under section 5(2) of the Act. The Application thus must be rejected.

No patent can be granted for a new form of a known substance

7.1 Assuming but not admitting that the invention as contained in the Application is not anticipated from the '206 patent and that it is the subject matter of section 5(2) of the Act, then too the subject matter of Application would be outside the scope of patentability in accordance with the Act.

7.2 The subject matter of the Application relates to the *polymorphic* and *amorphous* form of a known chemical substance.

7.3 No invention is patentable if it falls within the ambit of section 3(d) of the Act.

7.4 Section 3(d) of the Act provides as follows:

> *"the mere discovery of a* ***new form of a known substance*** *which does not result in the enhancement of the known efficacy of that substance or the mere discovery of any new property or new use for a known substance or of the mere use of a known process, machine or apparatus unless such known process results in a new product or employs at least one new reactant*
>
> *EXPLANATION—For the purposes of this clause, salts, esters, ethers,* ***polymorphs****, metabolites,* ***pure form****, particle size, isomers, mixtures of isomers, complexes, combinations and other derivatives of known substance shall be considered to be the same substance, unless they differ significantly in properties with regard to efficacy"*

7.5 It is clear from the above provision that no patent can be granted to a substance unless the new form whether polymorphic or amorphous claims an enhancement of efficacy as compared to the earlier known substance. Further the purer form of a known substance cannot be the subject matter of a patent in light of the specific mandate of section 3(d).

7.6 In the instant case '206 patent and the US 5,635,523 and the US 5,674,882 patents claims pharmaceutical efficacy. The Application does not assert any efficacy pharmaceutical or otherwise.

7.7 In the absence of any claim to an enhanced pharmaceutical efficacy no patent can be granted on the basis of the Application.

The invention is not sufficiently and clearly described in the Application

8.1 Section 25(g) of the Act states that no patent shall be granted if:

"the complete specification does not sufficiently and clearly describe the invention or the method by which it is to be performed;"

This effectively means that each claim must be definite and that the invention must be enabled.

8.2 Claims 1 and 2 in the Application claim the form without any reference to the purity. Claims 3 to 6 in the Application claims *substantially pure* polymorphs.

8.3 In the specification, the term "substantially pure" has been defined as:

- when used in reference to a polymorph of ritonavir, refers to a polymorph of ritonavir, Form I or Form 11, which is greater than about 90% pure.
- when used in reference to amorphous ritonavir, refers to amorphous ritonavir which is greater than about 90% pure.

8.4 The processes described in the specifications do not at any place distinguish between processes that lead to 90% and greater purity from other

processes. In fact the Application does not claim any process for realising the form of claims 1 or 2.

8.5 Claims 7-30 relate to processes "*for the preparation of the substantially pure crystalline or amorphous polymorph*". These claims are indefinite since nowhere does the Application disclose the process for realising Form II with 90% or greater purity. By including the desired result in the claim the claim does not become definite. It continues to be indefinite.

8.6 It would thus follow that a patent cannot be granted on the basis of the Application since all claims are clearly indefinite and claims 3-6 are not enabled.

RELIEF SOUGHT & PERSONAL HEARING

9.1 In light of the above submissions it is therefore humbly prayed that:

(1) the Patent Application No. IN/PCT/2001/0018/MUM dated 03.01.2001 may be rejected; and

(2) no patent be granted on the basis of the Application.

9.2 It is further requested that we, the Opponent, may be granted a personal hearing.

NAME, ADDRESS, & OTHER PARTICULARS

10. Our address for service in India is:

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On behalf of the Opponents
Anil Misra
(Patent Agent for the Opponent)

ANNEXURE 1

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°, 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 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.

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°.

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 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)

^{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 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.

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)-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

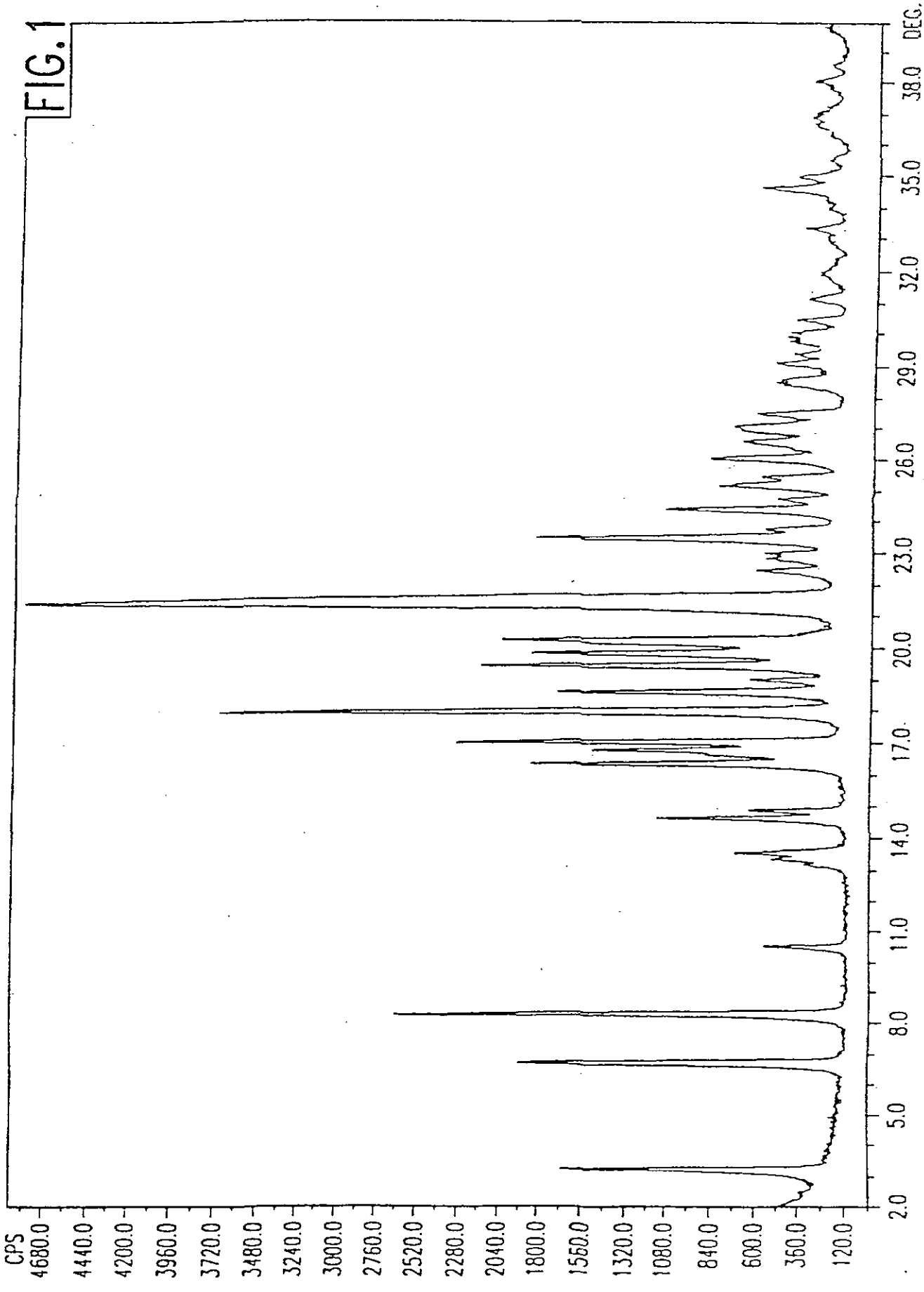
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FIG.2

