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*Attorneys for Plaintiffs
Merck, Sharp & Dohme
Corp. and Bristol-Myers
Squibb Company*

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

<hr/>)	
MERCK, SHARP & DOHME CORP., and)	
BRISTOL-MYERS SQUIBB COMPANY)	
	Plaintiffs,)	
v.)	Civil Action No. _____
)	
CIPLA USA, INC., and)	
CIPLA LIMITED)	
)	
	Defendants.)	
<hr/>)	

COMPLAINT FOR PATENT INFRINGEMENT

Plaintiffs Merck, Sharp & Dohme Corp. (“Merck”) and Bristol-Myers Squibb Company and Bristol-Myers Squibb Pharma Co. (collectively, “BMS”), by their undersigned attorneys and for their Complaint against Cipla USA, Inc. (“Cipla USA”) and Cipla Limited (collectively, “Defendants”), allege 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, § 100 *et seq.*, and in particular under 35 U.S.C. § 271(e). This action relates to Abbreviated New Drug Application (“ANDA”) No. 204766, which

Defendants filed or caused to be filed under 21 U.S.C. § 355(j) with the United States Food and Drug Administration (“FDA”) for approval to market a generic version of BMS’s successful Sustiva[®] tablets that are sold in the United States, including this District.

The Parties

2. Plaintiff Merck is a corporation organized and existing under the laws of the State of New Jersey, having a principal place of business at One Merck Dr., P.O. Box 100, Whitehouse Station, NJ 08889-0100.

3. Plaintiff Bristol-Myers Squibb Company is a corporation organized and existing under the laws of the State of Delaware, having its principal place of business at 345 Park Avenue, New York, NY 10154.

4. On information and belief, Cipla USA is a corporation organized and existing under the laws of the State of Delaware, having a principal place of business at 9100 S. Dadeland Blvd., Suite 1500, Miami, FL 33156.

5. On information and belief, Cipla Limited is an Indian corporation, having a principal place of business at Mumbai Central, Mumbai – 400 008, India.

6. On information and belief, Cipla USA acts as the agent of Cipla Limited.

Jurisdiction and Venue

7. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331, 1338(a), 1400(b), 2201 and 2202.

8. This Court has personal jurisdiction over Cipla Limited by virtue of, *inter alia*, Cipla Limited’s continuous and systematic contacts with New Jersey, and its course of conduct that is designed to cause the performance of acts that will result in foreseeable harm in New Jersey.

9. This Court has personal jurisdiction over Cipla USA by virtue of, *inter alia*, Cipla USA's presence in New Jersey, its continuous and systematic contacts with New Jersey, and its course of conduct that is designed to cause the performance of acts that will result in foreseeable harm in New Jersey.

10. Venue is proper in this judicial district pursuant to 28 U.S.C. §§ 1391 and 1400(b).

THE PATENTS

11. United States Patent No. 6,639,071 ("the '071 Patent"), entitled "Crystal Forms of (-)-6-Chloro-4-Cyclopropylethynyl-4-Trifluoromethyl-1,4-Dihydro-2H-3,1-Benzoxazin-2-One," was duly and legally issued by the United States Patent and Trademark Office ("USPTO") on October 28, 2003 to inventors Louis S. Crocker, Joseph L. Kukura, II, Andrew S. Thompson, Christine Stelmach, and Steven D. Young. The '071 Patent was assigned to Merck & Co., Inc., which subsequently changed the name for the assignee to Merck Sharp & Dohme Corp. At all times from the issuance of the '071 Patent to the present, Merck or one of its predecessors in interest has been the owner of the '071 Patent. Pursuant to an agreement entered into between Merck and The DuPont Merck Pharmaceutical Company ("DPMC"), whereas DPMC was ultimately acquired by BMS, BMS has substantial rights to the '071 Patent, including but not limited to, rights associated with being a licensee of the '071 Patent, and the right to sue for infringement of the '071 Patent. The '071 Patent is listed in the Approved Drug Products with Therapeutic Equivalence Evaluations ("FDA Orange Book") for Sustiva[®]. A true and correct copy of the '071 Patent is attached as Exhibit A.

12. United States Patent No. 6,939,964 ("the '964 Patent"), entitled "Crystal Forms of (-)-6-Chloro-4-Cyclopropylethynyl-4-Trifluoromethyl-1,4-Dihydro-2H-3,1-Benzoxazin-2-One," was duly and legally issued by the USPTO on September 6, 2005 to inventors Louis S. Crocker,

Joseph L. Kukura, II, Andrew S. Thompson, Christine Stelmach, and Steven D. Young. The '964 Patent claims priority to the '071 Patent. The '964 Patent was assigned to Merck & Co., Inc., which subsequently changed the name for the assignee to Merck Sharp & Dohme Corp. At all times from the issuance of the '964 Patent to the present, Merck or one of its predecessors in interest has been the owner of the '964 Patent. Pursuant to an agreement entered into between Merck and DPMC, whereas DPMC was ultimately acquired by BMS, BMS has substantial rights to the '964 Patent, including but not limited to, rights associated with being a licensee of the '964 Patent, and the right to sue for infringement of the '964 Patent. The '964 Patent is also listed in the FDA Orange Book for Sustiva[®]. A true and correct copy of the '964 Patent is attached as Exhibit B.

ACTS GIVING RISE TO THIS ACTION

13. By letter dated May 17, 2013, purporting to be a notice pursuant to 21 U.S.C. § 355(j)(2)(B)(ii) ("Notice Letter"), Defendants notified BMS and Merck (collectively, "Plaintiffs") that Defendants had submitted ANDA No. 204766 to the FDA under section 505(j) of the Federal Food Drug and Cosmetic Act (21 U.S.C. § 355(j)) seeking approval to engage in the commercial manufacture, importation, use, and sale of 600 mg efavirenz tablets ("Defendants' ANDA product") as a generic version of BMS's Sustiva[®] drug product.

14. Defendants' ANDA was submitted to obtain FDA approval to engage in the commercial manufacture, importation, use, sale, and/or importation of Defendants' ANDA product prior to the expiration of the '071 and '964 Patents. The '071 and '964 Patents are listed in the FDA Orange Book as being applicable to BMS's Sustiva[®] drug product.

