Charles M. Lizza
William C. Baton
Elina Slavin
SAUL EWING ARNSTEIN & LEHR LLP
One Riverfront Plaza, Suite 1520
Newark, NJ 07102-5246
(973) 286-6700
clizza@saul.com

Attorneys for Plaintiff
Bristol-Myers Squibb Company

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

BRISTOL-MYERS SQUIBB COMPANY, Plaintiff, v. EMCURE PHARMACEUTICALS LIMITED, HERITAGE PHARMA LABS INC., and HERITAGE PHARMACEUTICALS INC., Defendants.	**Civil Action No. _____** **COMPLAINT FOR PATENT INFRINGEMENT** **(Filed Electronically)**

Plaintiff Bristol-Myers Squibb Company ("BMS"), by its attorneys, hereby alleges as follows:

NATURE OF THE ACTION

1. This is an action for patent infringement arising under the patent laws of the United States, Title 35, United States Code, against Defendants Emcure Pharmaceuticals Limited, Heritage Pharma Labs Inc., and Heritage Pharmaceuticals Inc. (collectively, "Emcure"). This action relates to Abbreviated New Drug Application ("ANDA") Nos. 078785 and 200196 filed by Emcure with the U.S. Food and Drug Administration ("FDA").

2. In ANDA Nos. 078785 and 200196, Emcure seeks approval to market 100 mg, 150 mg, 200 mg, and 300 mg capsules of atazanavir sulfate, generic versions of BMS's Reyataz® drug product (the "Emcure ANDA Products"), prior to expiration of U.S. Patent No. 6,087,383 ("the '383 patent").

PARTIES

3. BMS is a corporation organized and existing under the laws of Delaware, having a place of business at Route 206 and Province Line Road, Princeton, New Jersey 08540.

4. BMS is engaged in the business of creating, developing, and bringing to market revolutionary biopharmaceutical products to help patients prevail against serious diseases, including treatments for HIV and AIDS. BMS markets and sells its Reyataz® capsules in this Judicial District and throughout the United States.

5. Upon information and belief, Emcure Pharmaceuticals Limited is an Indian corporation having a principal place of business at Emcure House, T 184, M.I.D.C. Bhosari, Pune, India.

6. Upon information and belief, Heritage Pharma Labs Inc. is a New Jersey corporation having a principal place of business at 21/B Cotters Lane, East Brunswick, New Jersey 08816.

7. Upon information and belief, Heritage Pharmaceuticals Inc. is a Delaware corporation having a principal place of business at 12 Christopher Way, Suite 300, Eatontown, New Jersey 07724.

8. Upon information and belief, Emcure is in the business of, among other things, developing, manufacturing, and selling generic versions of branded pharmaceutical products for the U.S. market.

JURISDICTION AND VENUE

9. This action arises under the patent laws of the United States, 35 U.S.C. §§ 100, *et seq.*, and this Court has jurisdiction over the subject matter of this action under 28 U.S.C. §§ 1331, 1338(a), 2201 and 2202.

10. Venue is proper in this Court under 28 U.S.C. § 1400(b), and this Court has personal jurisdiction over Emcure. Moreover, Emcure, through its counsel, by e-mail dated August 21, 2017, agreed that it does not contest jurisdiction or venue in this Court in this matter. Furthermore, venue and jurisdiction are proper for other reasons that will be presented to the Court if challenged.

PATENT-IN-SUIT

11. On July 11, 2000, the U.S. Patent and Trademark Office duly and legally issued the '383 patent, titled "Bisulfate Salt of HIV Protease Inhibitor." A true and correct copy of the '383 patent is attached hereto as Exhibit A. The claims of the '383 patent are valid and enforceable. BMS is the owner of the '383 patent and has the right to enforce it. The expiration date of the '383 patent is December 21, 2018. BMS also was awarded a period of pediatric exclusivity through June 21, 2019.

12. BMS is the holder of New Drug Application ("NDA") No. 021567, by which the FDA granted approval for the marketing and sale of 150 mg, 200 mg, and 300 mg strength atazanavir sulfate capsules. BMS markets atazanavir sulfate capsules in the United States, under the trade name "Reyataz®." The FDA's official publication of approved drugs (the "Orange Book") includes Reyataz® together with the '383 patent.

INFRINGEMENT BY EMCURE

13. By two letters sent by FedEx on August 11, 2017, Emcure notified BMS that Emcure had submitted ANDA Nos. 078785 and 200196 to the FDA under Section 505(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 355(j)) ("the Reyataz Notice Letters"). BMS received the Reyataz Notice Letters no earlier than August 14, 2017.

14. The Reyataz Notice Letters state that Emcure seeks approval from the FDA to engage in the commercial manufacture, use, and sale of the Emcure products before the expiration of the '383 patent. Upon information and belief, Emcure intends to—directly or indirectly—engage in the commercial manufacture, use, and sale of the Emcure ANDA Products promptly upon receiving FDA approval to do so.