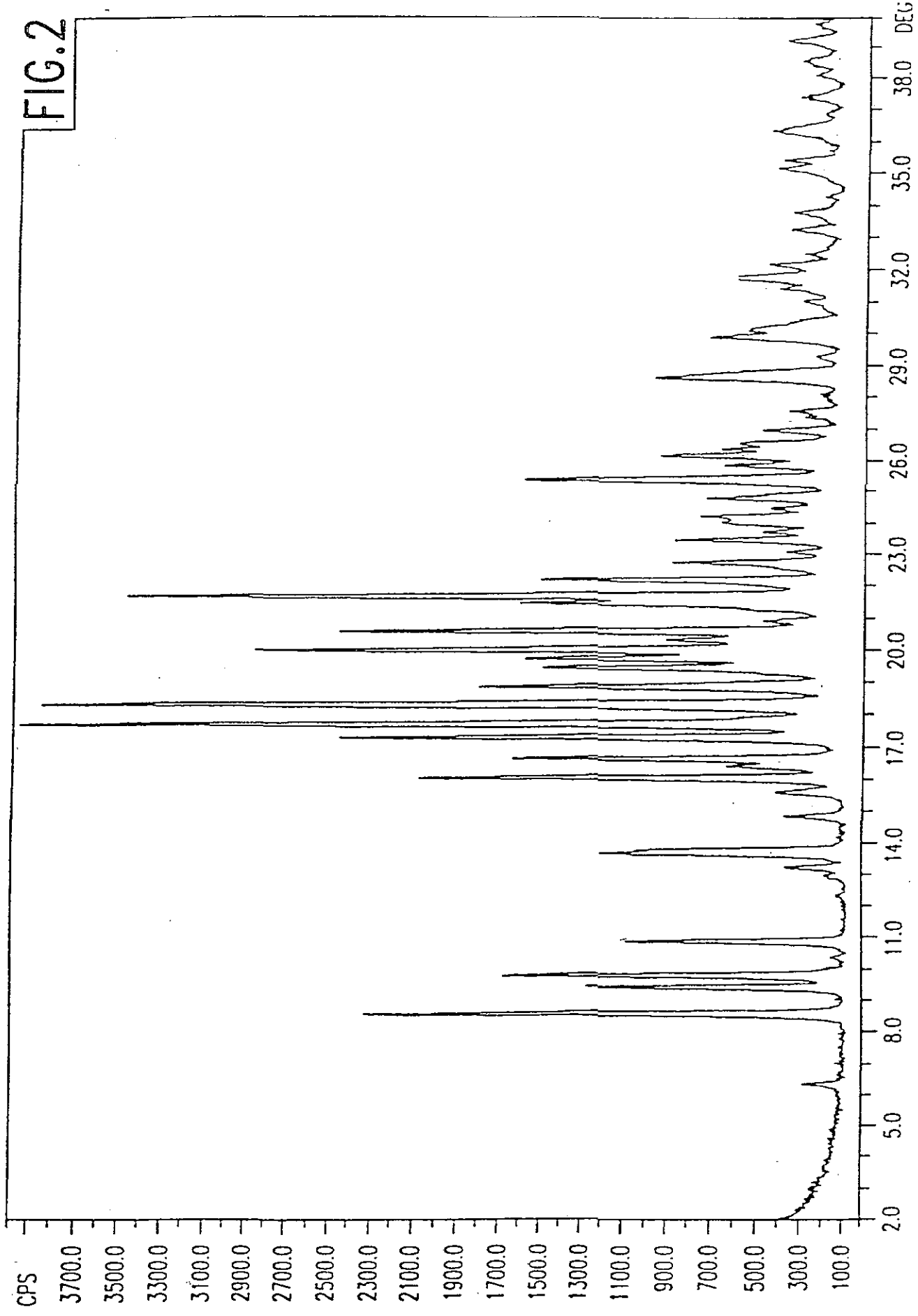
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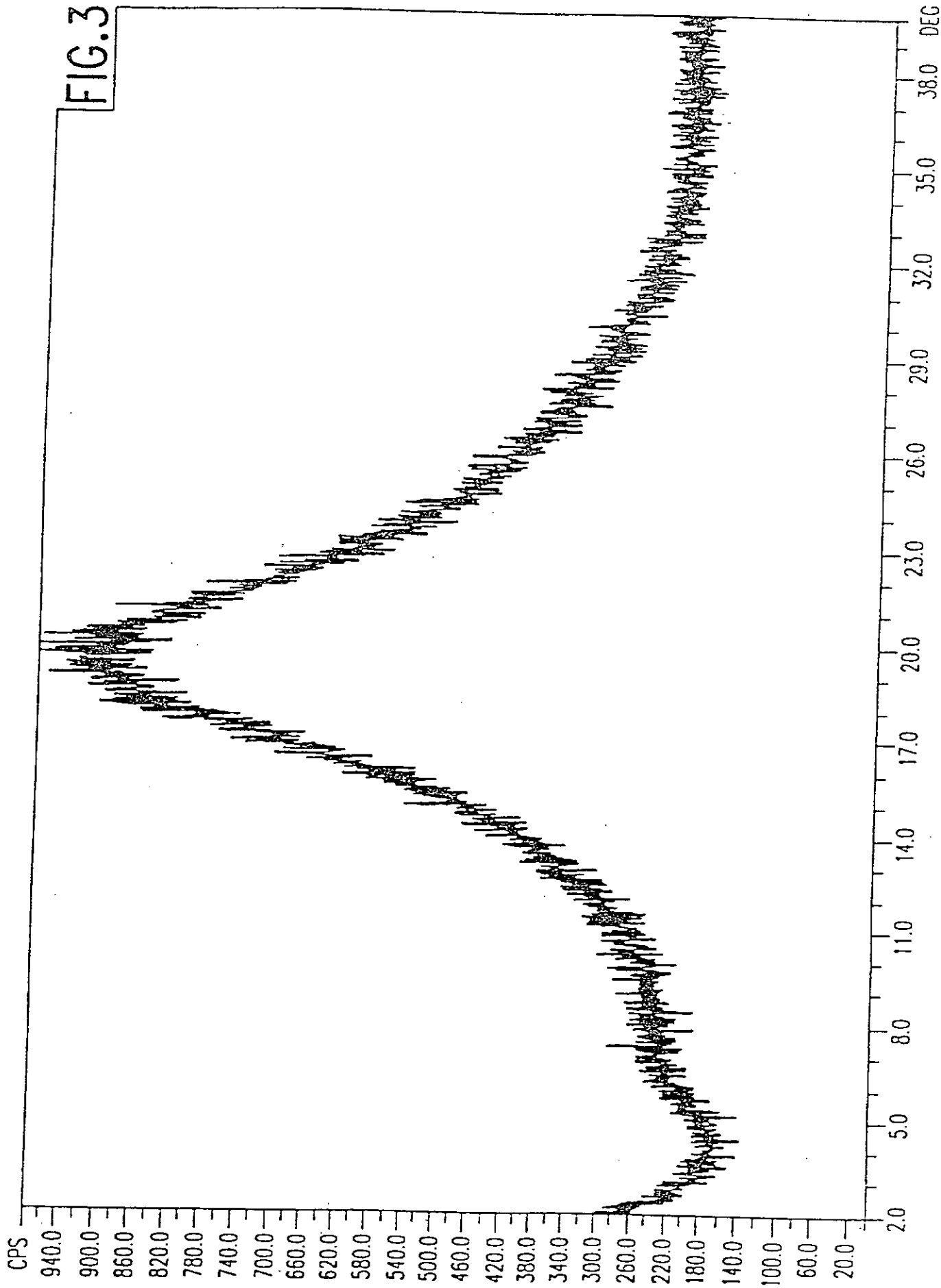
FIG.3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540.0
500.0
460.0
420.0
380.0
340.0
300.0
260.0
220.0
180.0
140.0
100.0
60.0
20.0
2.0
5.0
8.0
11.0
14.0
17.0
20.0
23.0
26.0
29.0
32.0
35.0
38.0
DEG