15. On information and belief, Defendants intend to engage in the commercial manufacture, importation, use, and sale of Defendants' ANDA product promptly upon receiving FDA approval to do so.

16. In the Notice Letter, Defendants notified Plaintiffs that their ANDA contained a "paragraph IV" certification that, in Defendants' opinion, the '071 and '964 Patents are invalid and/or will not be infringed by the commercial manufacture, use, sale, offer to sale or importation of Defendants' ANDA product.

17. The Notice Letter also included an Offer of Confidential Access, pursuant to 21 U.S.C. § 355(j)(5)(C), to certain information from ANDA No. 204766 for the sole and exclusive purpose of determining whether an infringement action referred to in § 355(j)(5)(B)(iii) can be brought by Plaintiffs. Plaintiffs accepted this Offer of Confidential Access on or around June 7, 2013.

18. On information and belief, based in part on the information from ANDA No. 204766 received pursuant to the Office of Confidential Access, Defendants' ANDA product infringes one or more claims of the '071 and '964 Patents.

COUNT 1
Infringement of U.S. Patent No. 6,639,071

19. Plaintiffs repeat and re-allege paragraphs 1-18 above as if set forth herein.

20. By filing ANDA No. 204766 under 21 U.S.C. § 355(j) for the purposes of obtaining approval to engage in the commercial manufacture, use, sale, and/or importation of Defendants' ANDA product prior to the expiration date of the '071 Patent, Defendants have committed an act of infringement of the '071 Patent under 35 U.S.C. § 271(e)(2) and such infringement will cause Plaintiffs irreparable harm unless enjoined by this Court.

21. On information and belief, Defendants lacked a good faith basis for alleging invalidity and/or non-infringement when ANDA No. 204766 was filed and when the paragraph IV certification was made. Defendants' ANDA is a wholly unjustified infringement of the '071 Patent.

22. On information and belief, the commercial manufacture, use, sale, and/or importation of Defendants' ANDA product by Defendants will infringe, induce infringement, and/or contributorily infringe one or more claims of the '071 Patent literally or under the doctrine of equivalents.

COUNT 2
Infringement of U.S. Patent No. 6,939,964

23. Plaintiffs repeat and re-allege paragraphs 1-18 above as if set forth herein.

24. By filing ANDA No. 204766 under 21 U.S.C. § 355(j) for the purposes of obtaining approval to engage in the commercial manufacture, use, sale, and/or importation of Defendants' ANDA product prior to the expiration date of the '964 Patent, Defendants have committed an act of infringement of the '964 Patent under 35 U.S.C. § 271(e)(2) and such infringement will cause Plaintiffs irreparable harm unless enjoined by this Court.

25. On information and belief, Defendants lacked a good faith basis for alleging invalidity and/or non-infringement when ANDA No. 204766 was filed and when the paragraph IV certification was made. Defendants' ANDA is a wholly unjustified infringement of the '964 Patent.

26. On information and belief, the commercial manufacture, use, sale, and/or importation of Defendants' ANDA product by Defendants will infringe, induce infringement, and/or contributorily infringe one or more claims of the '964 Patent literally or under the doctrine of equivalents.

COUNT 3

Declaratory Judgment of Patent Infringement of U.S. Patent No. 6,639,071

27. Plaintiffs repeat and re-allege paragraphs 1-18 above as if set forth herein.

28. This claim arises under the Declaratory Judgment Act, 28 U.S.C. §§ 2201, 2202, based upon an actual controversy between the parties. Defendants have taken immediate and active steps to obtain FDA permission to sell in the United States and, after obtaining FDA permission, to commence the sale in the United States of Defendants' ANDA product before the expiration date of the '071 Patent. There is a real and actual controversy between the parties with respect to Defendants' activities and infringement of the '071 Patent.

29. The manufacture and/or sale of Defendants' ANDA product by Defendants during the term of the '071 Patent will constitute patent infringement of the '071 Patent under 35 U.S.C. § 271(a) and/or (b).

30. On information and belief, by seeking FDA approval for Defendants' ANDA product as described in ANDA No. 204766, Defendants intend to import into the United States and/or sell, offer to sell, and/or use within the United States, all for purposes not exempt under 35 U.S.C. § 271(e)(1), Defendants' ANDA product, which would infringe the '071 Patent.

31. Plaintiffs will be irreparably harmed if Defendants are not enjoined from infringing the '071 Patent.

COUNT 4

Declaratory Judgment of Patent Infringement of U.S. Patent No. 6,939,964

32. Plaintiffs repeat and re-allege paragraphs 1-18 above as if set forth herein.

33. This claim arises under the Declaratory Judgment Act, 28 U.S.C. §§ 2201, 2202, based upon an actual controversy between the parties. Defendants have taken immediate and active steps to obtain FDA permission to sell in the United States and, after obtaining FDA

permission, to commence the sale in the United States of Defendants' ANDA product prior to the expiration date of the '964 Patent. There is a real and actual controversy between the parties with respect to Defendants' activities and infringement of the '964 Patent.

34. The manufacture and sale of Defendants' ANDA product by Defendants during the term of the '964 Patent will constitute patent infringement of the '964 Patent under 35 U.S.C. § 271(a) and/or (b).

35. On information and belief, by seeking FDA approval for Defendants' ANDA product as described in ANDA No. 204766, Defendants intend to import into the United States and/or sell, offer to sell, and/or use within the United States, all for purposes not exempt under 35 U.S.C. § 271(e)(1), Defendants' ANDA product, which would infringe the '964 Patent.