15. By filing ANDA Nos. 078785 and 200196, Emcure has necessarily represented to the FDA that the Emcure ANDA Products have the same active ingredient as Reyataz®, have the same method of administration, dosage form, and strengths as Reyataz®, and are bioequivalent to Reyataz®.

16. Upon information and belief, the Emcure ANDA Products contain atazanavir bisulfate.

17. Upon information and belief, the Emcure ANDA Products will be manufactured by, or at the direction of, Emcure.

18. In the Reyataz Notice Letters, Emcure states that the Emcure ANDA contains a Paragraph IV certification asserting that the '383 patent is invalid, unenforceable and/or will not be infringed by the commercial manufacture, use, and sale of the Emcure ANDA Products.

19. This Complaint is being filed before the expiration of forty-five days from the date BMS received the Reyataz Notice Letters.

COUNT I

(INFRINGEMENT OF THE '383 PATENT: ANDA NO. 078785)

20. Each of the preceding paragraphs 1 to 19 is incorporated as if fully set forth herein.

21. Emcure's submission of ANDA No. 078785 to obtain approval to engage in the commercial manufacture, use, offer to sell, sale, and/or importation of 100 mg, 150 mg, and 200 mg capsules of atazanavir sulfate prior to the expiration of the '383 patent constituted a technical act of infringement. Upon information and belief, the product described in ANDA No. 078785 would infringe claims 1 and 2 of the '383 patent under 35 U.S.C. § 271(e)(2)(A).

22. Emcure's commercial manufacture, use, offer to sell, sale, and/or importation of 100 mg, 150 mg, and 200 mg capsules of atazanavir sulfate prior to the expiration of the '383 patent, and its inducement of and/or contribution to such conduct, would further infringe claims 1 and 2 of the '383 patent under 35 U.S.C. §§ 271(a), (b) and/or (c).

23. Upon FDA approval of Emcure's ANDA No. 078785, Emcure will infringe claims 1 and 2 of the '383 patent by making, using, offering to sell, and selling 100 mg, 150 mg, and 200 mg capsules of atazanavir sulfate, in the United States and/or importing such products into the United States, or by actively inducing and contributing to infringement of the '383 patent by others, under 35 U.S.C. § 271(a)-(c), unless enjoined by the Court.

24. If Emcure's marketing and sale of 100 mg, 150 mg, and 200 mg capsules of atazanavir sulfate prior to expiration of the '383 patent and all other relevant exclusivities are not enjoined, BMS will suffer substantial and irreparable harm for which there is no remedy at law.

COUNT II

(INFRINGEMENT OF THE '383 PATENT: ANDA NO. 200196)

25. Each of the preceding paragraphs 1 to 24 is incorporated as if fully set forth herein.

26. Emcure's submission of ANDA No. 200196 to obtain approval to engage in the commercial manufacture, use, offer to sell, sale, and/or importation of 300 mg capsules of atazanavir sulfate prior to the expiration of the '383 patent constituted a technical act of infringement. Upon information and belief, the product described in ANDA No. 200196 would infringe claims 1 and 2 of the '383 patent under 35 U.S.C. § 271(e)(2)(A).

27. Emcure's commercial manufacture, use, offer to sell, sale, and/or importation of 300 mg capsules of atazanavir sulfate prior to the expiration of the '383 patent, and its inducement of and/or contribution to such conduct, would further infringe claims 1 and 2 of the '383 patent under 35 U.S.C. §§ 271(a), (b) and/or (c).

28. Upon FDA approval of Emcure's ANDA No. 200196, Emcure will infringe claims 1 and 2 of the '383 patent by making, using, offering to sell, and selling 300 mg capsules of atazanavir sulfate, in the United States and/or importing such products into the United States, or by actively inducing and contributing to infringement of the '383 patent by others, under 35 U.S.C. § 271(a)-(c), unless enjoined by the Court.

29. If Emcure's marketing and sale of the Emcure ANDA Products prior to expiration of the '383 patent and all other relevant exclusivities are not enjoined, BMS will suffer substantial and irreparable harm for which there is no remedy at law.

PRAYER FOR RELIEF

WHEREFORE, Plaintiff BMS respectfully requests the following relief:

1. A Judgment that the claims of the '383 patent are not invalid, are not unenforceable, and are infringed by Emcure's submission of ANDA Nos. 078785 and 200196, and that Emcure's making, using, offering to sell, or selling in the United States, and/or importing into the United States the Emcure ANDA Products will infringe the '383 patent.

2. An Order pursuant to 35 U.S.C. § 271(e)(4)(A) providing that the effective date of any approval of ANDA Nos. 078785 and 200196 shall be a date which is not earlier than the latest expiration date of the ’383 patent, including any extensions and/or additional periods of exclusivity to which BMS is or becomes entitled.

3. An Order permanently enjoining Emcure, its affiliates, subsidiaries, and each of its officers, agents, servants and employees and those acting in privity or concert with them, from making, using, offering to sell, or selling in the United States, or importing into the United States the Emcure ANDA Products until after the latest expiration date of the ‘383 patent, including any extensions and/or additional periods of exclusivity to which BMS is or becomes entitled.