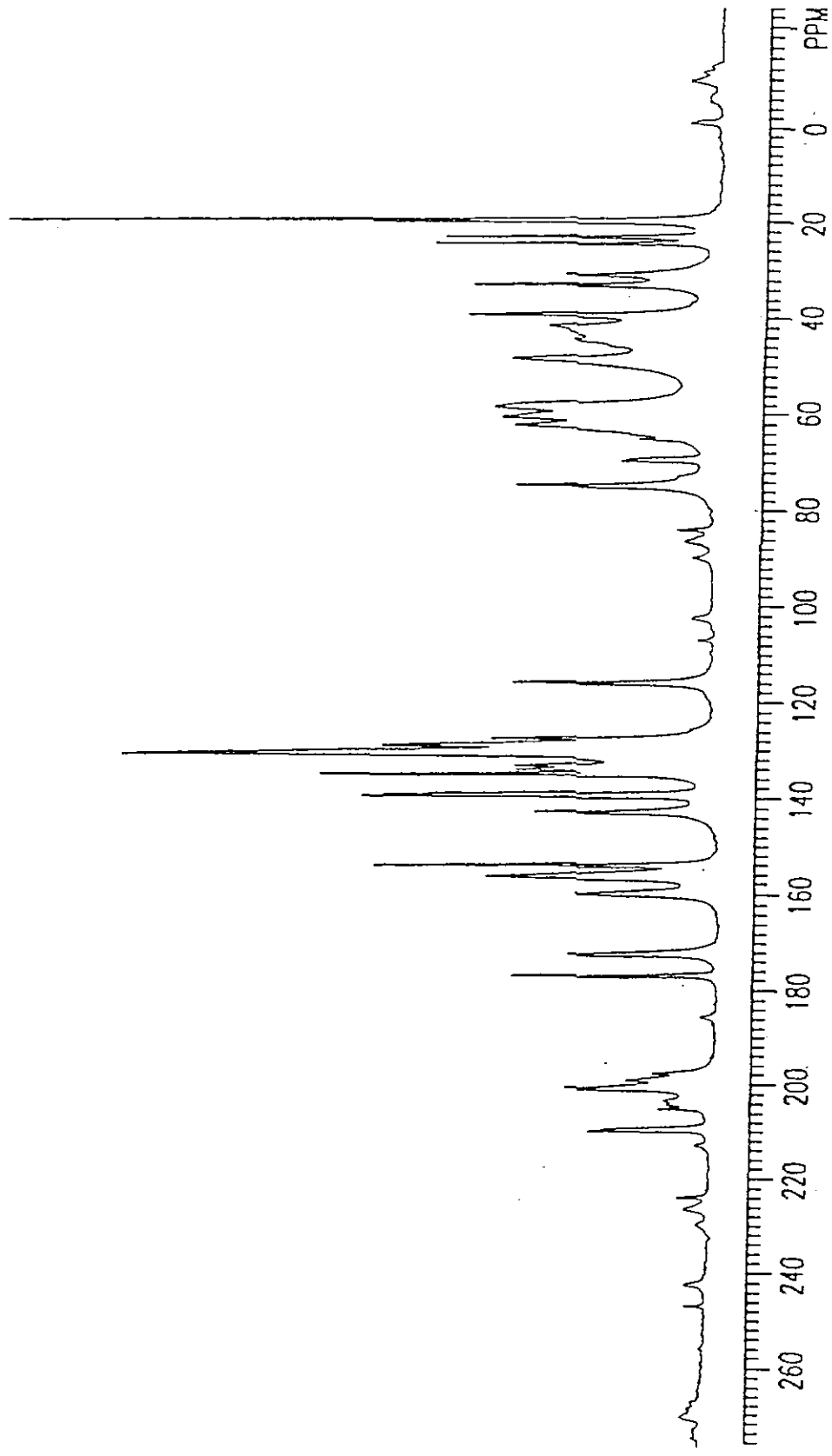


FIG.4

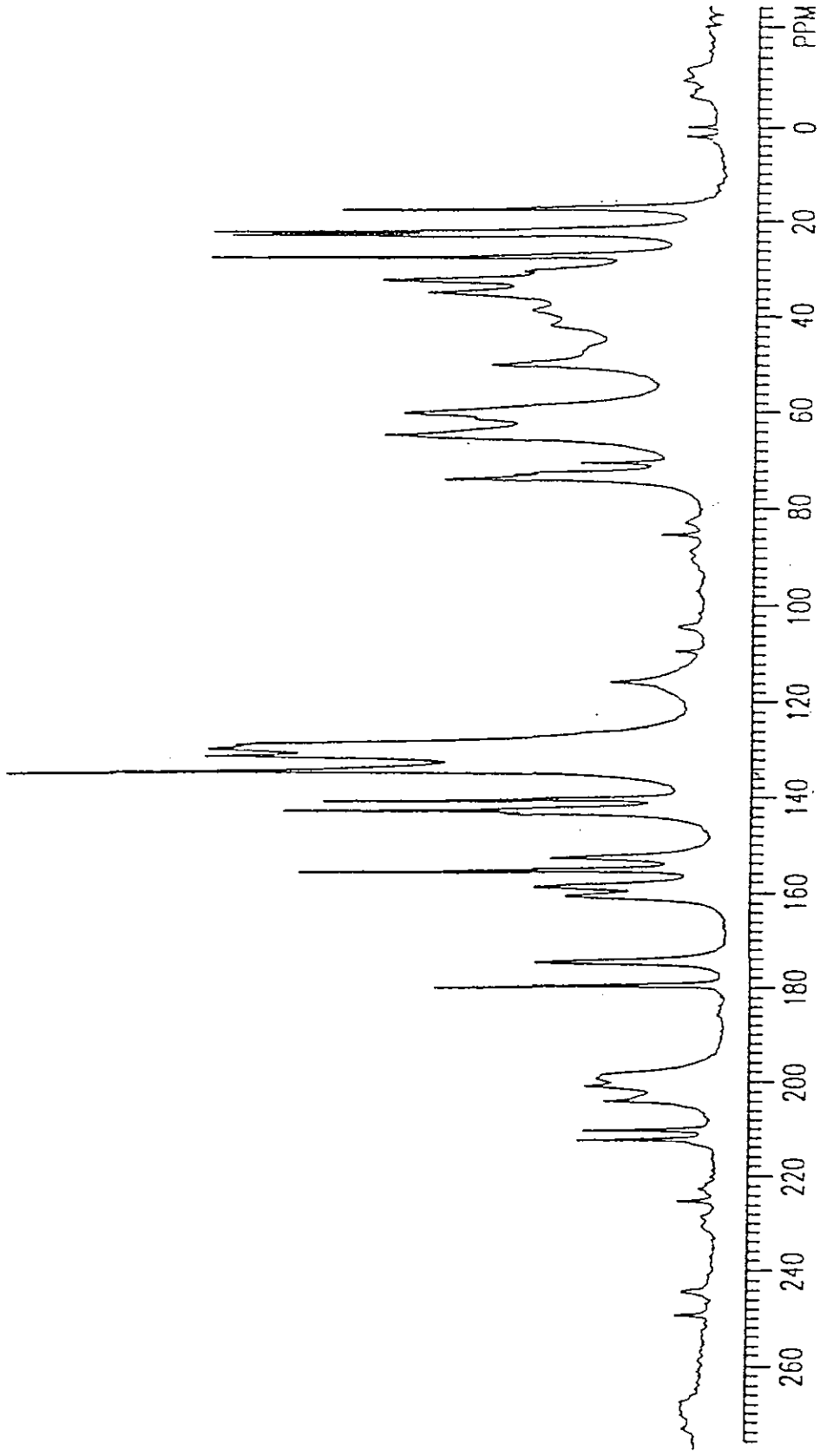


FIG.5

FIG.6

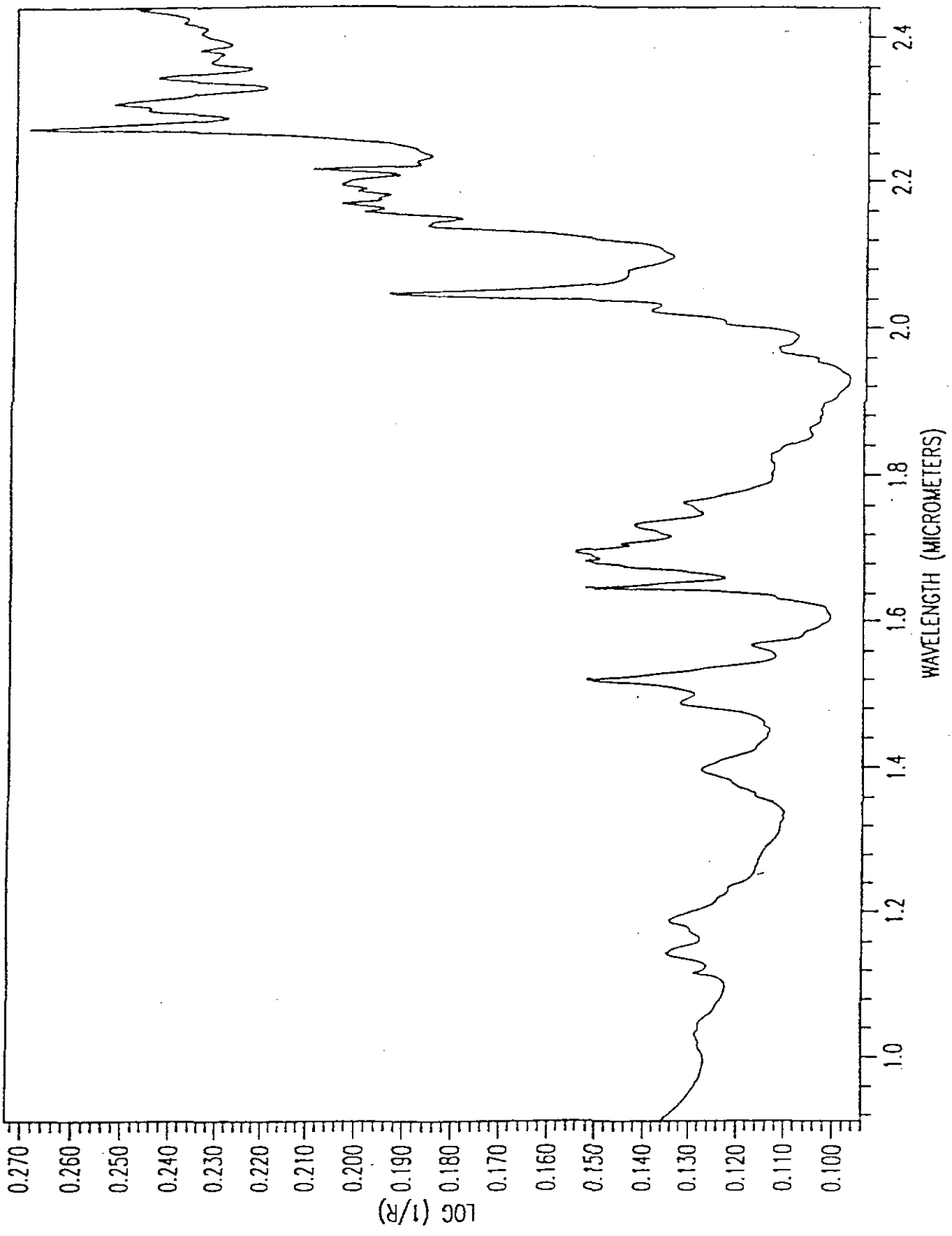

LOG (1/R)
0.270
0.260
0.250
0.240
0.230
0.220
0.210
0.200
0.190
0.180
0.170
0.160
0.150
0.140
0.130
0.120
0.110
0.100
WAVELENGTH (MICROMETERS)
1.0
1.2
1.4
1.6
1.8
2.0
2.2
2.4

