



FORMULARIO UNICO DE OPOSICION
2000-12

1	OPOSICION A:	
☒	Patente de Invención	☐ Marca Colectiva
☐	Patente de Modelo de Utilidad	☐ Marca de Certificación
☐	Diseño Industrial	☐ Lema Comercial
☐	Esquema de Trazado para Circuitos Integrados	
	Marcas de Productos o Servicios	
2	SOLICITUD PUBLICADA Número del expediente: 06 111.944 Solicitante: BRISTOL-MYERS SQUIBB COMPANY Apoderado: JUAN PABLO CADENA SARMIENTO Título de la nueva creación o denominación del signo: PROCESO PARA PREPARAR BISULFATO DE ATAZANAVIR Y NUEVAS FORMAS. Gaceta: 583 de 18 de diciembre de 2007, Número de Publicación 817	
3	OPOSICION PRESENTADA POR:	
OPOSITOR	Nombre: Lafranco S.A. Dirección: Carrera 1 No. 46-84 Teléfono: (092) 449.30.51 Fax: Domicilio: Cali - Valle	IDENTIFICACION C.C. ☐ NIT ☒ C.E. ☐ Otro ☐ Número: 890 301 463 -8
REPRESENTANTE O APODERADO (74)	Nombre: José Luis Reyes Villamizar Dirección: Cra. 17 No. 88-23, Of. 205 Teléfono: 621.26.31 E-mail: info@reyes-abogados.com Fax: 621.25.42 Domicilio: Bogotá, D.C.	IDENTIFICACION C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Número: 79'152.473 de Usaquén TP 44655

4	FUNDAMENTOS DE LA OPOSICION: Causal: Incumplimiento de requisitos de patentabilidad (Título II, Capítulo I, Decisión 486 de 2000). Se violan los artículos 14, 16 (las patentes de invención deben ser nuevas, tener nivel inventivo y ser susceptibles de aplicación industrial) y 18 (una invención tiene nivel inventivo si no es obvia para una persona versada en la materia).
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Justificación: VER ANEXO

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Comprobante de pago No. 08-22721 (Oposición) Fecha Marzo 14 de 2008
08-22728 (Prórroga) Fecha Marzo 19 de 2008

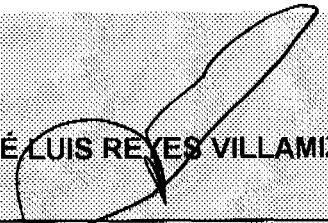
6

Anexos:

- ☒ Comprobante de pago de la tasa
- ☒ Poderes, si fuere el caso
- ☒ Pruebas de los fundamentos de la oposición
- ☒ Certificado de existencia y representación legal de las partes, cuando sean personas jurídicas
- ☐ Documentos que acrediten el legítimo interés, si fuere el caso
- ☒ Copia de la oposición para el traslado al solicitante.

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NOMBRE: JOSÉ LUIS REYES VILLAMIZAR

FIRMA: 
C.C.No. 79.152.473 T.P. No. 44655

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~~224~~

Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

E.

S.

D.

REF: EXPEDIENTE 06-111-944

TÍTULO SOLICITADO: "PROCESO PARA PREPARAR BISULFATO DE ATAZANAVIR Y NUEVAS FORMAS"

PUBLICACIÓN: Gaceta 583 de 18-12-2007, número de publicación 817.

PRIORIDAD: US 60/568,043 de 04/05/2004; US 60/607,533 de 07/09/2004; US 11/119,558 de 02/05/2005

SOLICITANTE: BRISTOL MYERS SQUIBB COMPANY

APODERADO: JUAN PABLO CADENA SARMIENTO

TRÁMITE: PRESENTACIÓN DE OPOSICIÓN

JOSÉ LUIS REYES VILLAMIZAR, mayor de edad, identificado como aparece al pie de mi firma, abogado en ejercicio, titular de la tarjeta profesional número 44655 del Consejo Superior de la Judicatura, obrando en calidad de apoderado de la sociedad **LABORATORIO FRANCO-COLOMBIANO, LAFRANCOL S.A.**, en ejercicio de lo dispuesto por el artículo 42 de la Decisión 486 de 2000, muy respetuosamente me permito formular la siguiente

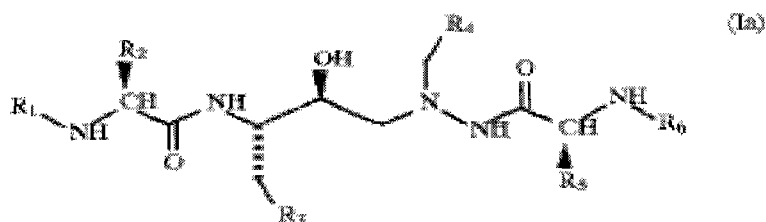
I. PETICIÓN

Negar el beneficio patentario a la solicitud contenida en el expediente **06-111-944**, por no cumplir con los requisitos de patentabilidad a que se refieren los artículos 14 y 18 de la Decisión 486 de la Comunidad Andina de Naciones, con base en los fundamentos de hecho y de derecho que me permito exponer a continuación.

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The compounds of formula I preferably have the formula Ia,



wherein the radicals are as defined.

Salts are especially the pharmaceutically acceptable salts of compounds of formula I.

Such salts are formed, for example, by compounds of formula I having a basic R_4 -CH₂-carrying nitrogen atom as acid addition salts, preferably with inorganic acids, for example hydrohalic acid, such as hydrochloric acid, sulfuric acid or phosphoric acid, or with strong organic sulfonic, sulfo or phosphoric acids or N-substituted sulfamic acids (preferably: pKa<1). Other salts may be present when basic heterocyclyl radicals, such as pyridyl, are present in R₄. Those salts includes especially acid addition salts with organic or inorganic acids, especially the pharmaceutically acceptable salts. Suitable inorganic acids are, for example, (...)

En la columna 30, revela:

The compounds of formula I, including their salts, may also be obtained in the form of hydrates, or their crystals may include, for example, the solvent used for crystallisation.

Si bien es cierto no se hace mención específica de la sal Bisulfato, ni del cristal A de Bisulfato de Atazanavir, no es menos que este compuesto forma una gran cantidad de sales con ácidos inorgánicos como el ácido sulfúrico o ácidos orgánicos, adicionalmente, se observa que los compuestos mencionados en la anterioridad son capaces de estar en forma de hidratos o en forma de cristales, lo que evidentemente demuestra que, la solicitud en trámite carece de nivel inventivo, ya que, una persona medianamente versada en la materia está en capacidad de generar la sal Bisulfato o cualquier otra que permita mejorar las características de solubilidad del Atazanavir o de cualquier otro fármaco y la forma más adecuada del mismo, ya sea forma cristalina, polimorfa, amorfa, etc.

- b) La patente americana US 6,087,383 de título "BISULFATE SAL OF HIV PROTEASE INHIBITOR" y publicada el 11 de julio de 2000, revela la sal

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COC(=O)NC(C)(C)C(=O)N[C@@H](Cc1ccccc1)[C@H](O)CC
CN(C)CN(C(=O)C(C)(C)C)NC(=O)COCH3
Cc1ccc(cc1)-c2ccccn2

En cuanto al proceso en sí, si bien es cierto aún no hemos encontrado una anterioridad que revele lo mismo, no lo es menos que tanto el proceso de la US 6,087,383 y el revelado en la solicitud colombiana permiten la obtención de los mismos compuestos (Bisulfato de Atazanavir), sin que el proceso reivindicado demuestre ventajas técnicas significativas frente al arte anterior, ni lleve a obtener un principio activo mejorado o distinto al conocido, circunstancia que compromete el nivel inventivo de la solicitud.

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Por lo expuesto anteriormente reitero la petición de declarar fundada la presente oposición, de negar en consecuencia el privilegio solicitado, y de ordenar el archivo del expediente respectivo.

IV. FUNDAMENTOS DE DERECHO

Son fundamentos de derecho el Capítulo I, artículos 14 y 18 (Requisitos de Patentabilidad), el artículo 30 (Reivindicaciones) y el artículo 42 (Oposiciones) de la Decisión 486 de 2000.

V. SOLICITUD DE PLAZO EXTRA PARA SUSTENTAR LA OPOSICIÓN

En desarrollo de lo dispuesto por el artículo 42, inciso 2º de la Decisión 486, solicito comedidamente a su Despacho el plazo adicional de sesenta días para sustentar la presente oposición. Para los anteriores efectos, me permito anexar la constancia de pago correspondiente.

VI. PRUEBAS

Ruego que se tengan como tales, sin perjuicio de que el Despacho considere oficiosamente, en particular de las allegadas por el suscrito a los expedientes mencionados en este escrito, las siguientes:

- informe Internacional de Búsqueda practicado por la Oficina Europea de patentes a la solicitud internacional WO 05/108349 publicada el 17 de noviembre de 2005 y más específicamente a su aplicación internacional PCT/US05/15333.
- La patente americana US 5,849,911 titulada "ANTIVIRALLY ACTIVE HETEROCYCLIC AZAHEXANE DERIVATIVES, publicada el 15-12-1998, columnas 4, 30, y capítulo reivindicatorio.
- La patente americana US 6,087,383 de título "BISULFATE SAL OF HIV PROTEASE INHIBITOR" y publicada el 11 de julio de 2000.

VII. ANEXOS

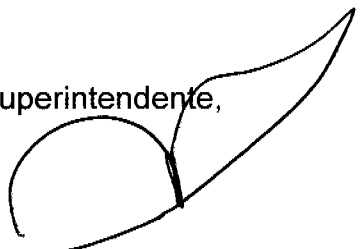
Para efectos del trámite correspondiente, me permito anexar al presente escrito los siguientes anexos:

- LRS
1. Certificados de existencia y representación legal de Lafrancol S.A.
 2. Poderes para actuar.
 3. Constancia de pago de las tasas de tramitación de oposición.
 4. Constancia de pago para sustentar la solicitud de prórroga a que se refiere el artículo 42, inciso 2º de la Decisión 486.
 5. Copia para correr traslado al solicitante.
 6. Las mencionadas en el acápite de pruebas

VIII. NOTIFICACIONES

El suscrito recibirá notificaciones en la secretaría de su Despacho o en mi oficina localizada en la Carrera 17 No. 88-23, Oficina 205, Fax (1) 621.25.42 de esta ciudad. Lafrancol S.A., las recibirá en sus oficinas localizadas en la Carrera 1 N° 46-84 de Cali.