4. Damages or other monetary relief, including, but not limited to, costs and pre- and post-judgment interest, to BMS if Emcure engages in commercial manufacture, use, offers to sell, sale, and/or importation in or into the United States of the Emcure ANDA Products prior to the latest expiration date of the ’383 patent, including any extensions and/or additional periods of exclusivity to which BMS is or becomes entitled.

5. Such further and other relief as this Court deems just and proper, including any appropriate relief under 35 U.S.C. § 285.

Dated: September 6, 2017

By: s/ Charles M. Lizza

Charles M. Lizza
William C. Baton
Elina Slavin
SAUL EWING ARNSTEIN & LEHR LLP
One Riverfront Plaza
1037 Raymond Blvd., Suite 1520
Newark, NJ 07102
(973) 286-6700
clizza@saul.com

Attorneys for Plaintiff
Bristol-Myers Squibb Company

Of Counsel:

Amy K. Wigmore (to be admitted *pro hac vice*)
Tracey C. Allen (to be admitted *pro hac vice*)
WILMER CUTLER PICKERING HALE AND DORR LLP
1875 Pennsylvania Avenue, N.W.
Washington, DC 20006
(202) 663-6000

CERTIFICATION PURSUANT TO LOCAL CIVIL RULES 11.2 & 40.1

I hereby certify that the matter captioned *Bristol-Myers Squibb Co. v. Zydus Pharms. (USA) Inc.*, Civil Action No. 17-5337 (PGS)(LHG) is related to the matter in controversy because the matter in controversy involves the same patent and drug product.

I further certify that, to the best of my knowledge, the matter in controversy is not the subject of any other action pending in any court or of any pending arbitration or administrative proceeding.

Dated: September 6, 2017

By: s/ Charles M. Lizza

Charles M. Lizza
William C. Baton
Elina Slavin
SAUL EWING ARNSTEIN & LEHR LLP
One Riverfront Plaza
1037 Raymond Blvd., Suite 1520
Newark, NJ 07102
(973) 286-6700
clizza@saul.com

Attorneys for Plaintiff
Bristol-Myers Squibb Company

Of Counsel:

Amy K. Wigmore (to be admitted *pro hac vice*)
Tracey C. Allen (to be admitted *pro hac vice*)
WILMER CUTLER PICKERING HALE AND DORR LLP
1875 Pennsylvania Avenue, N.W.
Washington, DC 20006
(202) 663-6000

EXHIBIT A

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**

[75] Inventors: **Janak Singh**, Lawrenceville; **Madhusudhan Pudipeddi**, Plainsboro; **Mark D. Lindrud**, Basking Ridge, all of N.J.

[73] Assignee: **Bristol-Myers Squibb Company**, Princeton, N.J.

[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**

U.S. PATENT DOCUMENTS

5,849,911 12/1999 Fassler et al. 544/335

FOREIGN PATENT DOCUMENTS

WO97/40029 10/1997 WIPO .