36. Plaintiffs will be irreparably harmed if Defendants are not enjoined from infringing the '964 Patent.

Relief Requested

WHEREFORE, Plaintiffs respectfully pray for the following relief:

(a) A judgment that Defendants have infringed one or more claims of the '071 and '964 Patents by the filing of ANDA No. 204766;

(b) A judgment ordering that the effective date of any approval of Defendants' ANDA No. 204766 under Section 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)) be a date that is not earlier than the expiration date of the '071 and '964 Patents, or any later date of exclusivity to which BMS or Merck are or become entitled;

(c) A declaration and adjudication that Defendants will infringe the '071 and '964 Patents by their threatened acts of manufacture, importation, sale, offer for sale, and/or use of products covered by said patent prior to expiration date of said patent;

(d) A permanent injunction enjoining Defendants and their officers, agents, servants, employees, and privies from infringing the '071 and '964 Patents;

(e) Damages under 35 U.S.C. § 271(e)(4)(C), which this Court should treble pursuant to 35 U.S.C. § 284, if Defendants infringe the '071 and '964 Patents by engaging in the commercial manufacture, importation, use, sale, offer to sell, or import its ANDA product in/into the United States prior to the expiration of the '071 or '964 Patents or the expiration of any other exclusivity to which BMS or Merck become entitled;

(f) A judgment that this is an exceptional case and that Plaintiffs are entitled to an award of reasonable attorneys' fees pursuant to 35 U.S.C. § 285;

(g) Costs and expenses in this action; and

(h) Such other relief as this Court may deem just and proper.

RESPECTFULLY SUBMITTED,

Dated: June 27, 2013

s/Liza M. Walsh
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CERTIFICATION PURSUANT TO L. CIV. R. 11.2

Pursuant to Local Civil Rule 11.2, I hereby certify that the matter in controversy is the subject of the following pending actions:

MERCK, SHARP & DOHME CORP.; and BRISTOL-MYERS SQUIBB COMPANY v. TEVA PHARMACEUTICALS USA, INC.; and TEVA PHARMACEUTICAL INDUSTRIES, LTD., Case No. 10-CV-1851(RJS) (AJP) (Southern District of New York).

BRISTOL-MYERS SQUIBB COMPANY; and BRISTOL-MYERS SQUIBB PHARMA CO. v. MYLAN PHARMACEUTICALS INC.; and MATRIX LABORATORIES LTD. v. MERCK & CO., INC.; and MERCK SHARP & DOHME CORP., C.A. No. 09-651 (LPS) (District of Delaware).

MERCK, SHARP & DOHME CORP.; BRISTOL-MYERS SQUIBB COMPANY; and BRISTOL-MYERS SQUIBB PHARMA CO. v. HETERO USA INC. and HETERO LABS LIMITED UNIT-III, Civil Action No. 13-cv-01402 (JBS)(AMD) (District of New Jersey).

CONNELL FOLEY LLP

Dated: June 27, 2013

s/Liza M. Walsh
Liza M. Walsh

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RULE 201.1 CERTIFICATION

We hereby certify that the above-captioned matter is not subject to compulsory arbitration in that the plaintiffs seek, *inter alia*, injunctive relief.

CONNELL FOLEY LLP

Dated: June 27, 2013

s/Liza M. Walsh
Liza M. Walsh

EXHIBIT A



US006639071B2

(12) **United States Patent**
Crocker et al.

(10) **Patent No.:** **US 6,639,071 B2**
(45) **Date of Patent:** **Oct. 28, 2003**

(54) **CRYSTAL FORMS OF (-)-6-CHLORO-4-CYCLOPROPYLETHYNYL-4-TRIFLUOROMETHYL-1,4-DIHYDRO-2H-3,1-BENZOXAZIN-2-ONE**

5,519,021 A 5/1996 Young et al. 514/230.5
5,633,405 A 5/1997 Thompson et al. 564/321
5,663,467 A 9/1997 Thompson et al. 585/359

FOREIGN PATENT DOCUMENTS

(75) Inventors: **Louis S. Crocker**, Belle Mead, NJ (US); **Joseph L. Kukura, II**, Somerset, NJ (US); **Andrew S. Thompson**, Mountainside, NJ (US); **Christine Stelmach**, Westfield, NJ (US); **Steven D. Young**, Lansdale, PA (US)

EP 0 169 618 1/1986
EP 0 582 455 1/1994
WO WO 95/20389 8/1995
WO WO 98/45278 10/1995
WO WO 96/37457 11/1996
WO WO 98/04535 2/1998
WO WO 98/14436 4/1998
WO WO 99/64405 12/1999

(73) Assignee: **Merck & Co., Inc.**, Rahway, NJ (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 25 days.

(21) Appl. No.: **10/000,537**

(22) Filed: **Oct. 19, 2001**

(65) **Prior Publication Data**

US 2002/0115664 A1 Aug. 22, 2002

Related U.S. Application Data

(60) Continuation of application No. 09/282,744, filed on Mar. 31, 1999, now abandoned, which is a division of application No. 09/008,824, filed on Jan. 20, 1998, now Pat. No. 5,965,729.

(60) Provisional application No. 60/037,385, filed on Feb. 5, 1997, and provisional application No. 60/042,807, filed on Apr. 8, 1997.

(51) **Int. Cl.⁷** **C07D 265/18**

(52) **U.S. Cl.** **544/92**

(58) **Field of Search** 544/92

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,518,597 A 5/1985 Narr et al. 514/228

OTHER PUBLICATIONS

T. L. Threifall, "Analysis of Organic Polymorphs", *Analyst*, vol. 120, pp. 2435-2460 (Oct. 1995).

D. Giron, "Thermal Analysis and calorimetric methods in the characterization of polymorphs and solvates", *Thermochimica Acta*, vol. 248, pp. 1-59 (1995).

A. S. Thompson et al., "Use of an Ephedrine Alkoxide to Mediate Enantioselective Addition of an Acetylide to a Prochiral Ketone: Assymmetric Synthesis of the Reverse Transcriptase Inhibitor L-743,726", *Tetrahedron Letters*, vol. 36, No. 49, pp. 8937-8940 (1995).

Primary Examiner—Richard L. Raymond

(74) *Attorney, Agent, or Firm*—Kenneth R. Walton; Melvin Winokur; Valerie J. Camara

(57) **ABSTRACT**

The instant invention describes a method for crystallizing (-)-6-chloro-4-cyclopropylethynyl-4-trifluoromethyl-1,4-dihydro-2H-3,1-benzoxazin-2-one from a solvent and anti-solvent system and producing the crystalline product. The desired final crystal form, Form I, can be produced when using methanol or ethanol. Form II is isolated from 2-propanol and can be converted to the desired crystal form at low drying temperatures, such as between about a temperature of 40° C. and 50° C.