Señor Superintendente,



JOSÉ LUIS REYES VILLAMIZAR

C.C. 79'152.473 de Usaquén
T.P. 44.655 de C.S.J.

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
17 November 2005 (17.11.2005)

PCT

(10) International Publication Number
WO 2005/108349 A3

(51) International Patent Classification:
A61K 31/44 (2006.01) C07D 213/56 (2006.01)

(21) International Application Number:
PCT/US2005/015333

(22) International Filing Date: 3 May 2005 (03.05.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/568,043 4 May 2004 (04.05.2004) US
60/607,533 7 September 2004 (07.09.2004) US
11/119,558 2 May 2005 (02.05.2005) US

(71) Applicant (for all designated States except US): **BRISTOL-MYERS SQUIBB COMPANY** [US/US]; Route 206 and Province Line Road, Princeton, NJ 08543-4000 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **KIM, Soojin** [US/US]; 21 Linden Avenue, West Orange, NJ 07052 (US). **LOTZ, Bruce, T.** [US/US]; 16 Windsor Lane, Yardville, NJ 08620 (US). **MALLEY, Mary, F.** [US/US]; 50 Merion Place, Lawrenceville, NJ 08648 (US). **GOUGOUTAS, Jack, Z.** [US/US]; 101 Westerly Road, Princeton, NJ 08540 (US). **DAVIDOVICH, Martha** [US/US]; 159 Fern Road, East Brunswick, NJ 08816 (US). **SRIVASTAVA, Sushil, K.** [IN/US]; 9 Kayann Drive, Dayton, NJ 08810 (US).

(74) Agents: **RODNEY, Burton et al.**; Bristol-Myers Squibb Company, P.O. Box 4000, Princeton, NJ 08543-4000 (US).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))

Published:

- with international search report

(88) Date of publication of the international search report:
2 November 2006

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

(54) Title: PROCESS FOR PREPARING ATAZANAVIR BISULFATE AND NOVEL FORMS

(57) Abstract: A process is provided for preparing the HIV protease inhibitor atazanavir bisulfate wherein a solution of atazanavir free base is reacted with concentrated sulfuric acid in an amount to react with less than about 15% by weight of the free base, seeds of Form A crystals of atazanavir bisulfate are added to the reaction mixture, and as crystals of the bisulfate form, additional concentrated sulfuric acid is added in multiple stages at increasing rates according to a cubic equation, to effect formation of Form A crystals of atazanavir bisulfate. A process is also provided for preparing atazanavir bisulfate as Pattern C material. A novel form of atazanavir bisulfate is also provided which is Form E3 which is a highly crystalline triethanolate solvate of the bisulfate salt from ethanol.

WO 2005/108349 A3

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US05/15333

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8): A61K 31/44(2006.01);C07D 213/56(2006.01)

USPC: 514/357;546/332

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/357; 546/332

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CASONLINE SEARCH, WEST

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,849,911 A(FASSLER et al) 15 December 1998 (15.12.1998), column 33, 36, various claims and examples.	1-40
Y	US 6,087,383 A (SINGH et al) 11 July 2000 (11.07.2000), column 1 and 2.	1-40

☐ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

Special categories of cited documents:	
"A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E" earlier application or patent published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O" document referring to an oral disclosure, use, exhibition or other means	"Z" document member of the same patent family
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search 24 July 2006 (24.07.2006)	Date of mailing of the international search report 16 AUG 2006
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (571) 273-3201	Authorized officer SHAIENDRA KUMAR Telephone No. (571)272-1600



US00584991A

United States Patent [19]

Fässler et al.

[11] **Patent Number:** 5,849,911[45] **Date of Patent:** Dec. 15, 1998[54] **ANTIVIRALLY ACTIVE HETEROCYCLIC AZAHEXANE DERIVATIVES**

- [75] Inventors: **Alexander Fässler**, Macclesfield, Great Britain; **Guido Bold**, Gimp-Oberfrick; **Hans-Georg Capraro**, Rheinfelden, both of Switzerland; **Marc Lang**, Mulhouse, France; **Satish Chandra Khanna**, Bottmingen, Switzerland

- [73] Assignee: **Novartis Finance Corporation**, Summit, N.J.

- [21] Appl. No.: **831,630**

- [22] Filed: **Apr. 9, 1997**

[30] **Foreign Application Priority Data**

Apr. 22, 1996 [CH] Switzerland 1018/96
Jan. 31, 1997 [CH] Switzerland 0223/97

- [51] Int. Cl.^o **C07D 241/02; C07D 263/34; A61K 31/42; A61K 277/54**

- [52] U.S. Cl. **544/335; 544/406; 546/332; 548/204; 548/338.1; 548/335; 548/267.6; 548/247; 548/236; 549/76; 549/77; 514/365; 514/357; 514/438; 514/381; 514/255; 514/399; 514/400; 514/256; 514/383; 514/374; 514/378**

- [58] Field of Search* **544/335, 406; 546/332; 548/204, 338.1, 335, 267.6, 247, 236; 549/76, 77; 514/365, 357, 438, 381, 255, 399, 400, 256, 383, 374, 378**

[56] **References Cited****U.S. PATENT DOCUMENTS**

4,556,654 12/1985 Showalter et al. 514/222
5,461,067 10/1995 Norbeck et al. 514/333
5,621,109 4/1997 Norbeck et al. 548/182

FOREIGN PATENT DOCUMENTS

0486948 5/1992 European Pat. Off. C07D 213/26
9318006 9/1993 WIPO C07D 243/08
9414436 7/1994 WIPO A61K 31/425
9419332 9/1994 WIPO .
9422840 10/1994 WIPO .
9502582 1/1995 WIPO C07D 255/02

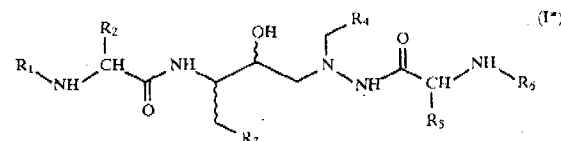
OTHER PUBLICATIONS

Sham, et al., J. Chem. Soc. Chem. Commun., 1993, p. 1052.
Fässler, et al., J. Med. Chem. vol. 39, 1996, pp. 3203-3216.
Fässler, et al., Bioorganic & Medicinal Chemistry Letters, vol. 3, No. 12, pp. 2837-2842.

Primary Examiner—S. Mark Clardy
Assistant Examiner—Sabiha N. Qazi
Attorney, Agent, or Firm—Hesna J. Pfeiffer

[57] **ABSTRACT**

There are described compounds of formula I*,



wherein

R₁ is lower alkoxycarbonyl,

R₂ is secondary or tertiary lower alkyl or lower alkylthio-lower alkyl,

R₃ is phenyl that is unsubstituted or substituted by one or more lower alkoxy radicals, or C₄-C₈cycloalkyl,

R₄ is phenyl or cyclohexyl each substituted in the 4-position by unsaturated heterocyclyl that is bonded by way of a ring carbon atom, has from 5 to 8 ring atoms, contains from 1 to 4 hetero atoms selected from nitrogen, oxygen, sulfur, sulfinyl (—SO—) and sulfonyl (—SO₂—) and is unsubstituted or substituted by lower alkyl or by phenyl-lower alkyl,

R₅, independently of R₂, has one of the meanings mentioned for R₂, and

R₆, independently of R₁, is lower alkoxycarbonyl, or salts thereof, provided that at least one salt-forming group is present.

The compounds are inhibitors of retroviral aspartate protease and can be used, for example, in the treatment of AIDS. They exhibit outstanding pharmacodynamic properties.

11 Claims, No Drawings

(R)—or (S)—configuration, the (S)—configuration being especially preferred in the case of the carbon atoms carrying the radical R_2 and/or R_3 in compounds of formula I. Accordingly, the compounds in question may be in the form of isomeric mixtures or in the form of pure isomers, preferably in the form of enantiomerically pure diastereoisomers.

Lower alkoxy carbonyl is preferably C_1 — C_4 alkoxy carbonyl wherein the alkyl radical may be branched or unbranched, and is especially ethoxycarbonyl or methoxycarbonyl.

Secondary or tertiary lower alkyl is especially sec-butyl, tert-butyl or isopropyl.

Lower alkylthio-lower alkyl is especially methylthio-ethyl.

Phenyl that is unsubstituted or substituted by one or more lower alkoxy radicals is especially phenyl that is unsubstituted or substituted by from one to three lower alkoxy radicals, especially methoxy. In the case when there are three methoxy substituents, these are especially in the 2,3,4-positions of the phenyl ring and in the case when there is one methoxy substituent, that substituent is especially in the 2-, 3- or, more especially, in the 4-position. Unsubstituted phenyl is preferred.

C_4 — C_8 cycloalkyl is especially cyclopentyl or, more especially, cyclohexyl.

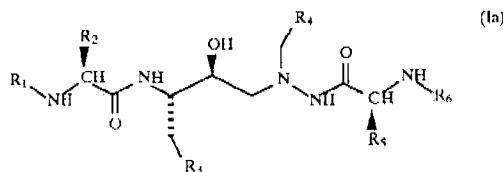
As R_3 phenyl is preferred to cyclohexyl.