FIG. 7

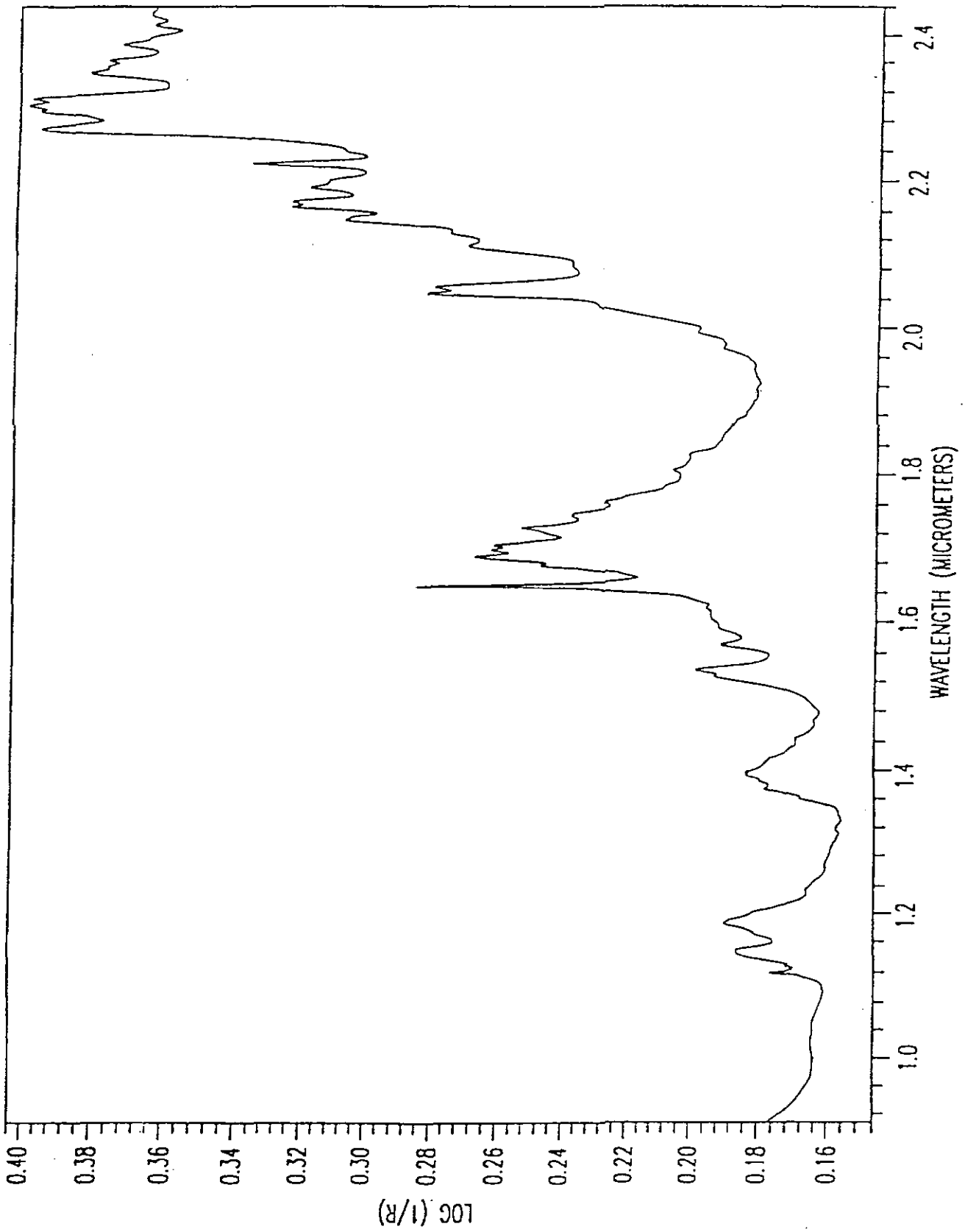

LOG (1/R)
0.40
0.38
0.36
0.34
0.32
0.30
0.28
0.26
0.24
0.22
0.20
0.18
0.16
1.0
1.2
1.4
1.6
1.8
2.0
2.2
2.4
WAVELENGTH (MICROMETERS)

FIG.8

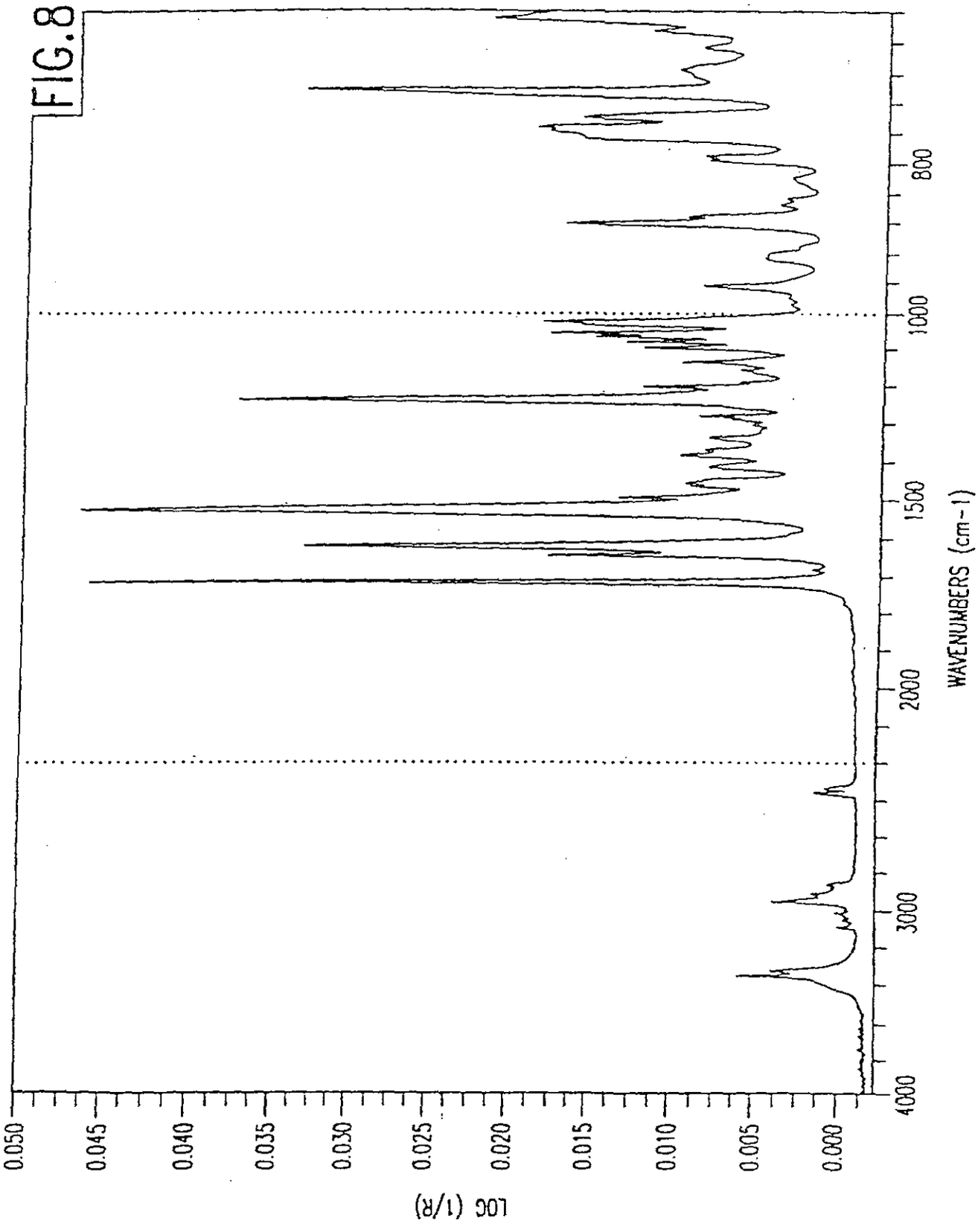

0.050
0.045
0.040
0.035
0.030
0.025
0.020
0.015
0.010
0.005
0.000
LOG (1/R)
4000
3000
2000
1500
1000
800
WAVENUMBERS (cm-1)