11 Claims, 6 Drawing Sheets

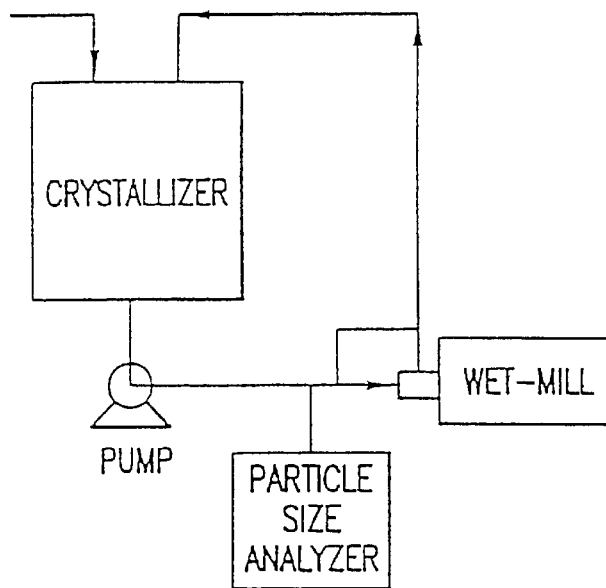


FIG. 1

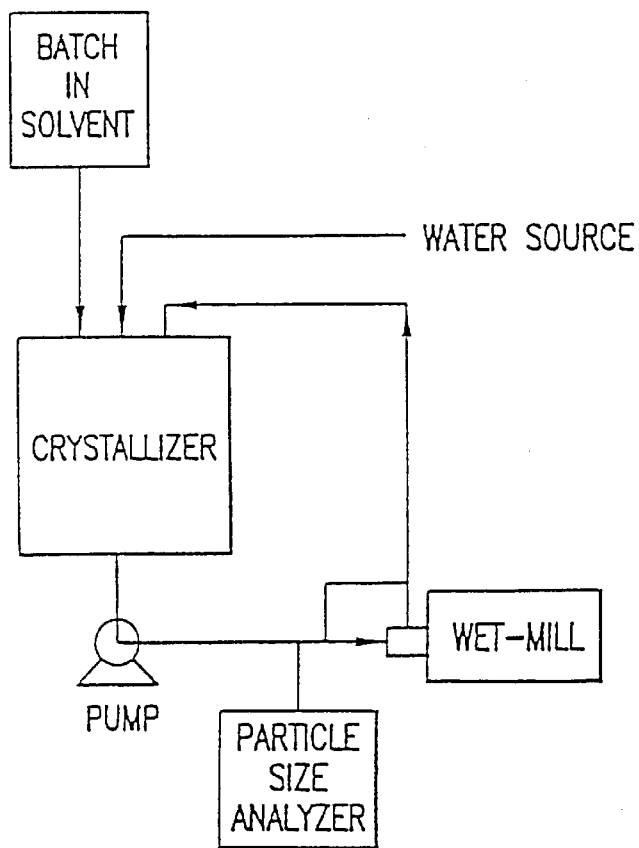


FIG. 2

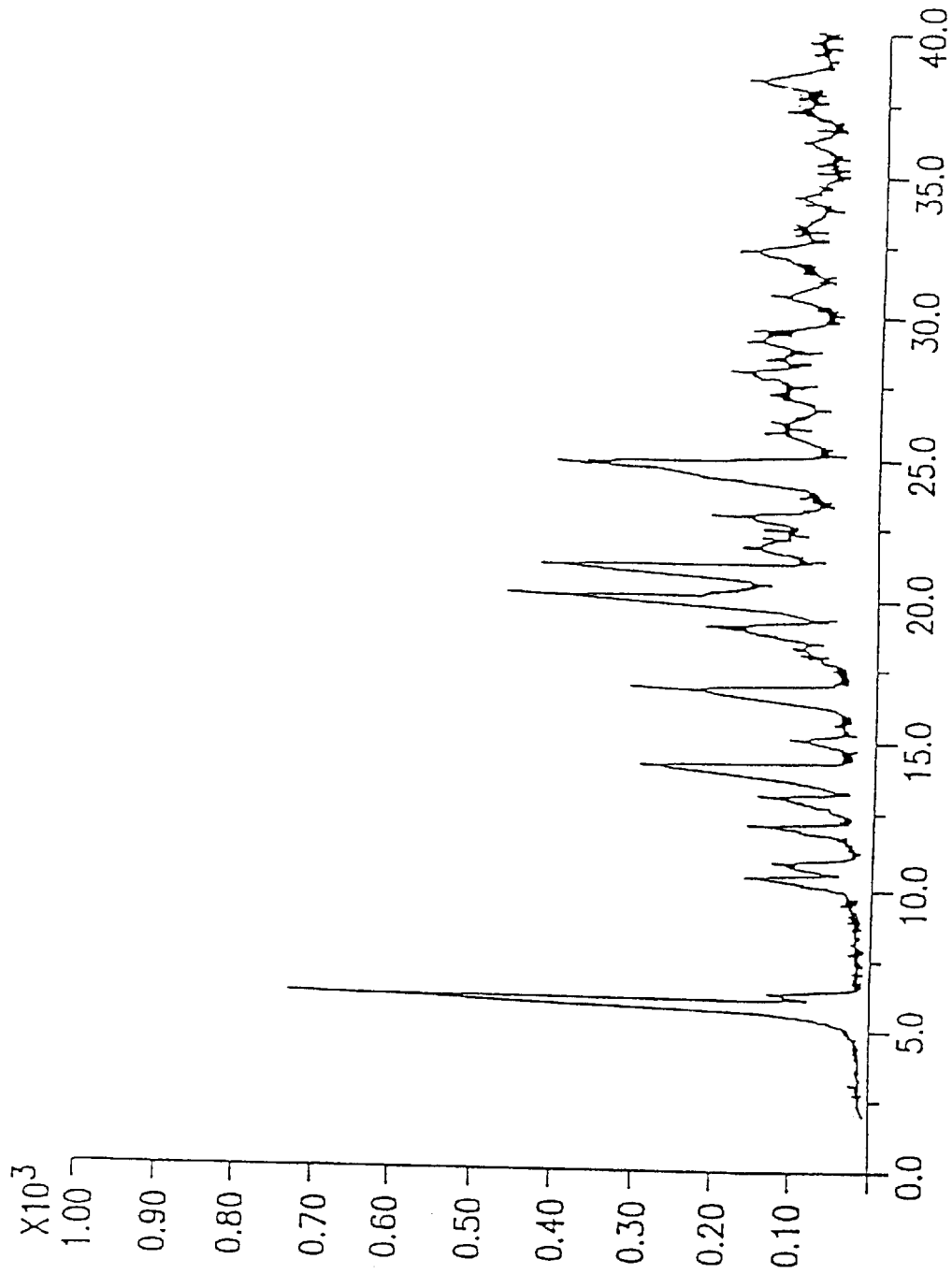


FIG. 3

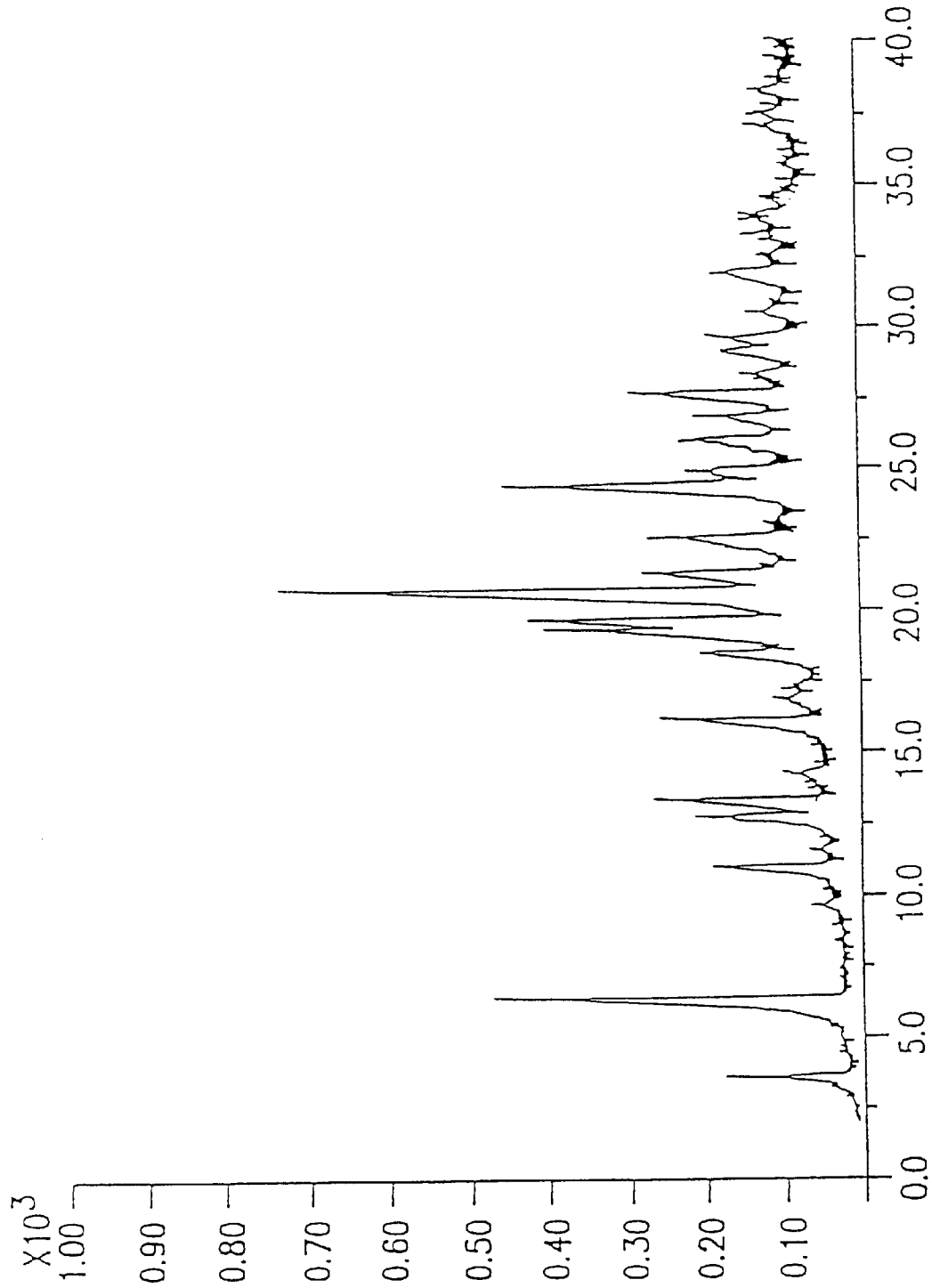


FIG. 4

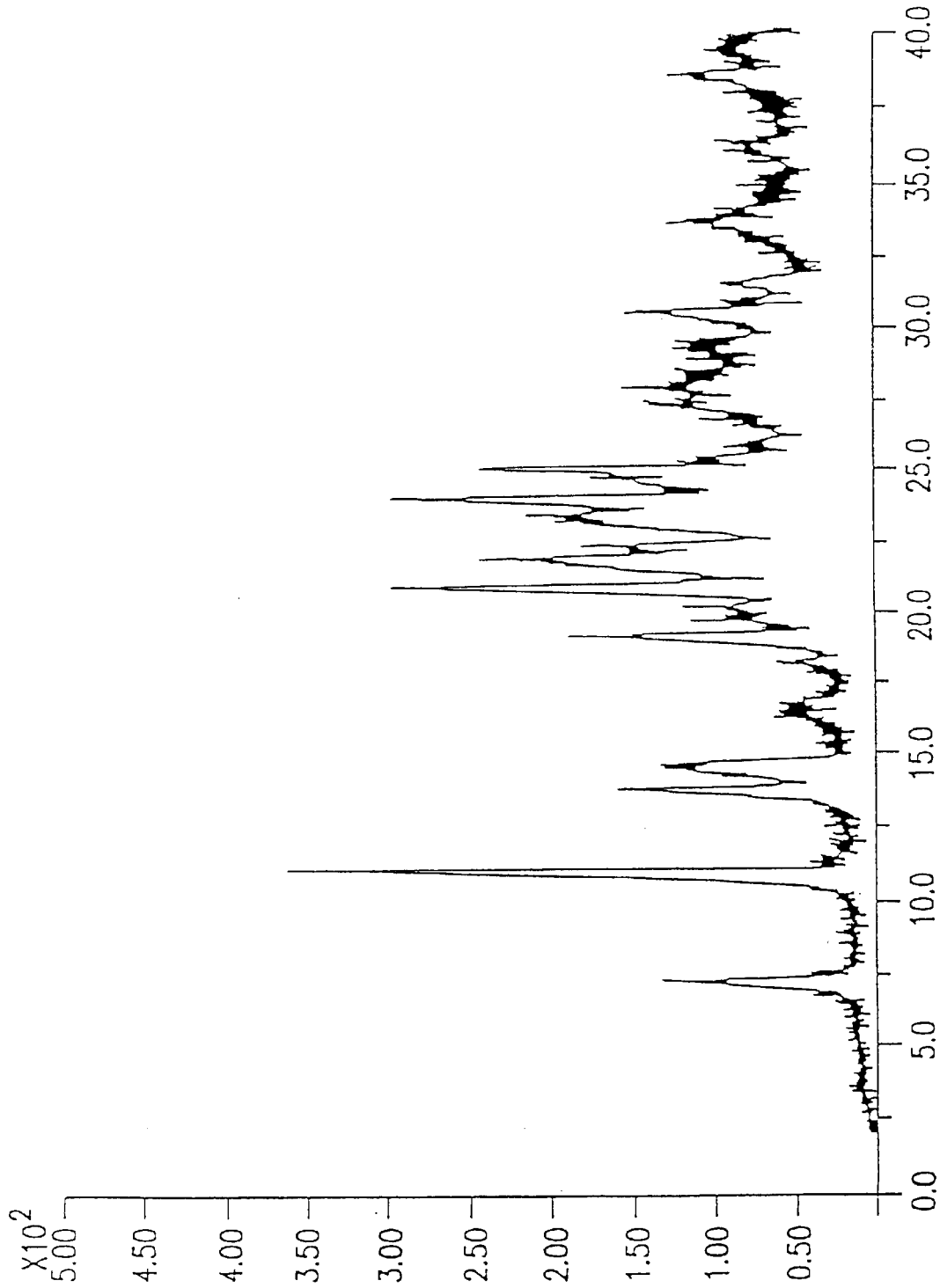


FIG.5

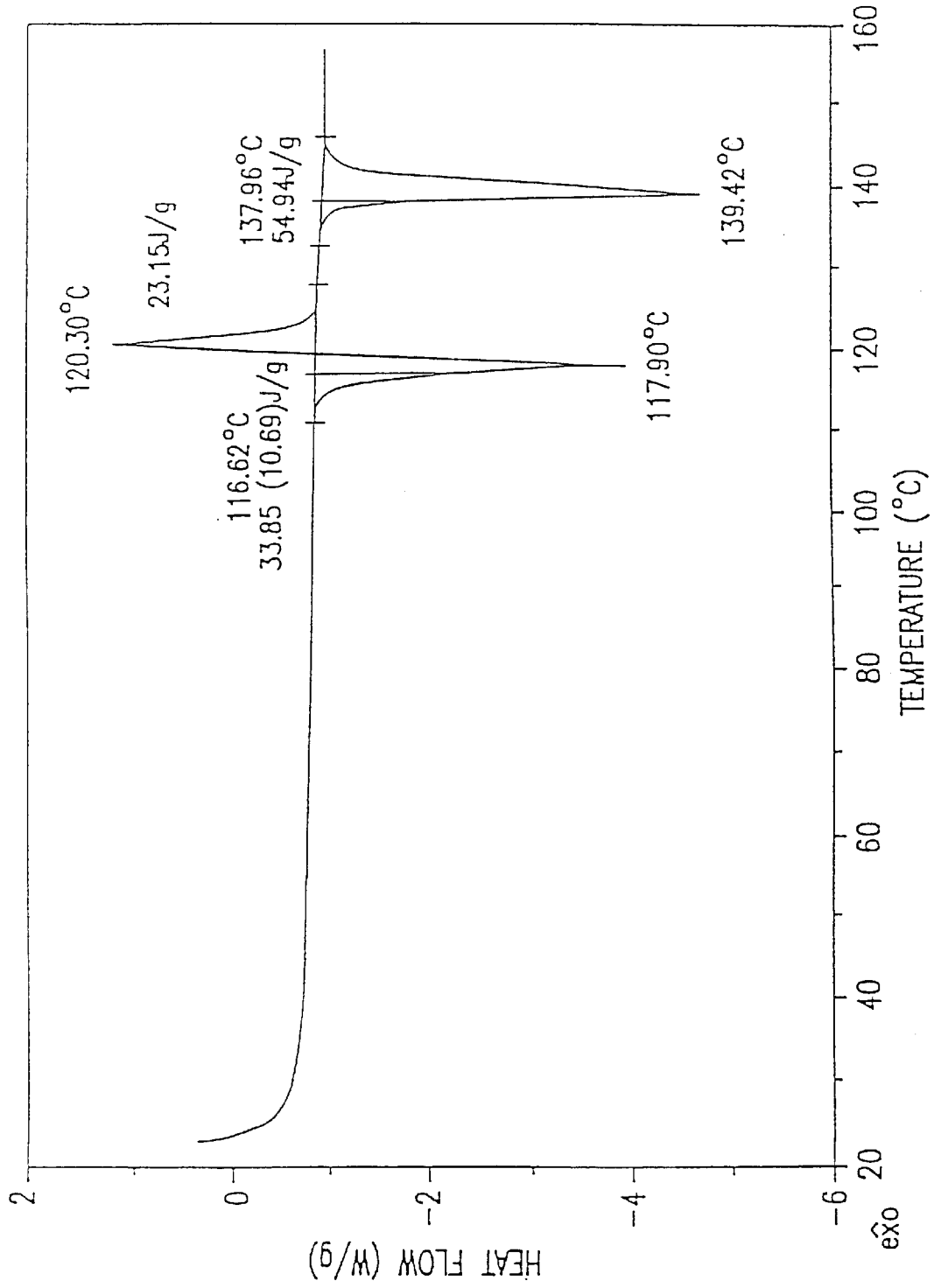


FIG. 6

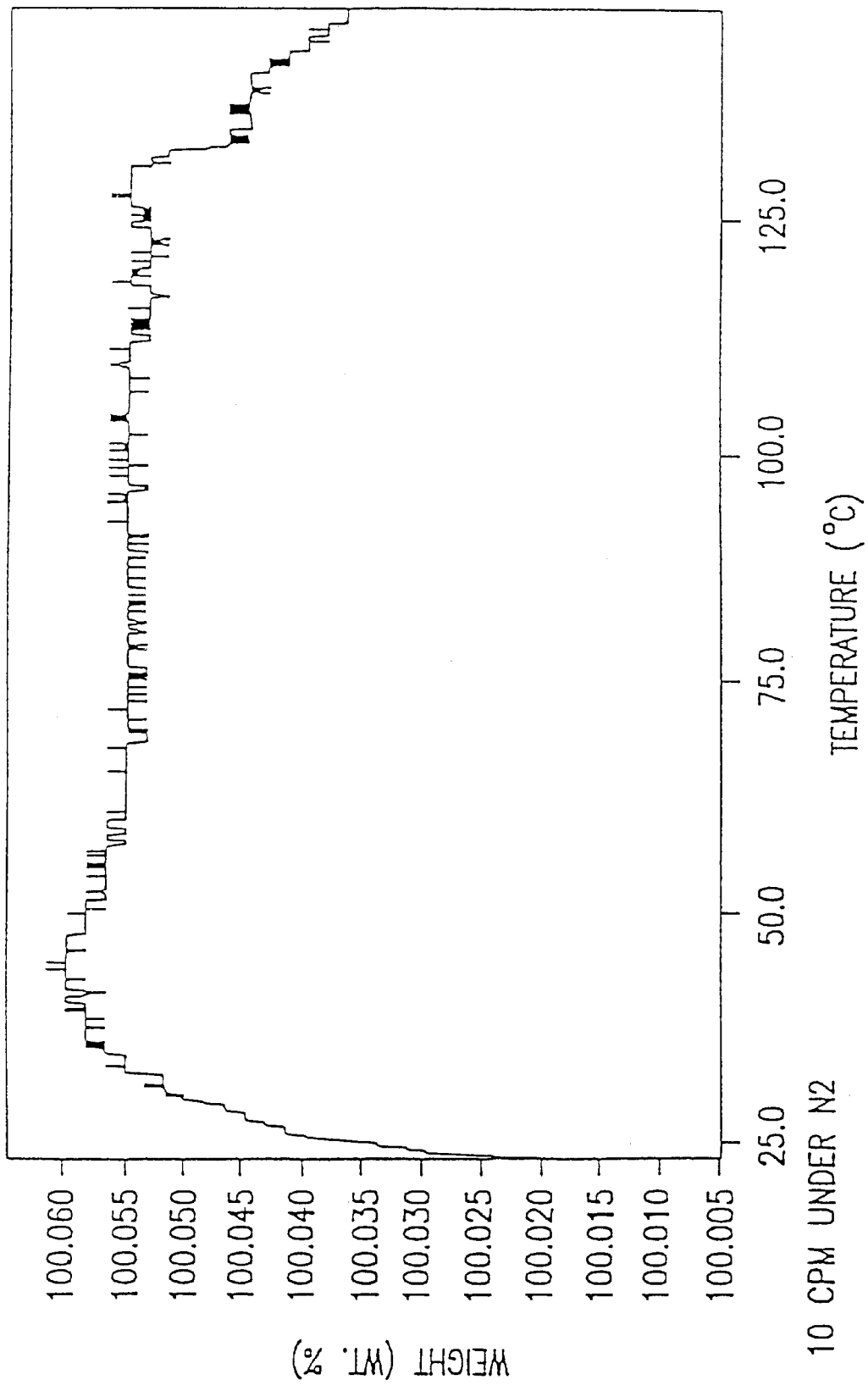


FIG. 7