In phenyl or cyclohexyl substituted in the 4-position by unsaturated heterocyclyl that is bonded by way of a ring carbon atom, has from 5 to 8 ring atoms, contains from 1 to 4 hetero atoms selected from nitrogen, oxygen, sulfur, sulfinyl ($-\text{SO}-$) and sulfonyl ($-\text{SO}_2-$) and is unsubstituted or substituted by lower alkyl or by phenyl-lower alkyl, the corresponding heterocyclyl has especially the following meanings:

Unsaturated heterocyclyl that is bonded by way of a ring carbon atom, has from 5 to 8 ring atoms, contains from 1 to 4 hetero atoms selected from nitrogen, oxygen, sulfur, sulfinyl ($-\text{SO}-$) and sulfonyl ($-\text{SO}_2-$) and is unsubstituted or substituted by lower alkyl, especially by methyl, or by phenyl-lower alkyl wherein the lower alkyl radical is unbranched or branched, especially by 1-methyl-1-phenylethyl, is especially one of the following radicals bonded by way of a ring carbon atom: thienyl (=thiophenyl); oxazolyl; thiazolyl; imidazolyl; 1,4-thiazinyl; triazolyl that is unsubstituted or, especially, substituted by 1-methyl-1-phenyl-ethyl or preferably by tert-butyl or especially by methyl, such as 1-, 2- or 4-(methyl or tert-butyl)triazol-3-yl; tetrazolyl that is unsubstituted or, especially, substituted by 1-methyl-1-phenylethyl or preferably by lower alkyl, such as by tert-butyl or especially by methyl, such as 2H-tetrazol-5-yl substituted by 1-methyl-1-phenyl-ethyl or preferably by lower alkyl, such as by tert-butyl or especially by methyl, or 1H-tetrazol-5-yl substituted by tert-butyl or especially by methyl; pyridinyl; pyrazinyl; and pyrimidinyl; more especially 2- or 3-thienyl (=thiophen-2-yl or thiophen-3-yl); thiazol-5-yl; thiazol-2-yl; 2H-tetrazol-5-yl that is unsubstituted or, especially, substituted in the 2-position by 1-methyl-1-phenyl-ethyl or preferably by tert-butyl or especially by methyl; 1H-tetrazol-5-yl substituted in the 1-position by methyl; pyridin-2-yl; pyridin-3-yl; pyridin-4-yl; or pyrazin-2-yl.

R_4 is preferably phenyl substituted in the 4-position by unsaturated heterocyclyl that is bonded by way of a ring carbon atom, has from 5 to 8 ring atoms, contains from 1 to 4 hetero atoms selected from nitrogen, oxygen, sulfur, sulfinyl ($-\text{SO}-$) and sulfonyl ($-\text{SO}_2-$) and is unsubstituted or substituted by lower alkyl or by phenyl-lower alkyl, wherein heterocyclyl preferably has the meanings defined above as being preferred.

The compounds of formula I preferably have the formula Ia,



wherein the radicals are as defined.

Salts are especially the pharmaceutically acceptable salts of compounds of formula I.

Such salts are formed, for example, by compounds of formula I having a basic R_4 — CH_2 —carrying nitrogen atom as acid addition salts, preferably with inorganic acids, for example hydrohalic acid, such as hydrochloric acid, sulfuric acid or phosphoric acid, or with strong organic sulfonic, sulfo or phosphoric acids or N-substituted sulfamic acids (preferably: $\text{pK}_a < 1$). Other salts may be present when basic heterocyclyl radicals, such as pyridyl, are present in R_4 . Those salts includes especially acid addition salts with organic or inorganic acids, especially the pharmaceutically acceptable salts. Suitable inorganic acids are, for example, hydrohalic acids, such as hydrochloric acid, sulfuric acid and phosphoric acid. Suitable organic acids are, for example, carboxylic, phosphonic, sulfonic or sulfamic acids, for example acetic acid, propionic acid, octanoic acid, decanoic acid, dodecanoic acid, glycolic acid, lactic acid, 2-hydroxybutyric acid, gluconic acid, glucosomonocarboxylic acid, fumaric acid, succinic acid, adipic acid, pimelic acid, suberic acid, azelaic acid, malic acid, tartaric acid, citric acid, glucaric acid, galactaric acid, amino acids, such as glutamic acid, aspartic acid, N-methylglycine, acetylaminocetic acid, N-acetylaspargine or N-acetylcysteine, pyruvic acid, acetoacetic acid, phosphoserine, 2- or 3-glycerophosphoric acid, glucose-6-phosphoric acid, glucose-1-phosphoric acid, fructose-1,6-bisphosphoric acid, maleic acid, hydroxymaleic acid, methylmaleic acid, cyclohexanecarboxylic acid, adamantanecarboxylic acid, benzoic acid, salicylic acid, 1- or 3-hydroxynaphthyl-2-carboxylic acid, 3,4,5-trimethoxybenzoic acid, 2-phenoxybenzoic acid, 2-acetoxybenzoic acid, 4-aminosalicylic acid, phthalic acid, phenylacetic acid, mandelic acid, cinnamic acid, glucuronic acid, galacturonic acid, methanesulfonic or ethanesulfonic acid, 2-hydroxyethanesulfonic acid, ethane-1,2-disulfonic acid, benzenesulfonic acid, 2-naphthalenesulfonic acid, 1,5-naphthalenedisulfonic acid, 2-, 3- or 4-methylbenzenesulfonic acid, methylsulfuric acid, ethylsulfuric acid, dodecylsulfuric acid, N-cyclohexylsulfamic acid, N-methyl-, N-ethyl- or N-propyl-sulfamic acid, or other organic protonic acids, such as ascorbic acid.

When negatively charged radicals are present, such as tetrazolyl in R_4 , salts may also be formed with bases, e.g. metal or ammonium salts, such as alkali metal or alkaline earth metal salts, e.g. sodium, potassium, magnesium or calcium salts or ammonium salts with ammonia or suitable organic amines, such as tertiary monoamines, e.g. triethylamine or tri(2-hydroxyethyl)-amine, or heterocyclic bases e.g. N-ethyl-piperidine or N,N'-dimethylpiperazine.

For the purposes of isolation or purification it is also possible to use pharmaceutically unsuitable salts, for example picrates or perchlorates. Only the pharmaceutically acceptable salts or the free compounds (optionally in the

such as dimethylformamide, at preferred temperatures of from -10° to 40° C., especially from 0° to about 30° C.

In a compound of formula I wherein R_1 is 4-(1- or 2-phenyl-lower alkyl), such as 1- or 2-(1-methyl-1-phenylethyl)-tetrazol-5-yl)phenyl, the phenyl-lower alkyl radical (preferably 1-methyl-1-phenylethyl) can be removed by treatment with a strong mineral acid, such as sulfuric acid, in aqueous solution, preferably at temperatures of from -20° to 30° C., for example at 0° C.

General Process Conditions

All the process steps given in this text can be carried out under reaction conditions known per se, but preferably under those specifically mentioned, in the absence or usually in the presence of solvents or diluents, preferably those solvents or diluents that are inert towards the reagents used and are solvents therefor, in the absence or presence of catalysts, condensation agents or neutralising agents, for example ion exchangers, such as cation exchangers, for example in the H^+ form, depending upon the nature of the reaction and/or the reactants at reduced, normal or elevated temperature, for example in a temperature range of from approximately -100° to approximately 190° C., preferably from approximately -80° to approximately 150° C., for example from -80° to -60° C., at room temperature, at from -20° to 40° C. or at the boiling point of the solvent used, under atmospheric pressure or in a closed vessel, optionally under pressure, and/or in an inert atmosphere, for example under an argon or nitrogen atmosphere.

In the case of all starting materials and intermediates, salts may be present when salt-forming groups are present. Salts may also be present during the reaction of such compounds, provided that the reaction will not be affected.

In all reaction steps, any isomeric mixtures that are formed can be separated into the individual isomers, for example diastereoisomers or enantiomers, or into any desired mixtures of isomers, for example racemates or diastereoisomeric mixtures, for example analogously to the methods described under the heading "Additional process steps".

In certain cases, for example in the case of hydrogenation, it is possible to carry out stereo-selective reactions so that, for example, individual isomers may be obtained more easily.

The solvents from which those suitable for a particular reaction can be selected include, for example, water, esters, such as lower alkyl-lower alkanoates, for example diethyl acetate, ethers, such as aliphatic ethers, for example diethyl ether, or cyclic ethers, for example tetrahydrofuran, liquid aromatic hydrocarbons, such as benzene or toluene, alcohols, such as methanol, ethanol or 1- or 2-propanol, nitrites, such as acetonitrile, halogenated hydrocarbons, such as methylene chloride, acid amides, such as dimethylformamide, bases, such as heterocyclic nitrogen bases, for example pyridine, carboxylic acid anhydrides, such as lower alkanonic acid anhydrides, for example acetic anhydride, cyclic, linear or branched hydrocarbons, such as cyclohexane, hexane or isopentane, or mixtures of those solvents, for example aqueous solutions, unless the description of the processes indicates otherwise. Such solvent mixtures can also be used in working-up, for example by chromatography or partitioning.

The invention relates also to those forms of the process in which a compound obtainable as intermediate at any stage is used as starting material and the remaining steps are carried out or the process is interrupted at any stage or a starting

material is formed under the reaction conditions or is used in the form of a reactive derivative or salt, or a compound obtainable in accordance with the process of the invention is produced under the process conditions and further processed in situ, it being preferable to use those starting materials which result in the compounds described above as being preferred, especially those described as being especially preferred, more especially preferred and/or very especially preferred.

The preparation of compounds of formula I is preferably carried out analogously to the processes and process steps given in the Examples.

The compounds of formula I, including their salts, may also be obtained in the form of hydrates, or their crystals may include, for example, the solvent used for crystallisation.

Pharmaceutical Compositions

The invention relates also to pharmaceutical compositions comprising compounds of formula I*, which means especially a compound of the formula I, and most especially of formula Ia.

The pharmacologically acceptable compounds of the present invention may be used, for example, in the preparation of pharmaceutical compositions that comprise an effective amount of the active ingredient together or in admixture with a significant amount of inorganic or organic, solid or liquid, pharmaceutically acceptable carriers.