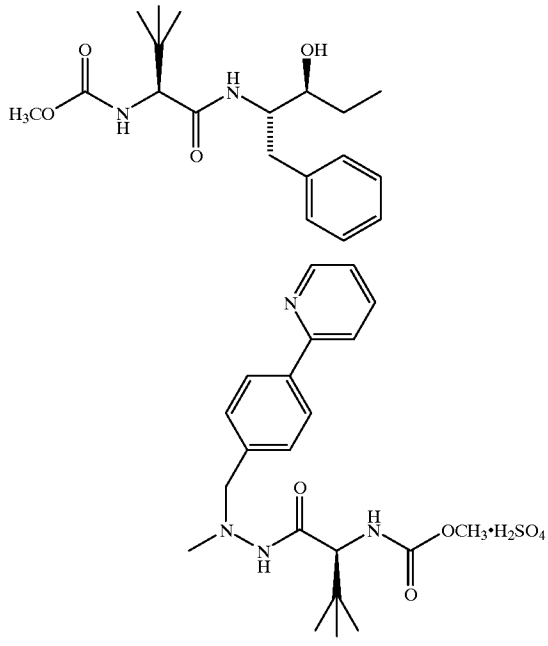
Primary Examiner—Bernard Dentz

Attorney, Agent, or Firm—David M. Morse

[57] **ABSTRACT**

The present invention provides the crystalline bisulfate salt of the formula

II