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CRYSTAL FORMS OF (-)-6-CHLORO-4-CYCLOPROPYLETHYNYL-4-TRIFLUOROMETHYL-1,4-DIHYDRO-2H-3,1-BENZOXAZIN-2-ONE

This is a division of application Ser. No. 09/282,744 filed, now abandoned, Mar. 31, 1999, which is a divisional of U.S. application Ser. No. 09/008,824, filed Jan. 20, 1998, now U.S. Pat. No. 5,965,729, which claims the benefit of U.S. provisional application Serial Nos. 60/037,385, filed Feb. 5, 1997 and 60/042,807, filed Apr. 8, 1997.

BACKGROUND OF THE INVENTION

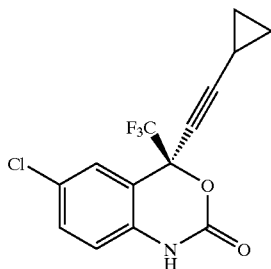
The synthesis of the reverse transcriptase inhibitor (RTI), (-)-6-chloro-4-cyclopropylethynyl-4-trifluoromethyl-1,4-dihydro-2H-3,1-benzoxazin-2-one, also known as DMP-266 has been described in U.S. Pat. No. 5,519,021 issued on May 21, 1996 and the corresponding PCT International Patent Application WO 95/20389, which published on Aug. 3, 1995. Additionally, the asymmetric synthesis of an enantiomeric benzoxazinone by a highly enantioselective acetylide addition and cyclization sequence has been described by Thompson, et al., *Tetrahedron Letters* 1995, 36, 937-940, as well as the PCT publication, WO 96/37457, which published on Nov. 28, 1996.