The invention relates also to a pharmaceutical composition suitable for administration to a warm-blooded animal, especially a human being, for the treatment or prevention of a disease that is responsive to inhibition of a retroviral protease, especially a retroviral aspartate protease, such as HIV-1 or HIV-II gag protease, for example a retroviral disease, such as AIDS or its preliminary stages, comprising a compound of formula I*, or a pharmaceutically acceptable salt thereof, in an amount effective in the inhibition of the retroviral protease, together with at least one pharmaceutically acceptable carrier.

The pharmaceutical compositions according to the invention are compositions for enteral, such as nasal, rectal or oral, or parenteral, such as intramuscular or intravenous, administration to warm-blooded animals (human beings and animals) that comprise an effective dose of the pharmacological active ingredient alone or together with a significant amount of a pharmaceutically acceptable carrier. The dose of the active ingredient depends on the species of warm-blooded animal, body weight, age and individual condition, individual pharmacokinetic data, the disease to be treated and the mode of administration.

The invention relates also to a method of treating diseases caused by viruses, especially by retroviruses, especially AIDS or its preliminary stages, wherein a therapeutically effective amount of a compound of formula I* or a pharmaceutically acceptable salt thereof is administered in a dose that is effective in the treatment of said disease especially to a warm-blooded animal, for example a human being, who on account of one of the mentioned diseases, especially AIDS or its preliminary stages, requires such treatment. The preferred dose to be administered to warm-blooded animals, for example human beings of approximately 70 kg body weight, is from approximately 3 mg to approximately 3 g, preferably from approximately 10 mg to approximately 1.5 g, for example approximately from 50 mg to 1000 mg per person per day, divided preferably into 1 to 3 single doses which may, for example, be of the same size. Usually, children receive half of the adult dose.

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lactic acid (90%), Cellulose-HP-M-603, silica gel (Aerosil 200) and deionised water (2 g).

Example 66

Formulation as solution (II):

The formulation comprises 18.4 mg of the title compound from Example 46 as active ingredient, 5 mg of Cellulose-HPM-603, 40 mg of N-methylpyrrolidone and double-distilled water ad 1 ml.

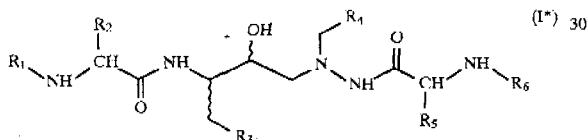
Example 67

Analogously to one of the afore-mentioned processes, there are prepared:

- A) 1-[4-(pyridin-2-yl)phenyl]-4(R)-hydroxy-5(S)-2,5-bis[N-(N-methoxycarbonyl-(L)-tert-leucyl)amino]-6-phenyl-2-azahexane;
- B) 1-[4-(pyridin-2-yl)phenyl]-4(R)-hydroxy-5(R)-2,5-bis[N-(N-methoxycarbonyl-(L)-tert-leucyl)amino]-6-phenyl-2-azahexane;
- C) 1-[4-(pyridin-2-yl)phenyl]-4(S)-hydroxy-5(S)-2-[N-(N-methoxycarbonyl-(L)-tert-leucyl)-amino]-5-[N-(N-methoxycarbonyl-(D)-tert-leucyl)amino]-6-phenyl-2-azahexane; or
- D) 1-[4-(pyridin-2-yl)phenyl]-4(S)-hydroxy-5(S)-2-[N-(N-methoxycarbonyl-(D)-tert-leucyl)-amino]-5-[N-(N-methoxycarbonyl-(L)-tert-leucyl)amino]-6-phenyl-2-azahexane.

What is claimed is:

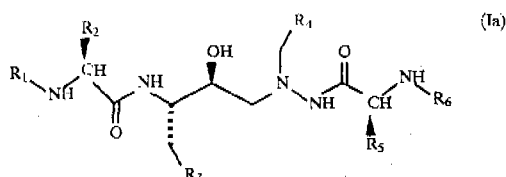
1. A compound of the formula I*,



wherein

- R₁ is lower alkoxy carbonyl,
- R₂ is secondary or tertiary lower alkyl or lower alkylthio-lower alkyl,
- R₃ is phenyl that is unsubstituted or substituted by one or more lower alkoxy radicals, or C₄-C₈cycloalkyl,
- R₄ is phenyl or cyclohexyl each substituted in the 4-position by unsaturated heterocyclyl that is bonded by way of a ring carbon atom, has from 5 to 8 ring atoms, contains from 1 to 4 hetero atoms selected from nitrogen, oxygen, sulfur, sulfinyl and sulfonyl and is unsubstituted or substituted by lower alkyl or by phenyl-lower alkyl,
- R₅, independently of R₂, has one of the meanings mentioned for R₂, and
- R₆, independently of R₁, is lower alkoxy carbonyl, or a salt thereof.

2. A compound according to claim 1 of formula Ia,



wherein the radicals are as defined in claim 1, or a salt thereof.

3. A compound of formula Ia according to claim 2, wherein

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R₁ is lower alkoxy carbonyl,

R₂ is isopropyl, sec-butyl or tert-butyl,

R₃ is phenyl or cyclohexyl,

R₄ is phenyl substituted in the 4-position by one of the following radicals bonded by way of a ring carbon atom: thienyl; oxazolyl; thiazolyl; imidazolyl; 1,4-thiazinyl; triazolyl that is unsubstituted or substituted by 1-methyl-1-phenyl-ethyl, tert-butyl or by methyl; tetrazolyl that is unsubstituted or substituted by 1-methyl-1-phenyl-ethyl, tert-butyl or by methyl; pyridinyl; pyrazinyl; and pyrimidinyl;

R₅ is isopropyl, sec-butyl, tert-butyl or methylthiomethyl, and

R₆ is lower alkoxy carbonyl,

or a salt thereof.

4. A compound of formula Ia according to claim 2, wherein

R₁ is methoxycarbonyl or ethoxycarbonyl,

R₂ is isopropyl, sec-butyl or tert-butyl,

R₃ is phenyl,

R₄ is phenyl substituted in the 4-position of the phenyl ring by 2- or 3-thienyl; thiazol-5-yl; thiazol-2-yl; 2H-tetrazol-5-yl that is unsubstituted or substituted in the 2-position by 1-methyl-1-phenyl-ethyl, tert-butyl or by methyl; 1H-tetrazol-5-yl substituted in the 1-position by methyl; pyridin-2-yl; pyridin-3-yl; pyridin-4-yl; or by pyrazin-2-yl;

R₅ is isopropyl, sec-butyl, tert-butyl or methylthiomethyl; and

R₆ is methoxycarbonyl or ethoxycarbonyl;

with the proviso that at least one of the two radicals R₂ and R₅ is tert-butyl, provided that R₄ is phenyl substituted in the 4-position of the phenyl ring by 2- or 3-thienyl; thiazol-5-yl; thiazol-2-yl; 2H-tetrazol-5-yl that is unsubstituted or substituted in the 2-position by 1-methyl-1-phenyl-ethyl, tert-butyl or by methyl; 1H-tetrazol-5-yl substituted in the 1-position by methyl; pyridin-3-yl; pyridin-4-yl; or by pyrazin-2-yl;

or a salt thereof.

5. A compound of formula Ia according to claim 2, wherein

R₁ is methoxycarbonyl or ethoxycarbonyl,

R₂ is isopropyl, sec-butyl or tert-butyl,

R₃ is phenyl,

R₄ is 4-(thiazol-2-yl)-phenyl, 4-(thiazol-5-yl)-phenyl, 4-(pyridin-2-yl)-phenyl or 4-(2-methyl-tetrazol-5-yl)-phenyl;

R₅ is isopropyl, sec-butyl, tert-butyl or methylthiomethyl; and

R₆ is methoxycarbonyl or ethoxycarbonyl; or a pharmaceutically acceptable salt thereof.

6. A compound of formula Ia according to claim 2, selected from the following compounds:

1-[4-(thiazol-5-yl)-phenyl]-4(S)-hydroxy-2-N-(N-methoxycarbonyl-(L)-valyl)amino-5(S)-N-(N-methoxycarbonyl-(L)-tert-leucyl)amino-6-phenyl-2-azabexane;

1-[4-(thiazol-5-yl)-phenyl]-4(S)-hydroxy-2-N-(N-methoxycarbonyl-(L)-iso-leucyl)amino-5(S)-N-(N-methoxycarbonyl-(L)-tert-leucyl)amino-6-phenyl-2-azabexane;

1-[4-(thiazol-5-yl)-phenyl]-4(S)-hydroxy-2-N-(N-methoxycarbonyl-(L)-S-methylcysteinyl)amino-5(S)-N-(N-methoxycarbonyl-(L)-tert-leucyl)amino-6-phenyl-2-azabexane;

- 1-[4-(thiazol-5-yl)-phenyl]-4(S)-hydroxy-2-N-(N-methoxycarbonyl-(L)-valyl)amino-5(S)-N-(N-methoxycarbonyl-(L)-tert-leucyl)amino-6-phenyl-2-azahexane;
- 1-[4-(thiazol-5-yl)-phenyl]-4(S)-hydroxy-2-N-(N-methoxycarbonyl-(L)-tert-leucyl)amino-5(S)-N-(N-methoxycarbonyl-(L)-valyl)amino-6-phenyl-2-azahexane;
- 1-[4-(thiazol-5-yl)-phenyl]-4(S)-hydroxy-2-N-(N-methoxycarbonyl-(L)-tert-leucyl)amino-5(S)-N-(N-methoxycarbonyl-(L)-iso-leucyl)amino-6-phenyl-2-azahexane;
- 1-[4-(thiazol-2-yl)-phenyl]-4(S)-hydroxy-5(S)-2,5-bis-[N-(N-methoxycarbonyl-(L)-tert-leucyl)-amino]-6-phenyl-2-azahexane;
- 1-[4-(thiazol-2-yl)-phenyl]-4(S)-hydroxy-2-N-(N-methoxycarbonyl-(L)-tert-leucyl)amino-5(S)-N-(N-methoxycarbonyl-(L)-valyl)amino-6-phenyl-2-azahexane;
- 1-[4-(thiazol-2-yl)-phenyl]-4(S)-hydroxy-2-N-(N-methoxycarbonyl-(L)-tert-leucyl)amino-5(S)-N-(N-methoxycarbonyl-(L)-iso-leucyl)amino-6-phenyl-2-azahexane;
- 1-[4-(pyridin-2-yl)-phenyl]-4(S)-hydroxy-5(S)-2,5-bis-[N-(N-methoxycarbonyl-(L)-valyl)amino]-6-phenyl-2-azahexane;
- 1-[4-(pyridin-2-yl)-phenyl]-4(S)-hydroxy-2-N-(N-methoxycarbonyl-(L)-valyl)amino-5(S)-N-(N-methoxycarbonyl-(L)-tert-leucyl)amino-6-phenyl-2-azahexane; and

1-[4-(pyridin-2-yl)-phenyl]-4(S)-hydroxy-2-N-(N-methoxycarbonyl-(L)-tert-leucyl)amino-5(S)-N-(N-methoxycarbonyl-(L)-valyl)amino-6-phenyl-2-azahexane;

or in each case a pharmaceutically acceptable salt thereof.