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

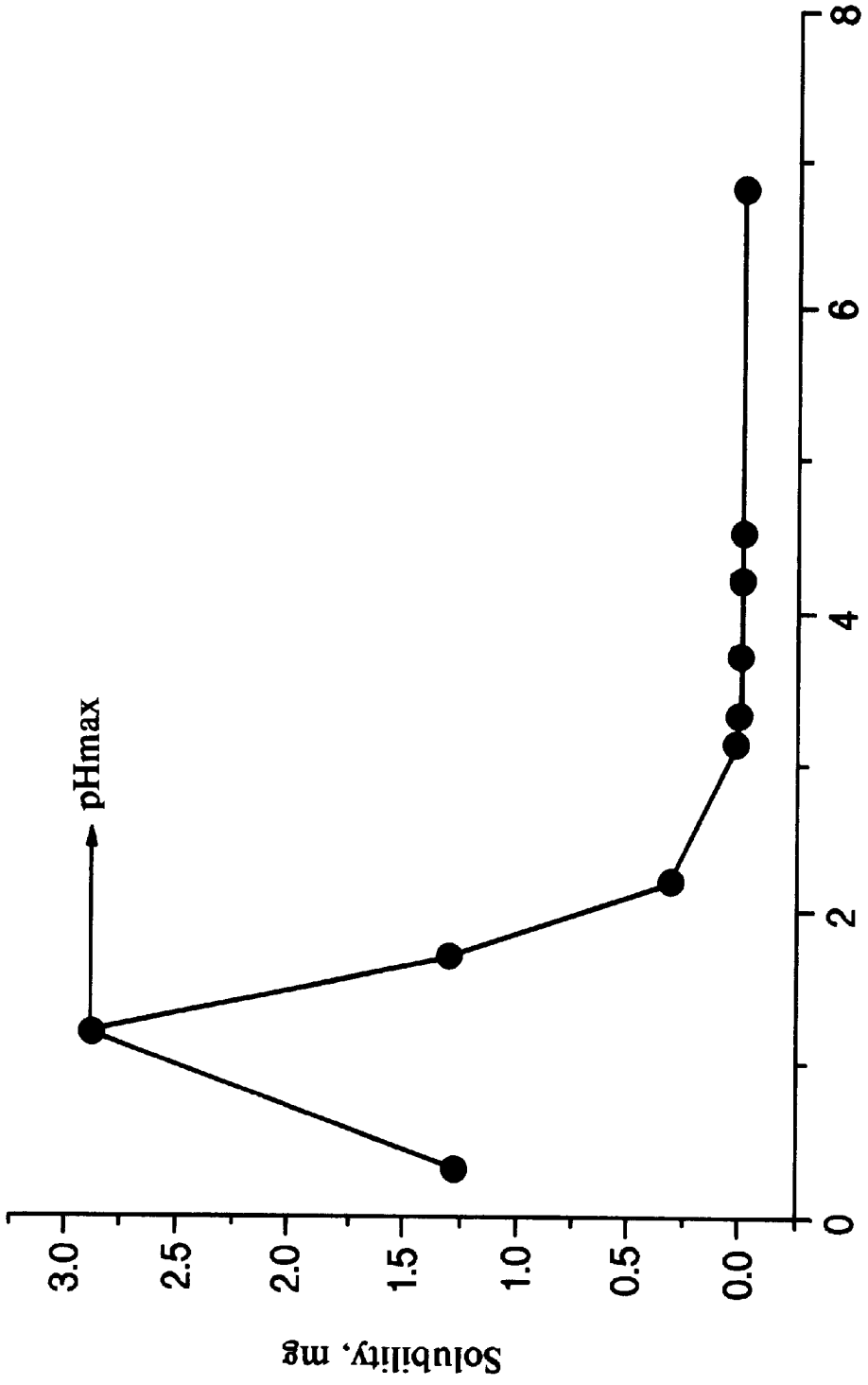


FIG. 1

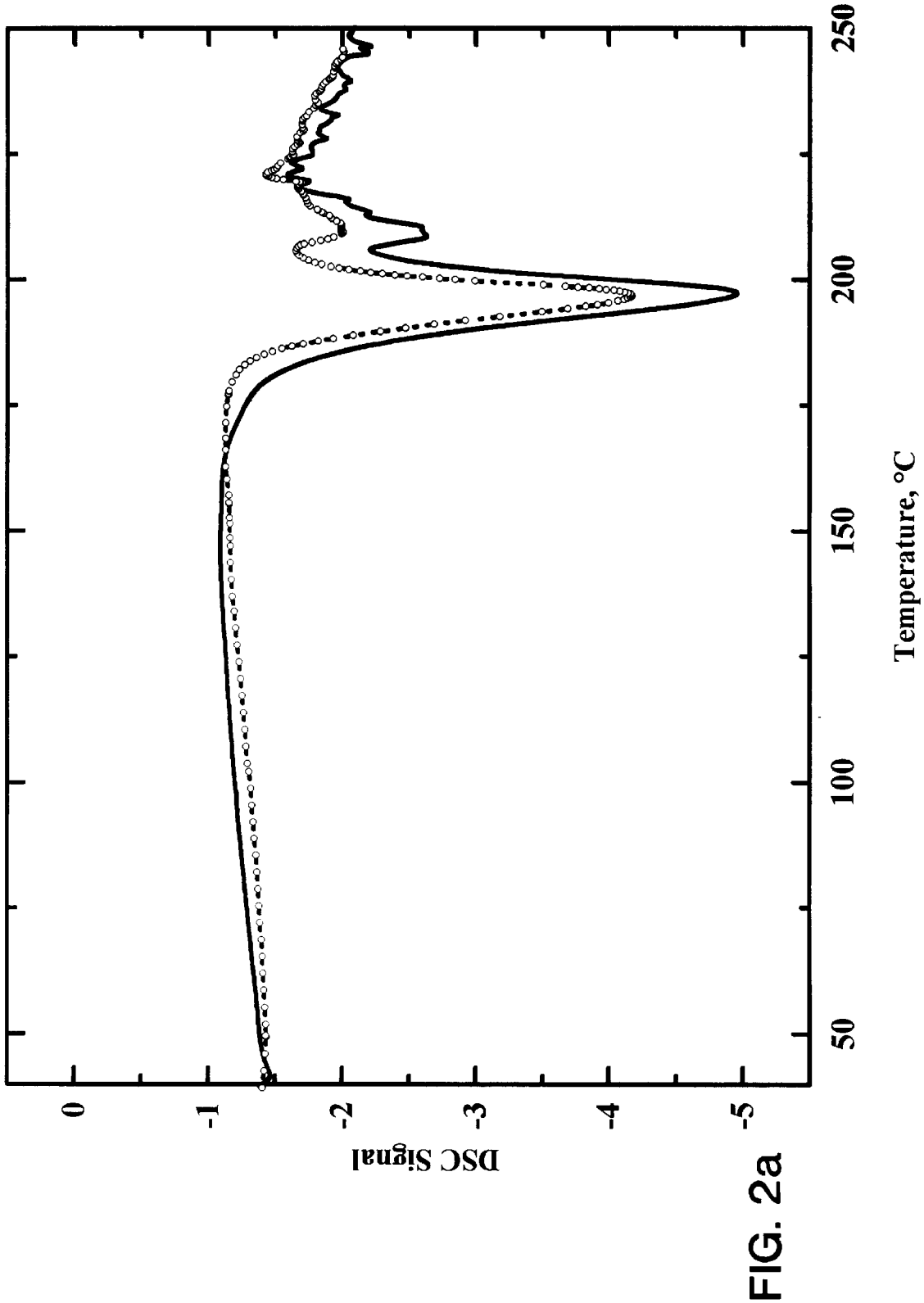


FIG. 2a

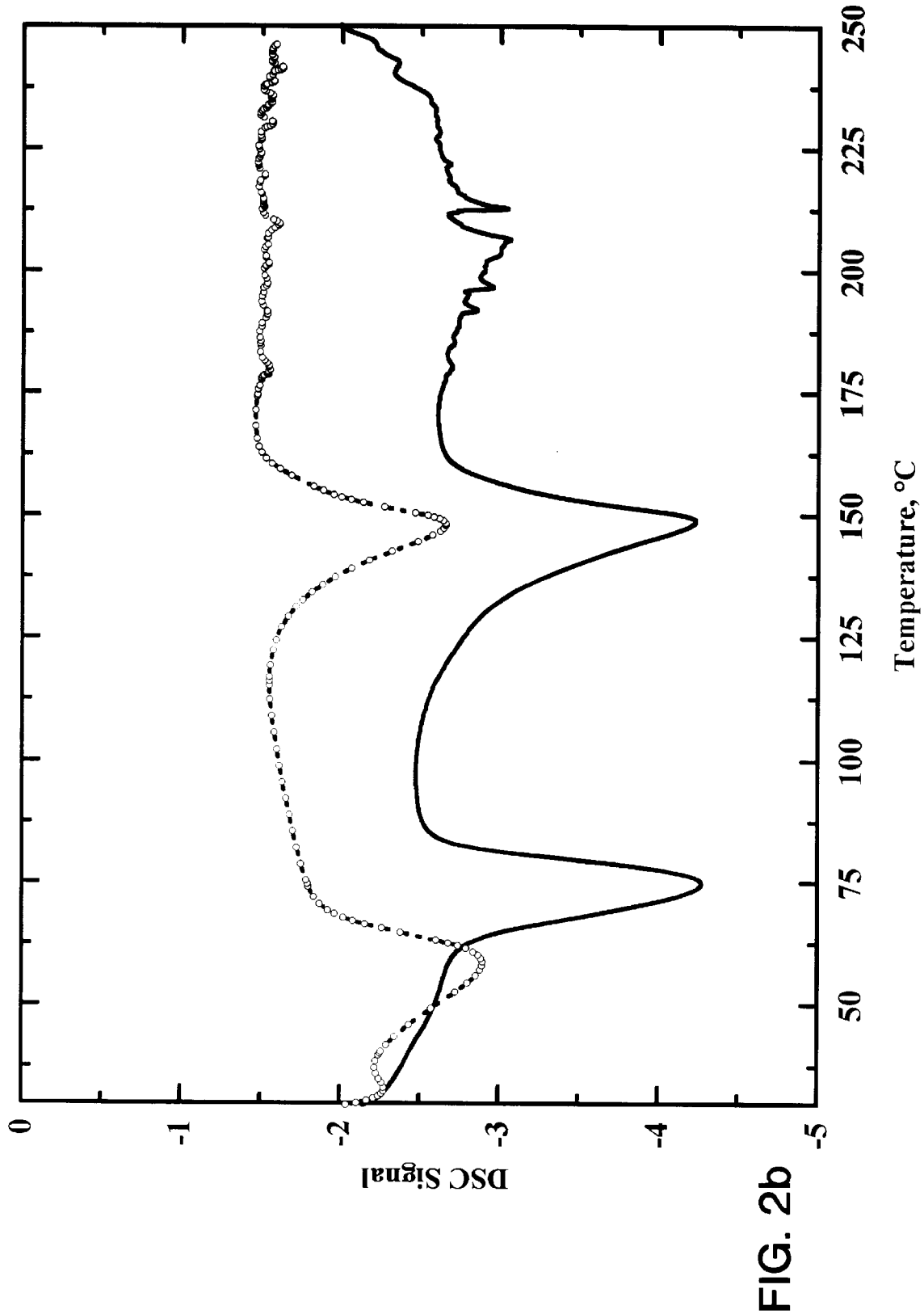
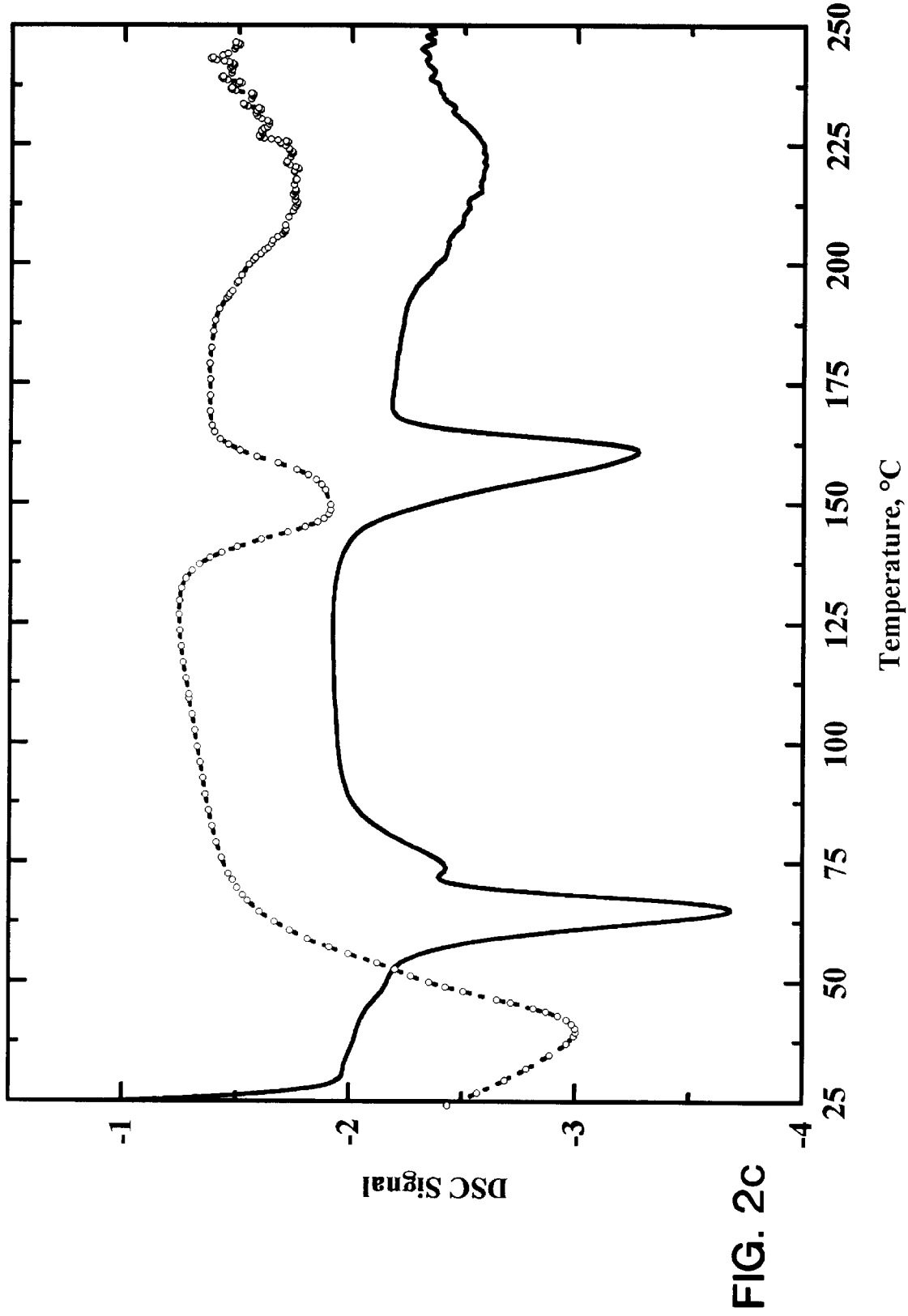

DSC Signal
0
-1
-2
-3
-4
-5
50
75
100
125
150
175
200
225
250
Temperature, °C

FIG. 2b


DSC Signal
-1
-2
-3
-4
25
50
75
100
125
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175
200
225
250
Temperature, °C