FIG.9

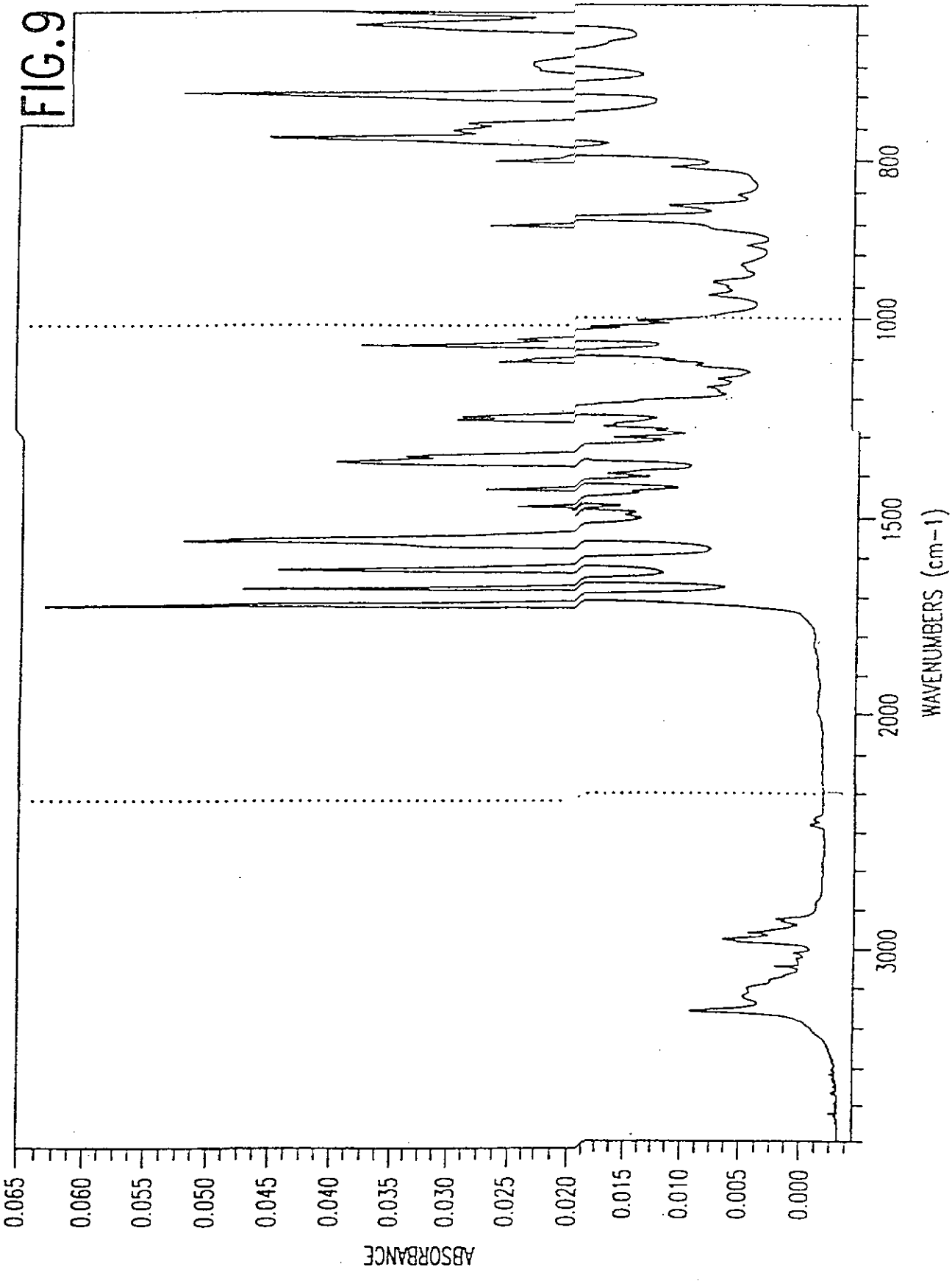
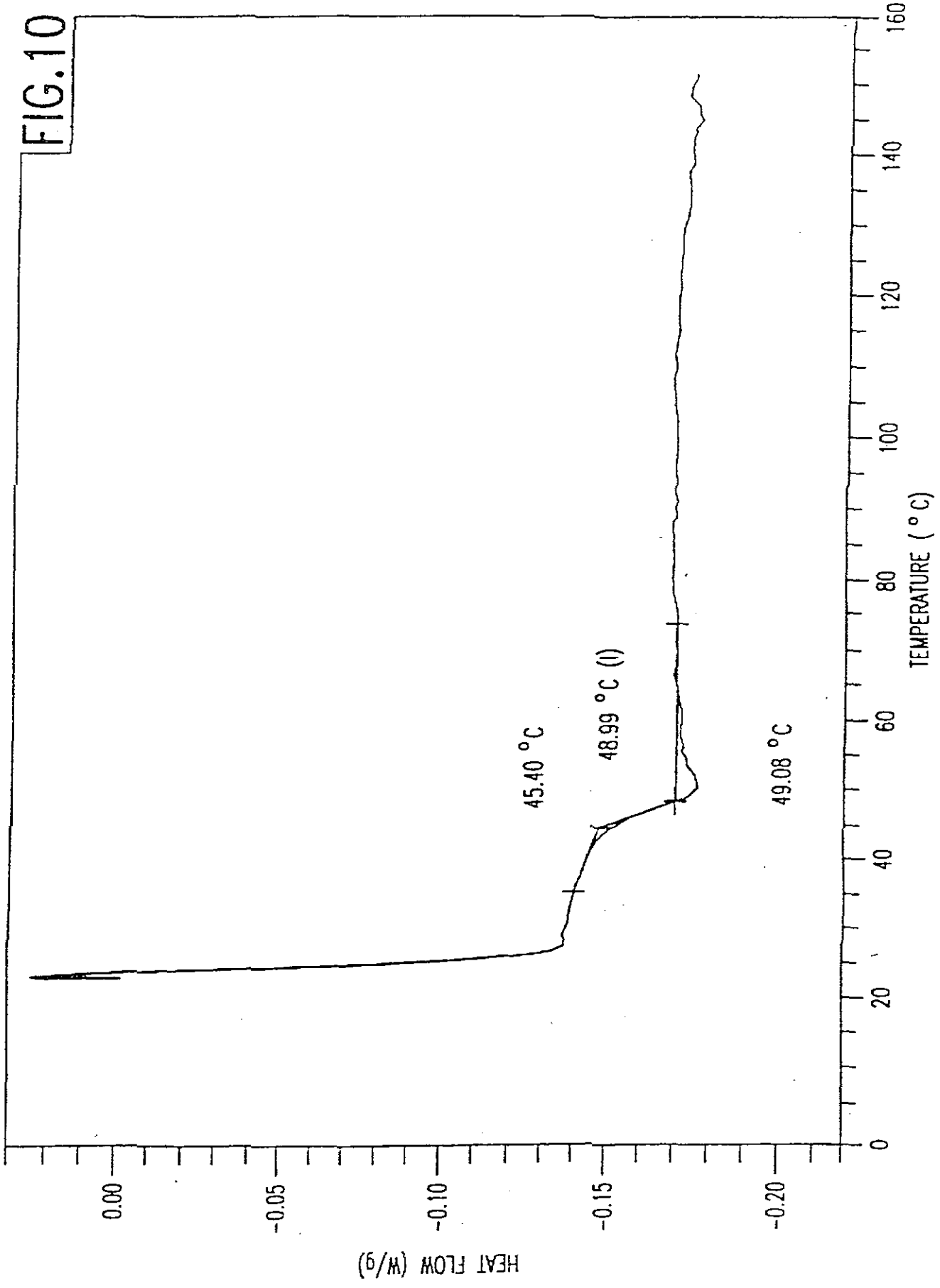

0.065
0.060
0.055
0.050
0.045
0.040
0.035
0.030
0.025
0.020
0.015
0.010
0.005
0.000
ABSORBANCE
3000
2000
1500
1000
800
WAVENUMBERS (cm-1)

FIG.10


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

ANNEXURE 2

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

[56] **References Cited**

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5,354,866	10/1994	Kempf et al.	546/265

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428849B12a	5/1991	European Pat. Off. .
441192B3	8/1991	European Pat. Off. .
441192B3a	8/1991	European Pat. Off. .
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3829594B1	3/1990	Germany .
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WO90/09191B8	8/1990	WIPO .
WO91/18866B10	12/1991	WIPO .
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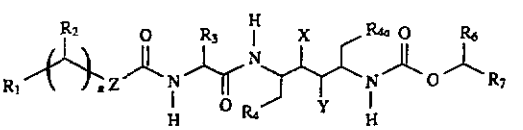
Primary Examiner—Jane Fan

Attorney, Agent, or Firm—Steven R. Crowley

[57] **ABSTRACT**

A retroviral protease inhibiting compound of the formula:



is disclosed.

19 Claims, No Drawings

RETROVIRAL PROTEASE INHIBITING COMPOUNDS

This invention was made with Government support under contract number AI27220 awarded by the National Institute of Allergy and Infectious Diseases. The Government has certain rights in this invention.

This is a continuation of U.S. patent application Ser. No. 08/158,587, filed Dec. 2, 1993 now abandoned, which is a continuation-in-part of U.S. patent application Ser. No. 998,114, filed Dec. 29, 1992, now abandoned which is a continuation-in-part of U.S. patent application Ser. No. 777,626, filed Oct. 23, 1991, now abandoned which is a continuation-in-part of U.S. patent application Ser. No. 746,020, filed Aug. 15, 1991, now abandoned which is a continuation-in-part of U.S. patent application Ser. No. 616,170, now abandoned filed Nov. 20, 1990, now abandoned which is a continuation-in-part of U.S. patent application Ser. No. 518,730, filed May 9, 1990, now U.S. Pat. No. 5,142,056 which is a continuation-in-part of U.S. patent application Ser. No. 456,124, filed Dec. 22, 1989, now abandoned which is a continuation-in-part of U.S. patent application Ser. No. 405,604, filed Sep. 8, 1989, now abandoned which is a continuation-in-part of U.S. patent application Ser. No. 355,945, filed May 23, 1989 now abandoned.