7. A compound of formula Ia according to claim 2 named 1-[4-(thiazol-5-yl)-phenyl]-4(S)-hydroxy-5(S)-2,5-bis-[N-(N-methoxycarbonyl-(L)-tert-leucyl)-amino]-6-phenyl-2-azahexane, or a salt thereof.

8. A compound of formula Ia according to claim 2 named 1-[4-(2-methyl-2H-tetrazol-5-yl)-phenyl]-4(S)-hydroxy-5(S)-2,5-bis-[N-(N-methoxycarbonyl-(L)-tert-leucyl)amino]-6-phenyl-2-azahexane, or a salt thereof.

9. A compound of formula Ia according to claim 2 named 1-[4-(pyridin-2-yl)-phenyl]-4(S)-hydroxy-5(S)-2,5-bis-[N-(N-methoxycarbonyl-(L)-tert-leucyl)-amino]-6-phenyl-2-azahexane, or a salt thereof.

10. A pharmaceutical composition suitable for administration to a warm-blooded animal for the treatment of AIDS or its preliminary stages, comprising a compound of formula I* according to claim 1, or a pharmaceutically acceptable salt thereof, together with at least one pharmaceutically acceptable carrier.

11. A method for the treatment of AIDS or its preliminary stages, wherein a therapeutically effective amount of a compound of formula I* according to claim 1, or a pharmaceutically acceptable salt thereof, is administered to a human, who on account of said disease requires such treatment, in a dose that is effective in the treatment of said disease.

* * * * *



US006087383A

United States Patent [19]

Singh et al.

[11] Patent Number: 6,087,383
[45] Date of Patent: Jul. 11, 2000

[54] BISULFATE SALT OF HIV PROTEASE INHIBITOR

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[73] Assignee: Bristol-Myers Squibb Company,
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[21] Appl. No.: 09/217,538

[22] Filed: Dec. 21, 1998

Related U.S. Application Data

[60] Provisional application No. 60/071,968, Jan. 20, 1998.

[51] Int. Cl.⁷ A61K 31/44; C07D 213/56

[52] U.S. Cl. 514/357; 546/332

[58] Field of Search 546/332; 514/357

[56] References Cited

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FOREIGN PATENT DOCUMENTS

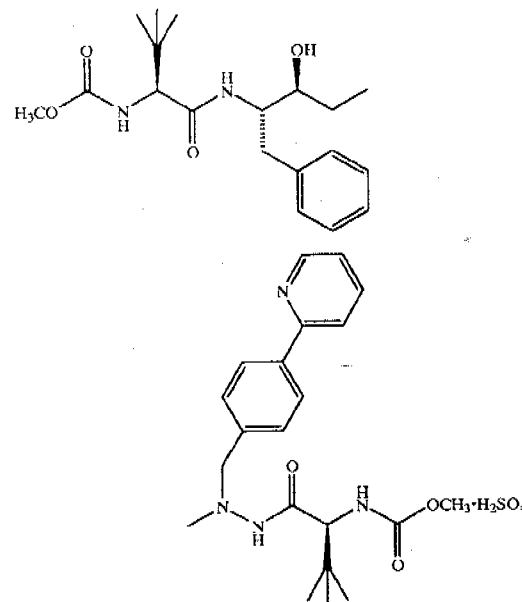
WO97/40029 10/1997 * WIPO.

Primary Examiner—Bernard Dentz

Attorney, Agent, or Firm—David M. Morse

[57] ABSTRACT

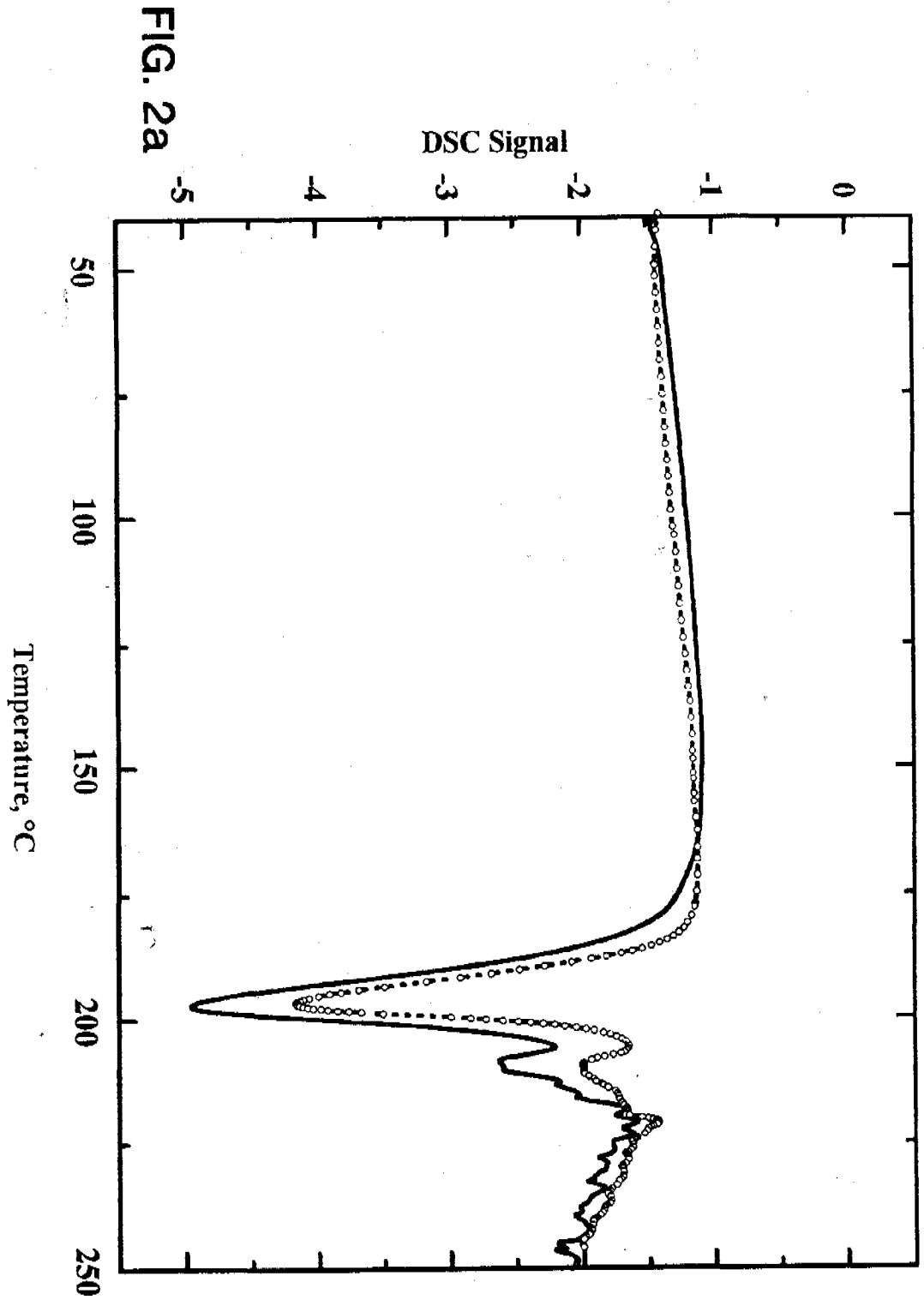
The present invention provides the crystalline bisulfate salt of the formula



which is found to have unexpectedly high solubility/dissolution rate and oral bioavailability relative to the free base form of this azapeptide HIV protease inhibitor compound.