FIG. 2C

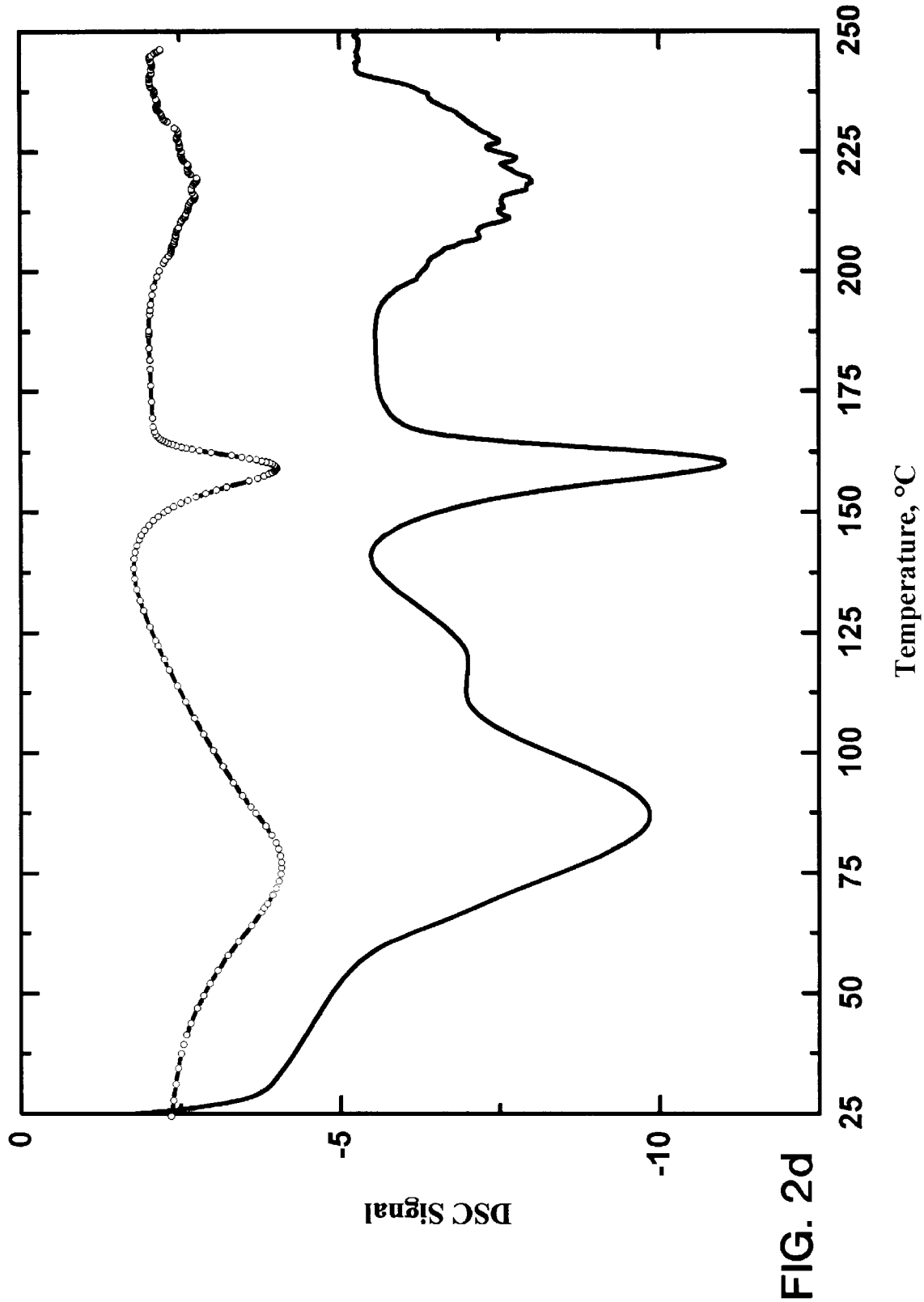

0
-5
-10
DSC Signal
25
50
75
100
125
150
175
200
225
250
Temperature, °C

FIG. 2d

BISULFATE SALT OF HIV PROTEASE INHIBITOR

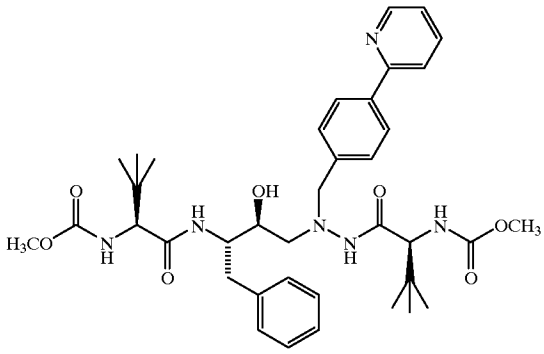
This application claims priority from Provisional Application 60/071,968 filed Jan. 20, 1998.