TECHNICAL FIELD

The present invention relates to novel compounds and a composition and method for inhibiting retroviral proteases and in particular for inhibiting human immunodeficiency virus (HIV) protease, a composition and method for treating a retroviral infection and in particular an HIV infection, processes for making such compounds and synthetic intermediates employed in these processes.

BACKGROUND OF THE INVENTION

Retroviruses are those viruses which utilize a ribonucleic acid (RNA) intermediate and a RNA-dependent deoxyribonucleic acid (DNA) polymerase, reverse transcriptase, during their life cycle. Retroviruses include, but are not limited to, the RNA viruses of the Retroviridae family, and also the DNA viruses of the Hepadnavirus and Caulimovirus families. Retroviruses cause a variety of disease states in man, animals and plants. Some of the more important retroviruses from a pathological standpoint include human immunodeficiency viruses (HIV-1 and HIV-2), which cause acquired immune deficiency syndrome (AIDS) in man, hepatitis B virus, which causes hepatitis and hepatic carcinomas in man, human T-cell lymphotrophic viruses I, II, IV and V, which cause human acute cell leukemia, and bovine and feline leukemia viruses which cause leukemia in domestic animals.

Proteases are enzymes which cleave proteins at specific peptide bonds. Many biological functions are controlled or mediated by proteases and their complementary protease inhibitors. For example, the protease renin cleaves the peptide angiotensinogen to produce the peptide angiotensin I. Angiotensin I is further cleaved by the protease angiotensin converting enzyme (ACE) to form the hypotensive peptide angiotensin II. Inhibitors of renin and ACE are known to reduce high blood pressure in vivo. An inhibitor of a retroviral protease will provide a therapeutic agent for diseases caused by the retrovirus.

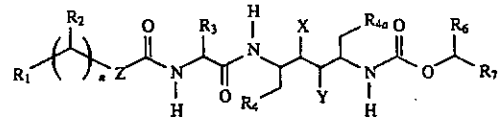
The genomes of retroviruses encode a protease that is responsible for the proteolytic processing of one or more polyprotein precursors such as the pol and gag gene products. See Wellink, Arch. Virol. 98 1 (1988). Retroviral proteases most commonly process the gag precursor into core proteins, and also process the pol precursor into reverse transcriptase and retroviral protease. In addition, retroviral proteases are sequence specific. See Pearl, Nature 328 482 (1987).

The correct processing of the precursor polyproteins by the retroviral protease is necessary for the assembly of infectious virions. It has been shown that in vitro mutagenesis that produces protease-defective virus leads to the production of immature core forms which lack infectivity. See Crawford, J. Virol. 53 899 (1985); Katoh, et al., Virology 145 280 (1985). Therefore, retroviral protease inhibition provides an attractive target for antiviral therapy. See Mitsuya, Nature 325 775 (1987).

Current treatments for viral diseases usually involve administration of compounds that inhibit viral DNA synthesis. Current treatments for AIDS involve administration of compounds such as 3'-azido-3'-deoxythymidine (AZT), 2',3'-dideoxycytidine (DDC) and 2',3'-dideoxyinosine (DDI) and compounds which treat the opportunistic infections caused by the immunosuppression resulting from HIV infection. None of the current AIDS treatments have proven to be totally effective in treating and/or reversing the disease. In addition, many of the compounds currently used to treat AIDS cause adverse side effects including low platelet count, renal toxicity and bone marrow cytopenia.

DISCLOSURE OF THE INVENTION

In accordance with the present invention, there are retroviral protease inhibiting compounds of the formula A:



A

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 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;

R_2 is hydrogen or loweralkyl;

R_3 is loweralkyl;

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

zoyl, pivaloyl, t-butylacetyl, phenylsulfonyl, benzyl, t-butyloxycarbonyl (Boc) and benzyloxycarbonyl (Cbz).

The term "O-protecting group" as used herein refers to a substituent which protects hydroxyl groups against undesirable reactions during synthetic procedures such as those O-protecting groups disclosed in Greene, "Protective Groups In Organic Synthesis,"(John Wiley & Sons, New York (1981)). O-protecting groups comprise substituted methyl ethers, for example, methoxymethyl, benzyloxymethyl, 2-methoxyethoxymethyl, 2-(trimethylsilyl)ethoxymethyl, t-butyl, benzyl and triphenylmethyl; tetrahydropyranyl ethers; substituted ethyl ethers, for example, 2,2,2-trichloroethyl; silyl ethers, for example, trimethylsilyl, t-butyldimethylsilyl and t-butyldiphenylsilyl; and esters prepared by reacting the hydroxyl group with a carboxylic acid, for example, acetate, propionate, benzoate and the like.

The term "loweralkyl" as used herein refers to straight or branched chain alkyl radicals containing from 1 to 6 carbon atoms including, but not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, n-pentyl, 1-methylbutyl, 2,2-dimethylbutyl, 2-methylpentyl, 2,2-dimethylpropyl, n-hexyl and the like.

The term "loweralkenyl" as used herein refers to a straight or branched chain alkyl radical containing from 2 to 6 carbon atoms and also having one carbon-carbon double bond including, but not limited to, vinyl, 2-propenyl, 2-methyl-2-propenyl, 3-butenyl, 4-pentenyl, 5-hexenyl and the like.

The term "phenyl" as used herein refers to a phenyl group which is unsubstituted or substituted with a substituent selected from loweralkyl, alkoxy, thioalkoxy, hydroxy and halo.

The term "phenylalkyl" as used herein refers to an phenyl group appended to a loweralkyl radical including, but not limited to, benzyl, 4-hydroxybenzyl, 4-chlorobenzyl, 1-naphthylmethyl and the like.

The term "alkylamino" as used herein refers to a loweralkyl radical appended to an —NH radical.

The term "cycloalkyl" as used herein refers to an aliphatic ring having 3 to 7 carbon atoms including, but not limited to, cyclopropyl, cyclopentyl, cyclohexyl and the like. A preferred cycloalkyl group is cyclopropyl

The term "cycloalkylalkyl" as used herein refers to a cycloalkyl group appended to a loweralkyl radical, including but not limited to cyclohexylmethyl.

The term "cycloalkenyl" as used herein refers to an aliphatic ring having 5 to 7 carbon atoms and also having one carbon-carbon double bond including, but not limited to, cyclopentenyl, cyclohexenyl and the like.

The term "cycloalkenyalkyl" as used herein refers to a cycloalkenyl group appended to a loweralkyl radical including, but not limited to, cyclopentenylmethyl, cyclohexenylmethyl and the like.

The terms "alkoxy" and "thioalkoxy" as used herein refer to $R_{15}O$— and $R_{15}S$—, respectively, wherein R_{15} is a loweralkyl group or benzyl.

The term "alkoxyalkyl" as used herein refers to an alkoxy group appended to a loweralkyl radical.

The term "thioalkoxyalkyl" as used herein refers to a thioalkoxy group appended to a loweralkyl radical.

The term "dialkylamino" as used herein refers to —$NR_{16}R_{17}$ wherein R_{16} and R_{17} are independently selected from loweralkyl groups.

The term "dialkylaminoalkyl" as used herein refers to —$NR_{18}R_{19}$ which is appended to a loweralkyl radical wherein R_{18} and R_{19} are independently selected from loweralkyl.

The term "halo" or "halogen" as used herein refers to —Cl,—Br,—I or —F.

The term "heterocyclic" as used herein refers to a heterocyclic group 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.

The term "(heterocyclic)alkyl" as used herein refers to a heterocyclic group appended to a loweralkyl radical including, but not limited to, pyrrolidinylmethyl and morpholinylmethyl.

The term "activated ester derivative" as used herein refer to acid halides such as acid chlorides, and activated esters including, but not limited to, formic and acetic acid derived anhydrides, anhydrides derived from alkoxycarbonyl halides such as isobutyloxycarbonylchloride and the like, N-hydroxysuccinimide derived esters, N-hydroxyphthalimide derived esters, N-hydroxybenzotriazole derived esters, N-hydroxy-5-norbornene-2,3-dicarboxamide derived esters, 2,4,5-trichlorophenol derived esters and the like.

In the compounds of the invention, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. As used herein, the term "stable compound" refers to a compound that is sufficiently stable to survive isolation to a useful degree of purity from a reaction mixture and formulation into a therapeutic dosage form suitable for administration.

Preferred compounds of the invention are selected from the group consisting of:

(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;

(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-4thiazolyl)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-methoxycarbonyl)amino-1,6-diphenyl-3-hydroxyhexane;

ANNEXURE 3

US005635523A

United States Patent [19]

Kempf et al.