2 Claims, 5 Drawing Sheets

235



18

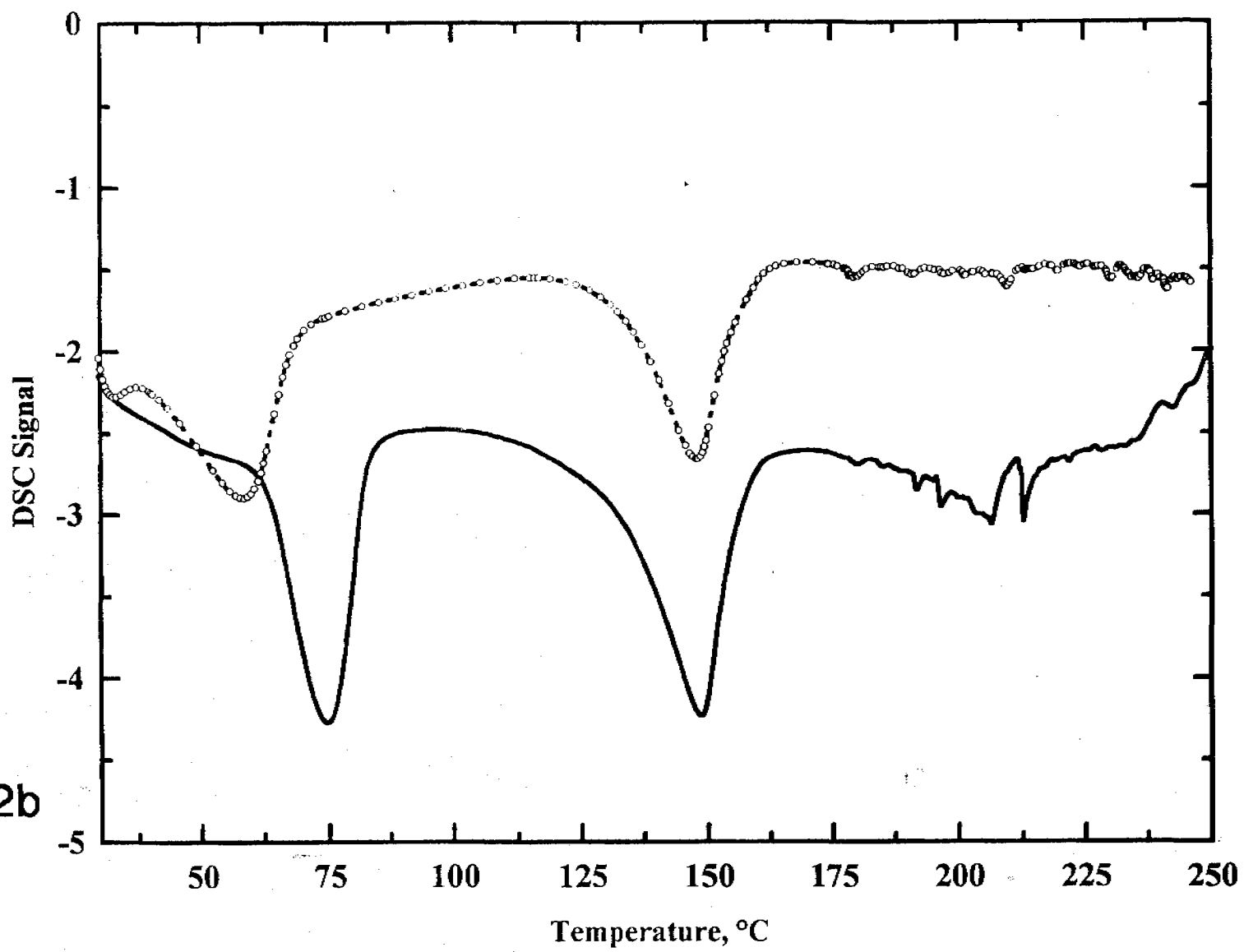


FIG. 2b

20
240

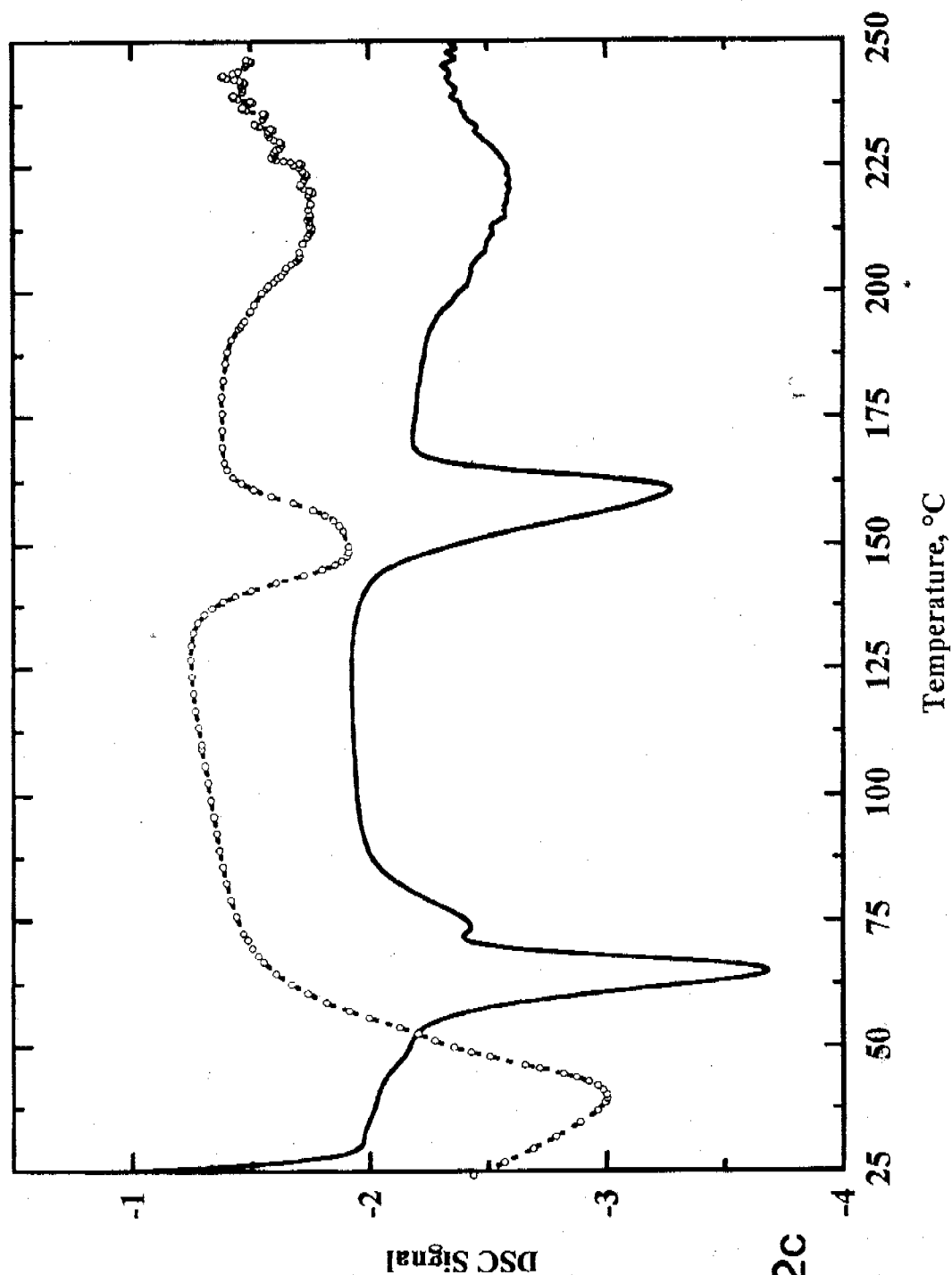


FIG. 2C

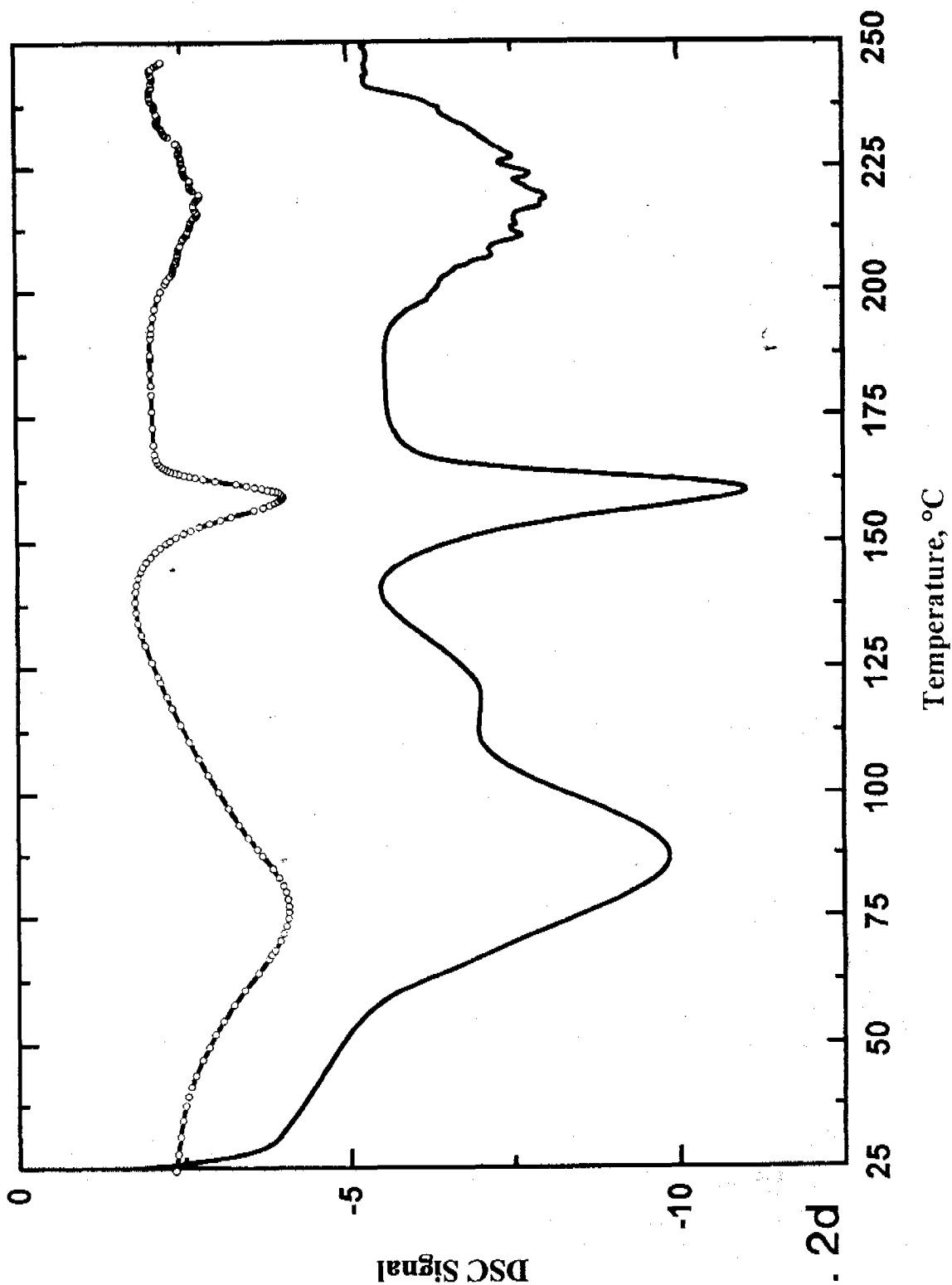


FIG. 2d

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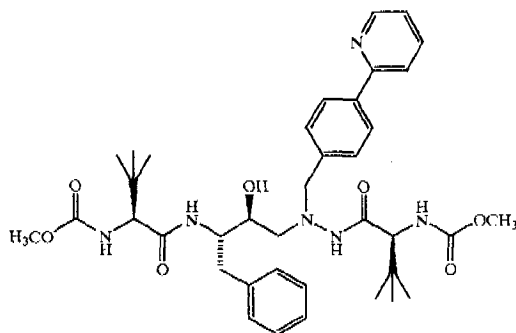
BISULFATE SALT OF HIV PROTEASE INHIBITOR

This application claims priority from Provisional Application 60/071,968 filed Jan. 20, 1998.