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

I

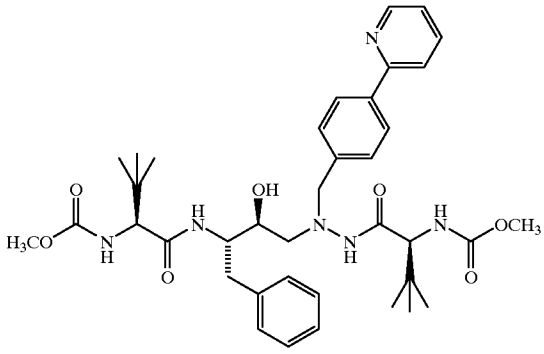


which exhibits unexpectedly superior aqueous solubility/dissolution behavior compared to other salts, and significantly improved oral bioavailability in animals compared to the free base. The bisulfate salt is thus useful for pharmaceutical dosage forms of the above-indicated protease inhibitor, particularly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

I



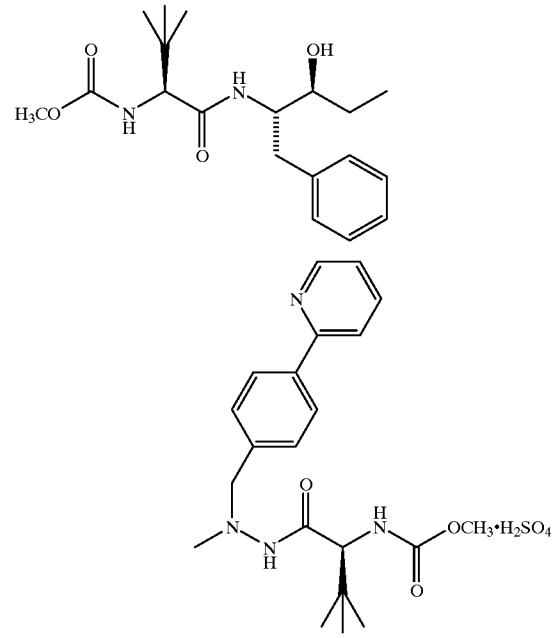
and the chemical name [3S-(3R*, 8'R*, 9'R*, 12R*)]-3,12-bis(1,1-dimethylethyl)-8-hydroxy-4,11-dioxo-9-(phenylmethyl)-6-[[4-(2-pyridinyl)phenylmethyl]-2,5,6,10,13-pentaazatetradecanedioic] acid, dimethyl ester and is under evaluation as a possible second generation HIV protease inhibitor.

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-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

II



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±3° 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 $pH>pH_{max}$ of a weakly basic organic compound, the equilibrium solid phase in an aqueous suspension of the compound is the free base. At $pH<pH_{max}$ 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±3° 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 occured 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 animals 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° C./75% relative humidity (RH) for as long as 9 months as shown in FIG. **2***a*. 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° 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° C./75% RH for as little as two weeks as shown in FIGS. **2***b, 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 apriori.

FIG. **2***a* represents Physical stability of the bisulfate salt. The solid line represents the unstressed material. The dotted line represents the material stressed at 40° C./75% RH for 9 months.

FIG. **2***b* represents Physical Stability of the hydrochloride salt. The solid line represents the unstressed material. The dotted line represents the material stressed at 40° C./75% RH for two weeks.

FIG. **2***c* represents Physical stability of the methane sulfonate salt. The solid line represents the unstressed material. The dotted line represents the material stressed at 40° C./75% RH for two weeks

FIG. **2***d* represents Physical stability of the sulfate salt. The solid line represents the unstressed material. The dotted line represents the material stressed at 40° 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

(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 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 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 $C_{38}H_{52}N_6O.1.0\ H_2SO_4$: 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 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 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. $C_{38}H_{52}N_6O_7.1.0\ H_2SO_4.0.2\ H_2O$: 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 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 $C_{38}H_{52}N_6O_7.1.0\ H_2SO_4.2.0\ H_2O$; 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 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 wet granulation with lactose, crospovidone and magnesium stearate.

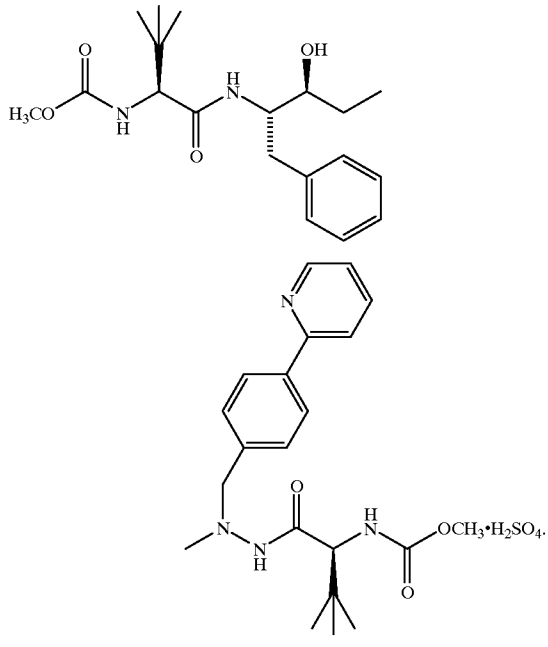
B. Capsules (100 mg free base equivalent)

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 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.

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