[11] Patent Number: 5,635,523

[45] Date of Patent: Jun. 3, 1997

[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.: **417,879**

[22] Filed: **Apr. 6, 1995**

Related U.S. Application Data

[60] Division 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 31/41***

[52] U.S. Cl. **514/365**; 514/374

[58] **Field of Search** 514/365, 374

[56] **References Cited**

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4,652,552	3/1987	Kettner et al.	514/18
5,142,056	8/1992	Kempf et al.	546/256
5,354,866	10/1994	Kempf et al.	546/256

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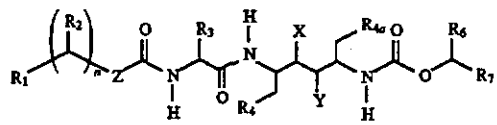
Primary Examiner—Russell Travers
Attorney, Agent, or Firm—Steven R. Crowley

[57] **ABSTRACT**

A retroviral protease inhibiting compound of the formula:



is disclosed.

10 Claims, No Drawings

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BACKGROUND OF THE INVENTION

Retroviruses are those viruses which utilize a ribonucleic acid (RNA) intermediate and a RNA-dependent deoxyribonucleic acid (DNA) polymerase, reverse transcriptase, during their life cycle. Retroviruses include, but are not limited to, the RNA viruses of the Retroviridae family, and also the DNA viruses of the Hepadnavirus and Caulimovirus families. Retroviruses cause a variety of disease states in man, animals and plants. Some of the more important retroviruses from a pathological standpoint include human immunodeficiency viruses (HIV-1 and HIV-2), which cause acquired immune deficiency syndrome (AIDS) in man, hepatitis B virus, which causes hepatitis and hepatic carcinomas in man, human T-cell lymphotrophic viruses I, II, IV and V, which cause human acute cell leukemia, and bovine and feline leukemia viruses which Cause leukemia in domestic animals.

Proteases are enzymes which cleave proteins at specific peptide bonds. Many biological functions are controlled or mediated by proteases and their complementary protease inhibitors. For example, the protease renin cleaves the peptide angiotensinogen to produce the peptide angiotensin I. Angiotensin I is further cleaved by the protease angiotensin converting enzyme (ACE) to form the hypotensive peptide angiotensin II. Inhibitors of renin and ACE are known to reduce high blood pressure in vivo. An inhibitor of a retroviral protease will provide a therapeutic agent for diseases caused by the retrovirus.

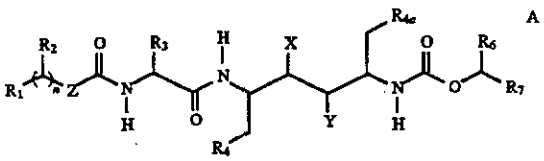
The genomes of retroviruses encode a protease that is responsible for the proteolytic processing of one or more polyprotein precursors such as the pol and gag gene products. See Wellink, Arch. Virol. 98 1 (1988). Retroviral proteases most commonly process the gag precursor into core proteins, and also process the pol precursor into reverse transciptase and retroviral protease. In addition, retroviral proteases are sequence specific. See Pearl, Nature 328 482 (1987).

The correct processing of the precursor polyproteins by the retroviral protease is necessary for the assembly of infectious virions. It has been shown that in vitro mutagenesis *that produces protease-defective virus leads to the* production of immature core forms which lack infectivity. See Crawford, J. Virol. 53 899 (1985); Katoh, et al., Virology 145 280 (1985). Therefore, retroviral protease inhibition provides an attractive target for antiviral therapy. See Mitsuya, Nature 325 775 (1987).

Current treatments for viral diseases usually involve administration of compounds that inhibit viral DNA synthesis. Current treatments for AIDS involve administration of compounds such as 3'-azido-3'-deoxythymidine (AZT), 2',3'-dideoxycytidine (DDC) and 2',3'-dideoxyinosine (DDI) and compounds which treat the opportunistic infections caused by the immunosuppression resulting from HIV infection. None of the current AIDS treatments have proven to be totally effective in treating and/or reversing the disease. In addition, many of the compounds currently used to treat AIDS cause adverse side effects including low platelet count, renal toxicity and bone marrow cytopenia.

DISCLOSURE OF THE INVENTION

In accordance with the present invention, there are retroviral protease inhibiting compounds of the formula A:



A

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 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;

R_2 is hydrogen or loweralkyl;

R_3 is loweralkyl;

R_4 and R_{4a} are independently selected from phenyl, thiazolyl and oxazolyl wherein the phenyl, thiazolyl or

ANNEXURE 4

US005674882A

United States Patent [19]

Kempf et al.

[11] Patent Number: 5,674,882

[45] Date of Patent: Oct. 7, 1997

[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.: **413,136**

[22] Filed: **Mar. 29, 1995**

Related U.S. Application Data

[60] Division 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, 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 31/41**

[52] **U.S. Cl.** **514/365**; 514/374

[58] **Field of Search** 514/365, 374

[56] **References Cited**

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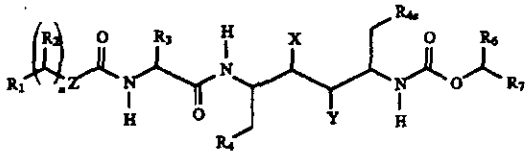
5,354,866	10/1994	Kempf et al.	546/265

Primary Examiner—Russell Travers
Attorney, Agent, or Firm—Steven R. Crowley

[57] **ABSTRACT**

A retroviral protease inhibiting compound of the formula:



is disclosed.

3 Claims, No Drawings

RETROVIRAL PROTEASE INHIBITING COMPOUNDS

This is a division of U.S. patent application Ser. No. 08/158,587, now abandoned filed Dec. 2, 1993, which is a a continuation-in-part of U.S. patent application Ser. No. 998,114, filed Dec. 29, 1992, now abandoned which is a continuation-in-part of U.S. patent application Ser. No. 777,626, filed Oct. 23, 1991, which is a continuation-in-part of U.S. patent application Ser. No. 746,020, filed Aug. 15, 1991, now abandoned which is a continuation-in-part of U.S. patent application Ser. No. 616,170, filed Nov. 20, 1990, now abandoned which is a continuation-in-part of U.S. patent application Ser. No. 518,730, filed May 9, 1990, now U.S. Pat. No. 5,142,056 which is a continuation-in-part of U.S. patent application Ser. No. 456,124, filed Dec. 22, 1989, now abandoned which is a continuation-in-part of U.S. patent application Ser. No. 405,604, filed Sep. 8, 1989, now abandoned which is a continuation-in-part of U.S. patent application Ser. No. 355,945, filed May 23, 1989 now *abandoned.*

This invention was made with Government support under contract number AI27220 awarded by the National Institute of Allergy and Infectious Diseases. The Government has certain rights in this invention.

TECHNICAL FIELD

The present invention relates to novel compounds and a composition and method for inhibiting retroviral proteases and in particular for inhibiting human immunodeficiency virus (HIV) protease, a composition and method for treating a retroviral infection and in particular an HIV infection, processes for making such compounds and synthetic intermediates employed in these processes.

BACKGROUND OF THE INVENTION

Retroviruses are those viruses which utilize a ribonucleic acid (RNA) intermediate and a RNA-dependent deoxyribonucleic acid (DNA) polymerase, reverse transcriptase, during their life cycle. Retroviruses include, but are not limited to, the RNA viruses of the Retroviridae family, and also the DNA viruses of the Hepadnavirus and Caulimovirus families. Retroviruses cause a variety of disease states in man, animals and plants. Some of the more important retroviruses from a pathological standpoint include human immunodeficiency viruses (HIV-1 and HIV-2), which cause acquired immune deficiency syndrome (AIDS) in man, hepatitis B virus, which causes hepatitis and hepatic carcinomas in man, human T-cell lymphotrophic viruses I, II, IV and V, which cause human acute cell leukemia, and bovine and feline leukemia viruses which cause leukemia in domestic animals.

Proteases are enzymes which cleave proteins at specific peptide bonds. Many biological functions are controlled or mediated by proteases and their complementary protease *inhibitors. For example, the protease renin cleaves the* peptide angiotensinogen to produce the peptide angiotensin I. Angiotensin I is further cleaved by the protease angiotensin converting enzyme (ACE) to form the hypotensive peptide angiotensin II. Inhibitors of renin and ACE are known to reduce high blood pressure in vivo. An inhibitor of a retroviral protease will provide a therapeutic agent for diseases caused by the retrovirus.

The genomes of retroviruses encode a protease that is responsible for the proteolytic processing of one or more polyprotein precursors such as the pol and gag gene products. See Wellink, Arch. Virol. 98 1 (1988). Retroviral

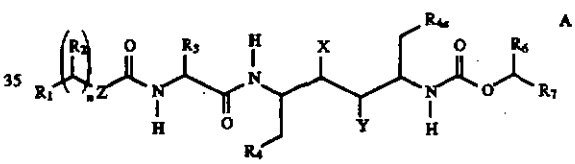
proteases most commonly process the gag precursor into core proteins, and also process the pol precursor into reverse transciptase and retroviral protease. In addition, retroviral *proteases are sequence specific. See Pearl, Nature* 328 482 (1987).

The correct processing of the precursor polyproteins by the retroviral protease is necessary for the assembly of infectious virions. It has been shown that in vitro mutagenesis that produces protease-defective virus leads to the production of immature core forms which lack infectivity. See Crawford, J. Virol. 53 899 (1985); Katoh, et al., Virology 145 280 (1985). Therefore, retroviral protease inhibition provides an attractive target for antiviral therapy. See Mitsuya, Nature 325 775 (1987).