BACKGROUND OF THE INVENTION

1. Field of the Invention

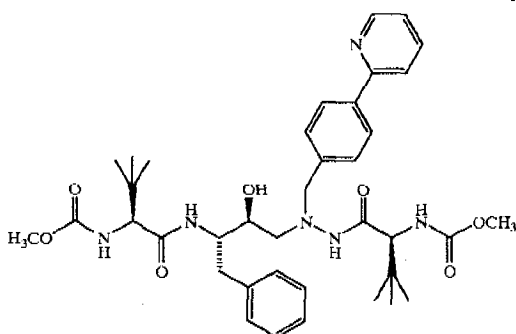
The present invention provides the novel crystalline bisulfate salt of the azapeptide HIV protease inhibitor of the formula



which exhibits unexpectedly superior aqueous solubility/dissolution behavior compared to other salts, and significantly improved oral bioavailability in animals compared to the free base. The bisulfate salt is thus useful for pharmaceutical dosage forms of the above-indicated protease inhibitor, particularly oral dosage forms.

2. Background Art

Published PCT patent application WO 97/40029 discloses a series of azapeptide HIV protease inhibitors reported to have a high degree of inhibitory activity against the HIV virus. One of the agents included within the scope of WO 97/40029 is the compound having the structural formula



and the chemical name [3S-(3R*, 8'R*, 9'R*, 12R*)]-3,12-bis(1,1-dimethylethyl)-8-hydroxy-4,11-dioxo-9-(phenylmethyl)-6-[[4-(2-pyridinyl)phenylmethyl]-2,5,6,10,13-pentaazatetradecanedioic acid, dimethyl ester and is under evaluation as a possible second generation HIV protease inhibitor.

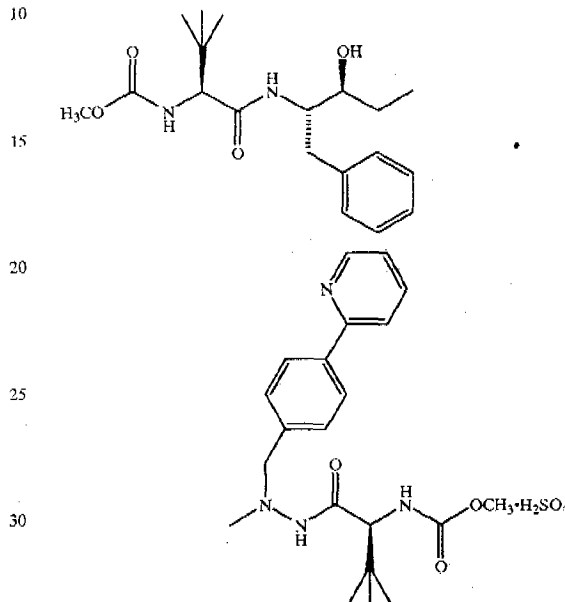
WO 97/40029 discloses the free base form of azapeptide derivatives such as compound I and also various pharmaceutically acceptable acid addition salts. While several organic and inorganic acids are mentioned as possible salt-

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forming agents, including sulfuric acid, there is no mention of the particular bisulfate salt which is the subject of the present application.

SUMMARY OF THE INVENTION

The present invention provides the bisulfate salt of compound I above having the structural formula



DETAILED DESCRIPTION OF THE INVENTION

Compound I as disclosed above is a weak organic base with an aqueous solubility of less than 1 µg/mL at 24±3° C. The crystalline free base form as a suspension in water or oil has poor oral bioavailability in animals, probably because of its extremely low solubility in these vehicles.

For development of pharmaceutical formulations, particularly oral dosage forms, the active ingredient must have sufficient oral bioavailability. Since the free base form of compound I did not possess such bioavailability, acid addition salts were explored by the present inventors. A number of commonly used acid addition salts such as the hydrochloride, benzenesulfonate, methanesulfonate, p-toluenesulfonate, phosphate, nitrate, 1,2-ethanedisulfonate, isethionate and sulfate were evaluated, in addition to the bisulfate salt of the present invention. All of these salts in their crystalline form exhibited lower aqueous solubility (1-3 mg/mL or less at 24±3° C.) than the bisulfate which had a solubility under the same conditions of approximately 4-5 mg/mL.

Solid state transformation was observed when the other acid addition salts mentioned above were suspended in water, probably due to their dissociation to form the free base. In the majority of cases, this transformation was accompanied by gel formation. Unlike the other salts mentioned above, the extra proton of the bisulfate salt prevents the conversion to the free base which, as mentioned above, is very insoluble in water and has poor oral bioavailability. The unusual solubility behavior of the bisulfate salt in water is further elaborated in the following.

In general, conversion of salts to the unionized form or vice versa can be explained on the basis of pH-solubility theory. The solubility of the free base in water was determined as a function of pH at $24 \pm 3^\circ \text{C}$. and is shown below. The pH at which the compound exhibits the highest solubility is referred to as pH_{max} and was found to be approximately 1.2. It has been reported in the literature that at $\text{pH} > \text{pH}_{\text{max}}$ of a weakly basic organic compound, the equilibrium solid phase in an aqueous suspension of the compound is the free base. At $\text{pH} < \text{pH}_{\text{max}}$ the equilibrium solid converts to the corresponding salt form. The term "equilibrium solid phase" refers to the undissolved or excess solid in a suspension of the compound in water after sufficient equilibration time. When a salt of a weak base is equilibrated in water in an amount exceeding its solubility limit (i.e., a suspension of the salt in water), the resulting pH of the suspension may fall on either side of the pH_{max} depending on the strength of the acid among other factors. When the resulting pH is greater than the pH_{max} , the suspended solid converts to the free base.

Studies conducted with methane sulfonate and hydrochloride salts, in particular, of the free base confirmed the above described general findings reported in the literature. Amounts in excess of the solubility of these salts were equilibrated in water at $24 \pm 3^\circ \text{C}$. for at least 24 hours. The pH of the suspensions after equilibration was 2.1 ± 0.1 which is greater than the pH_{max} . The undissolved solids from these suspensions were isolated, air-dried, and characterized. By thermal and elemental analysis the undissolved solids from these suspensions were identified as the free base. This behavior was expected based on the pH-solubility profile shown in FIG. 1 and the studies reported in the literature.

When an excess amount of the bisulfate salt was equilibrated in water a modification occurred in the solid phase in equilibrium with solution. However, the undissolved solid phase after equilibration was not the free base, although the pH (1.9 ± 0.2) of the suspension was greater than the pH_{max} and comparable to the pH of the suspensions of methane sulfonate and hydrochloride salts described above. The solid phase after at least 24 hours of equilibration was identified by elemental analysis as a hydrated form of 2:1 salt of the free base form and sulfuric acid (referred to as the sulfate salt). This behavior of the bisulfate salt is unexpected based on pH-solubility theory.

When an excess amount of the sulfate salt, in turn, was equilibrated in water a modification occurred in the solid phase in equilibrium with solution. The undissolved solid from this suspension was isolated, air-dried, and characterized. Thermal and elemental analysis of this undissolved solid phase was similar to that of the free base although the conversion of the sulfate salt to the free base was not as definitive as that of the methane sulfonate and hydrochloride salts. From a pharmaceutical point of view the propensity of salts to convert to the free base in an aqueous environment is not desirable due to the low oral bioavailability of the free base. Thus, the bisulfate salt due its unique solubility behavior in water offered unexpected superiority.

The solubility behavior of the bisulfate salt in water was also unexpected considering the interaction of compound I free base and sulfuric acid in water. For example, the free base exhibited a solubility of less than 1 mg/mL in water at a pH of ~ 1.8 adjusted with sulfuric acid, compared to 4–5 mg/mL solubility of the bisulfate salt in water at comparable pH conditions. Based on pH-solubility theory the free base and the salt are expected to exhibit similar solubility at a given pH.

The enhanced solubility/dissolution behavior of the bisulfate contributes to its improved oral bioavailability in ani-

mals relative to the free base. The absolute oral bioavailability of the bisulfate salt was found to be approximately 20% in dogs when administered in unformulated solid form placed in a gelatin capsule. In comparison, the crystalline free base had minimal oral bioavailability in dogs.