Current treatments for viral diseases usually involve administration of compounds that inhibit viral DNA synthesis. Current treatments for AIDS involve administration of compounds such as 3'-azido-3'-deoxythymidine (AZT), 2',3'-dideoxycytidine (DDC) and 2',3'-dideoxyinosine (DDI) and compounds which treat the opportunistic infections caused by the immunosuppression resulting from HIV infection. None of the current AIDS treatments have proven to be totally effective in treating and/or reversing the disease. In addition, many of the compounds currently used to treat AIDS cause adverse side effects including low platelet count, renal toxicity and bone marrow cytopenia.

DISCLOSURE OF THE INVENTION

*In accordance with the present invention, there are retro*viral protease inhibiting compounds of the formula A:



A

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 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;

R_2 is hydrogen or loweralkyl;

R_3 is loweralkyl;

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

ANNEXURE 5

US005567823A

United States Patent [19]

Tien et al.

[11] Patent Number: 5,567,823

[45] Date of Patent: Oct. 22, 1996

[54] **PROCESS FOR THE PREPARATION OF AN HIV PROTEASE INHIBITING COMPOUND**

[75] Inventors: **Jien-Heh J. Tien**, Libertyville, Ill.; **Jerome A. Menzia**, Kenosha, Wis.; **Arthur J. Cooper**, Lake Villa, Ill.

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

[21] Appl. No.: **469,965**

[22] Filed: **Jun. 6, 1995**

[51] **Int. Cl.**[6] **C07D 417/12**

[52] **U.S. Cl.** **548/204**

[58] **Field of Search** 548/204

[56] **References Cited**

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Primary Examiner—Robert Gerstl

Attorney, Agent, or Firm—Steven R. Crowley

[57] **ABSTRACT**

Processes are disclosed for the preparation 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 *or an acid addition salt thereof and (2S,3S,5S)-5-(N-(N-((N-*Methyl-N-((2-isopropyl-4-thiazolyl) methyl)amino)carbonyl)-D-valinyl)amino)-2-(N-((5-thiazolyl) methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane or an acid addition salt thereof.

8 Claims, No Drawings

give a final aqueous pH of about 10.5. The aqueous layer was drained and discarded. The organic layer was washed with 25% sodium chloride solution (513 kg) and the aqueous layer was drained and discarded. The organic layer was filtered into a 300 gallon glass lined reactor and the, solvent was distilled under vacuum at an internal temperature of 40° C. or less. The residue was dissolved in ethyl acetate (576 kg, 640 L) and the solvent was distilled under vacuum until a volume of approximately 290 L was reached.

EXAMPLE 2

(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

To a 750 gallon glass lined reactor was charged N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine (57.0 kg, 182 moles) and ethyl acetate (916 kg, 1018 L). The mixture was stirred until everything was in solution and then N-methylmorpholine (28.0 kg, 277 moles) was charged to the reactor and the resulting solution was cooled to −18° C. A solution of isobutyl chloroformate (24.4 kg, 180 moles) in ethyl acetate (101 kg, 112 L) was prepared in a separate reactor. The isobutyl chloroformate solution was charged (over about 50 minutes) into the cold solution of the valine derivative and N-methylmorpholine prepared above, maintaining the temperature at between −18° C. and −14° C. After stirring at −14° C. for about 30 minutes, N-hydroxysuccinimide (21.2 kg, 184 moles) was added to the mixture. After stirring for an additional 30 minutes, the mixture was warmed to about 0° C. and stirred for about one hour.

The resulting solution from Example 1 was cooled to about 0° C and charged slowly into the above solution. A rinse of the 300 gallon reactor with ethyl acetate (50 kg, 56L) was also added. The reaction mixture was warmed to 25 ° C. and was stirred for 24 hours. The reaction mixture was washed twice with 10% potassium carbonate solution (2×711 kg), once with 10% citric acid solution (1025 kg) and once with water (640 kg). The aqueous layers were drained and discarded after each separation. The solvent was distilled under vacuum at an internal temperature of about 50° C. or less. The residue was dissolved in ethyl acetate (576 kg, 640 L) and the solvent was distilled once more. The residue was dissolved in ethyl acetate (500 kg, 556 L) and warmed to about 60° C. until a clear solution was obtained. The solution was filtered into a clean 300 gallon reactor and a rinse of ethyl acetate (77 kg, 86 L) was also filtered into the 300 gallon reactor. Heptane (218 kg, 320 L) was charged to the ethyl acetate solution in the 300 gallon reactor. The mixture was heated to about 80° C. until a clear solution was obtained. The solution was cooled at a rate of less than 25° C. per hour to a final temperature of 22° C. and was stirred for another 12 hours after the product began to crystallize. The thick slurry was centrifuged in four separate loads to isolate the product. Each isolated load was washed with approximately 45 kg of a 2:1 (v/v) solution of ethyl acetate/heptane. The last wash was used to also rinse the reactor. The product was dried in a blender drier under vacuum at 55° C. for about 24 hours to provide 101.9 kg of the desired product.

m.p. 121°–123° C. ^{1}H NMR: (CD_3OD, 300 MHz) δ 7.78–7.96(m, 1H), 7.85 (s, 1H), 7.07–7.33 (m, 11H), 6.68–6.75 (m, 1H), 6.17–6.28 (m, 1H), 5.22 (s, 2H), 4.47–4.67 (m, 2H), 4.32–4.45 (m, 1H), 3.98–4.10 (m, 2H), 3.72–3.82 (m, 1H), 3.28–3.40 (m,1H), 3.02 (s, 3H), 2.67–2.92 (m, 4H), 1.92–2.08 (m, 1H), 1,56–1.80 (m, 2H), 1.37–1.46 (m, 6H), 0.84–0.96 (m, 6H). ^{13}C NMR; (CD_3OD, 75 MHz) δ 176.0, 169.8, 155.7, 153.7, 152.4, 149.3, 139.3, 139.2, 135.8, 135.2, 126.3, 126.0, 124.9, 124.8, 122.9, 122.8, 111.2, 111.1,66.5, 57.6, 57.5, 54.5, 52.9, 52.8, 45.4, 37.3, 35.7, 34.9, 30.9, 30.0, 27.7, 19.3, 19.2, 15.7, 14.5.

EXAMPLE 3

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-D-valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino-1,6-diphenyl-3-hydroxyhexane

The title compound is prepared following the procedure of Example 2 with replacement of N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-D-valine.

m.p.68°–69° C. ^{1}H NMR (DMSO-d_6) δ 0.56 (d, J=6Hz, 3H), 0.63 (d, J=6Hz, 3H), 1.28 (d, J=7Hz, 6H), 1.47 (m, 2H), 1.77 (octet, J=6Hz, 1H), 2.5–2.7 (m, 4H), 2.85 (s, 3H), 3.20 (heptet, J=7Hz, 1H), 3.4 (m, 1H), 3.6 (m, 1H),3.90 (dd, J=8, 6Hz, 1H), 3.93 (m, 1H), 4.43 (AA', 2H), 4.65 (d, J=6Hz, 1H), 5.15 (AA', 2H), 6.02 (br d, J=9Hz, 1H), 6.90 (br d, J=9Hz, 1H), 7.1–7.2 (m,11H), 7.70 (br d, J=9Hz, 1H), 7.85 (s, 1H). 9.04 (s, 1H). Mass spectrum: $(M+H)^+$ =721.

EXAMPLE 4

Alternative Preparation 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

To a 250 mL 4-neck round bottom flask equipped with a mechanical stirrer, nitrogen atmosphere, 60 mL side arm addition funnel and a thermocouple was charged N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine (5.03 g, 16 mmoles) and ethyl acetate (93 mL). The mixture was stirred until all of the solids were dissolved and was then cooled to −15° C. To the cooled solution was added N-methylmorpholine (1.77 ML, 16 mmoles). The mixture was cooled to −18° C. Isobutyl chloroformate (2.08 mL, 16 mmoles) in ethyl acetate (8 mL) was added, maintaining the temperature of the reaction mixture below −14.5° C. After stirring for 1 hour at −17° C., 1-hydroxybenzotriazole (2.46 g, 16 mmoles) was added in one portion. The resulting slurry was warmed to 0° C. and was maintained at or below 0° C. as (2S,3S,5S)-5-amino-2-(N-((5-thiazolyl-)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane (6.4 g, 15 mmoles) in ethyl acetate (25 mL) was added. The resulting mixture was stirred at 0° C. for 1 hour and then allowed to warm to room temperature and stirred for 15 hours. To the reaction mixture was added 75 mL of 5% aqueous sodium bicarbonate. The organic layer was separated and washed again with 75 mL of 5% aqueous sodium bicarbonate, followed by washing twice with 75 mL of 10% aqueous citric acid each time and, finally, with 75 mL of water. The solvent was removed under vacuum and the residue crystallized from 270 mL of heptane/ethyl acetate 1:1 to provide 9.25 g of the desired product.

EXAMPLE 5

Alternative Preparation 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