In addition to optimal solubility, satisfactory physical stability in the solid-state is another desirable property of pharmaceutical salt forms. The term physical stability indicates the ability of the salt form to retain its crystal structure (including solvents of crystallization, if any) under storage/stress conditions. Significant changes in the physical nature of the salt form as indicated by thermal methods such as differential scanning calorimetry are undesirable. The bisulfate salt exhibited excellent solid-state physical stability when stored at $40^\circ \text{C}/75\%$ relative humidity (RH) for as long as 9 months as shown in FIG. 2a. Differential scanning calorimetry revealed no significant changes in the thermal behavior of the stressed sample of the bisulfate salt compared to that of the unstressed sample (stored at $2-8^\circ \text{C}$. in a closed container). The methane sulfonate, hydrochloride, and the sulfate salts, on the other hand, showed significant changes in their thermal behavior when stored at $40^\circ \text{C}/75\%$ RH for as little as two weeks as shown in FIGS. 2b, c, and d. While differences in physical stability of salt forms is not unusual, the propensity of a particular salt to form solvates (or crystal modifications) and its ability to retain the solvent of crystallization (the physical stability of crystal modifications) under storage/stress conditions cannot be predicted a priori.

FIG. 2a represents Physical stability of the bisulfate salt. The solid line represents the unstressed material. The dotted line represents the material stressed at $40^\circ \text{C}/75\%$ RH for 9 months.

FIG. 2b represents Physical Stability of the hydrochloride salt. The solid line represents the unstressed material. The dotted line represents the material stressed at $40^\circ \text{C}/75\%$ RH for two weeks.

FIG. 2c represents Physical stability of the methane sulfonate salt. The solid line represents the unstressed material. The dotted line represents the material stressed at $40^\circ \text{C}/75\%$ RH for two weeks.

FIG. 2d represents Physical stability of the sulfate salt. The solid line represents the unstressed material. The dotted line represents the material stressed at $40^\circ \text{C}/75\%$ RH for two weeks.

The bisulfate salt may be prepared by forming a solution of free base of compound I with sulfuric acid in solvents such as acetonitrile, isopropanol, ethanol, or acetone and then isolating the so-produced bisulfate salt.

Because of its high bioavailability as well as its good crystallinity and stability, the bisulfate salt is very useful in preparing oral dosage forms of compound I. The examples which follow illustrate preparation of representative oral formulations.

The bisulfate salt, and formulations thereof, are used as described in WO 97/40029 for the treatment of diseases caused by viruses, especially retroviruses such as the HIV virus.

DESCRIPTION OF SPECIFIC EMBODIMENTS

Example 1

Preparation of Bisulfate Salt from Ethanol

To a 500 mL three-necked round bottomed flask equipped with an overhead stirrer and dropping funnel, 15.013 g

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(0.0213 mole) of free base compound I and 113 mL of 200 proof ethanol were added with stirring. To this suspension, 1.28 mL concentrated sulfuric acid was added dropwise over 90 seconds. After the addition of sulfuric acid, a clear amber-colored solution was obtained. The solution was 5
polish filtered using #1 Whatman filter paper and washed with 5 mL of 200 proof ethanol. To this solution was added 58 mL of heptane and 37.5 mg (0.25 wt %) of seed crystals of the compound of formula II followed by 55 mL of additional heptane. The resulting mixture was stirred for 6 10
hours at 300 rpm. The resulting crystal slurry was filtered and washed with 50 mL ethanol/heptane (1:1) solution and dried under vacuum at 60° C. overnight to afford 15.11 g of the desired crystalline bisulfate salt (88.4 mole % yield) having formula II above.

Characterizing Properties of Bisulfate Salt

Anal. Calcd. for $C_{38}H_{52}N_6O_7 \cdot 1.0 H_2SO_4$: C, 56.84; H, 6.78; N, 10.37; S, 3.99. Found: C, 56.72; H, 6.65; N, 10.41; S, 3.83. m.p. 195.0°, $H_2O=0.28\%$ (KF).

Example 2

Preparation of Bisulfate Salt from Acetone

5M H_2SO_4 (8.52 mL, 42.6 mM) was added dropwise to a suspension of the free base compound of formula I (30.0 g., 42.6 mM) in acetone (213 mL) stirred mechanically in a 50° C. oil-bath. A clear solution was obtained almost immediately. The solution was seeded with crystals of the free 5
base compound of formula II. After two minutes, a precipitate formed which became a paste. The mixture was stirred at 50° C. for one hour, at 25° C. for 30 minutes and at 0° C. for 2 hours. The solid was filtered and the first filtrate was used to transfer the remaining material in the flask to the 10
filtration funnel. The product was washed with acetone, then heptane, and dried under vacuum overnight to give 31.48 g (corrected yield 92%) of the bisulfate salt of formula II, m.p. 198–199° C. dec.

Anal. Calcd. $C_{38}H_{52}N_6O_7 \cdot 1.0 H_2SO_4 \cdot 0.2 H_2O$: C, 56.59; H, 6.80; N, 10.42; S, 3.98; H_2O , 0.45. Found: C, 56.66; H, 6.78; N, 10.50; S, 4.20; H_2O , 0.45 (KF).

Example 3

Preparation of Bisulfate Salt from Isopropanol

Aqueous sulfuric acid (5.0 M, 0.20 mL, 1 mM) was added to a suspension of the free base compound of formula I (0.704 g, 1.00 mM) in isopropanol (4.0 mL) chilled in an ice-bath. The ice-bath was removed and the mixture stirred at room temperature. The suspension had dissolved after 15 5
minutes. The solution was seeded with crystals prepared as in Examples 1 or 2 above and stirred for 5 hours. The solid was filtered and the filtrate was used to transfer the solid from the flask to the funnel. The product was washed with heptane and dried under vacuum to give 0.752 g of crystalline bisulfate salt of formula II, yield 90%, m.p. 160–190° C., dec.

Anal. Calcd. for $C_{38}H_{52}N_6O_7 \cdot 1.0 H_2SO_4 \cdot 2.0 H_2O$: C, 54.40; H, 6.97; N, 10.02; S, 3.82; H_2O , 4.29. Found: C, 54.25; H, 6.73; N, 10.02; S, 3.67; H_2O , 4.53 (KF).

The crystals obtained from isopropanol showed a powder x-ray diffraction pattern different from the crystals obtained

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from acetonitrile, ethanol-heptane or acetone. They are now referred to as Type-II crystals. The Type-I crystals appear to be an anhydrous/desolvated crystalline material while the Type-II crystals are a hydrated, hygroscopic crystalline form.

Example 4

Preparation of Capsule Formulations of Bisulfate Salt

A. Capsules (50 and 200 mg free base equivalent)

Capsules are provided for oral administration in which the capsule is a size #0, gray, opaque, hard gelatin capsule containing the bisulfate salt of formula II formulated as a 15
wet granulation with lactose, croscopovidone and magnesium stearate.

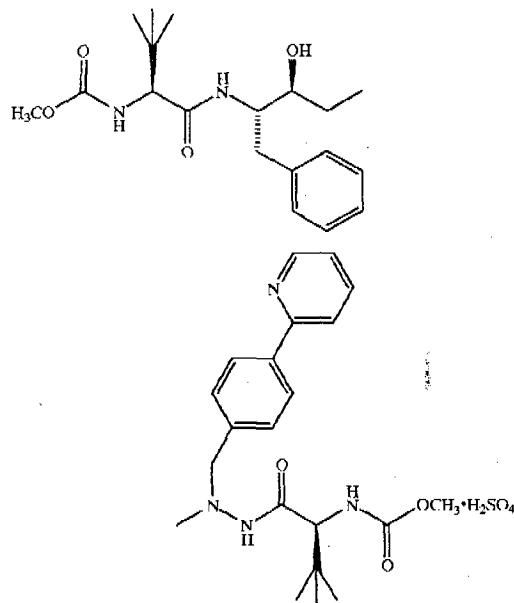
B. Capsules (100 mg free base equivalent)

Capsules are provided for oral administration in which the capsule is a size #0, gray, opaque, hard gelatin capsule containing the bisulfate salt of formula II suspended in Gelucire 44/14. Gelucire 44/14 is a saturated polyglycolized 25
glyceride consisting of mono-, di- and triglycerides and mono- and di-fatty acid esters of polyethylene glycol. Capsules are prepared by melting Gelucire 44/14 at 45–70° C. followed by addition of the bisulfate salt with stirring. The molten mixture is filled into hard gelatin capsules and allowed to cool and solidify.

We claim:

1. The bisulfate salt having the formula

II



2. A pharmaceutical dosage form comprising the bisulfate salt of claim 1 and a pharmaceutically acceptable carrier.

* * * * *

DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No 06-111944

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCION**

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **583** DE

FECHA **18 DE DICIEMBRE DE 2007** EL TÉRMINO HÁBIL SEÑALADO POR

LA LEY EXPIRA EL **14 DE MARZO DEL 2008**.

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI X

NO

2020
Bogotá, D.C.,

Doctor:
Juan Pablo Cadena Sarmiento
Apoderado

Oficio N°: 10348

ASUNTO:	Radicación PCT N°	06-111944
	Trámite	011
	Evento	379
	Actuación	440
	Folios	027

Con fundamento en lo previsto por el artículo 43 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica que la oposición presentada por el doctor José Luis Reyes Villamizar, en su calidad de apoderado de Laboratorio Franco Colombiano Lafrancol S.A., reúne los requisitos formales exigidos por la ley al momento de su presentación.

En cumplimiento de lo dispuesto en la citada norma, se le concede el término de sesenta (60) días hábiles siguientes a la fecha de notificación del presente oficio, para que haga valer sus argumentaciones y presente pruebas.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.


ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones.

El anterior oficio fue notificado por fijación en lista de fecha, _____.

202021

2020
Bogotá, D.C.,

Doctor:
Juan Pablo Cadena Sarmiento
Apoderado

Oficio N° 0340

ASUNTO:	Radicación PCT N°	06-111944
	Trámite	011
	Evento	379
	Actuación	440
	Folios	028

Con fundamento en lo previsto por el artículo 43 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica que la oposición presentada por el doctor José Luis Reyes Villamizar, en su calidad de apoderado de Tecnoquímicas S.A., reúne los requisitos formales exigidos por la ley al momento de su presentación.

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ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones.

El anterior oficio fue notificado por fijación en lista de fecha, _____.

202021