The compound was previously crystallized from a heptanetetrahydrofuran (THF) solvent system. The crystallization procedure required the use of high temperatures (about 90° C.) to dissolve the final product. Crystals formed by nucleation during the cooling process. The crystals which were produced were Form II and are converted to the desired Form I while drying under vacuum at 90° C. This crystallization provided minimal purification and produced material with inconsistent physical properties. The final product slurry was extremely difficult to mix and handle due to its high viscosity and heterogeneous nature.

The instant invention describes a method for crystallizing (-)-6-chloro-4-cyclopropylethynyl-4-trifluoromethyl-1,4-dihydro-2H-3,1-benzoxazin-2-one from a solvent and anti-solvent system and producing the crystalline product. The desired final crystal form, Form I, can be produced when using methanol or ethanol. Form II is isolated from 2-propanol and can be converted to the desired crystal form at low drying temperatures, as low as 40° C.

SUMMARY OF THE INVENTION

A process for the crystallization of a compound of the structural formula



comprising the use of a solvent to effect the dissolution of the compound followed by the addition of an anti-solvent to initiate the crystallization.

BRIEF DESCRIPTION OF THE FIGURES

FIG. 1. Flowsheet of the controlled anti-solvent addition crystallization method.

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FIG. 2. Flowsheet of the heel crystallization method.

FIG. 3. X-ray powder diffraction pattern for Form I of (-)-6-chloro-4-cyclopropylethynyl-4-trifluoromethyl-1,4-dihydro-2H-3,1-benzoxazin-2-one.

FIG. 4. X-ray powder diffraction pattern for Form II of (-)-6-chloro-4-cyclopropylethynyl-4-trifluoromethyl-1,4-dihydro-2H-3,1-benzoxazin-2-one.

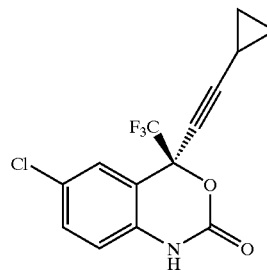
FIG. 5. X-ray powder diffraction pattern for Form III of (-)-6-chloro-4-cyclopropylethynyl-4-trifluoromethyl-1,4-dihydro-2H-3,1-benzoxazin-2-one.

FIG. 6. DSC curve for Form m of (-)-6-chloro-4-cyclopropylethynyl-4-trifluoromethyl-1,4-dihydro-2H-3,1-benzoxazin-2-one.

FIG. 7. TG analysis for Form III of (-)-6-chloro-4-cyclopropylethynyl-4-trifluoromethyl-1,4-dihydro-2H-3,1-benzoxazin-2-one.

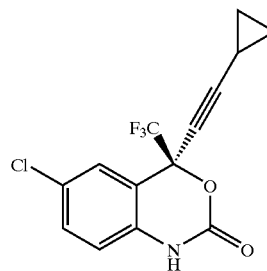
DETAILED DESCRIPTION OF THE INVENTION

A process for the crystallization of a compound of the structural formula



comprising the use of a solvent to effect the dissolution of the compound followed by the addition of an anti-solvent to initiate crystallization.

A process for the crystallization of a compound of the structural formula



comprising the steps of:

- (1) dissolving the compound in a solvent in a ratio of about 3.0 ml to about 10.0 ml of solvent to 1 gram of the compound;
- (2) filtering the solution of the compound to remove any particulate matter;
- (3) adding the anti-solvent to the stirring solution at room temperature over a period of about 30 minutes to about an hour to reach the saturation point of the solution containing the compound;
- (4) adding to the solution a solid seed charge of the compound in the amount of about 2 to about 10 percent by weight to form a slurry;
- (5) milling the slurry to reduce the thickness of the slurry;

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- (6) adding the remaining water to reach the desired solvent composition of about 30% to about 50% and milling the slurry as needed during the addition;
- (7) slowly cooling the slurry to about 5° C. to about 20° C.;
- (8) aging for about 2 to about 16 hours until the supernatant concentration reaches equilibrium;
- (9) milling the slurry, as needed, to reduce the thickness of the slurry;
- (10) filtering the milled slurry to isolate a wet cake of the crystalline compound;
- (11) washing the wetcake once with about 1 to about 2 bed volumes of the final crystallization solvent composition and then twice with water using about 5–10 ml water per gram of compound; and
- (12) drying the washed wetcake at about 40° C. to about 90° C. under vacuum for about 1 hour to about 3 days, or until the loss on dryness is less than 0.5 weight percent.

The controlled anti-solvent crystallization process as recited above wherein the solvent is defined as alcohol, wherein alcohol is a straight or branched chain (C₁–C₆)-alkanol. A preferred embodiment of the solvents useful in the controlled anti-solvent crystallization process is (C₁–C₆)-alkanol, such as, methanol, ethanol, and 2-propanol. The preferred alcohol is 2-propanol.

The preferred alcohol is 2-propanol for reasons relating to obtaining consistent crystal forms. Although methanol and ethanol solvent systems have been shown to be capable of producing the desired Form I crystal structure, a slight contamination of Form III crystals in a crystallization slurry in these systems can convert the entire slurry to containing exclusively Form III crystals, which are relatively difficult to convert to the desired Form I structure. Any known crystal structure of this compound placed in an about 25% to 35% (v/v) 2-propanol water solvent system has been shown to quickly convert to the Form II crystal structure, which can readily convert to the desired Form I crystal structure during drying.

The anti-solvent as recited above is defined as a solvent in which the compound has limited solubility. In the instant process, the preferred anti-solvent is water.

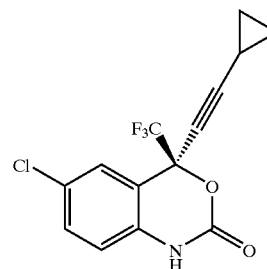
The temperature of the solution during the anti-solvent addition (Step 3) was about 20° C. to about 25° C. The temperature of the slurry being about 5° C. to about 20° C., and preferably at about 10° C.

The temperature used during the drying of the washed wetcake (Step 12) is about 40° C. to about 90° C., and preferably about 40° C. to about 60° C.

The solvent system (solvent plus anti-solvent) used ranged from about 30% to about 50% solvent volume to anti-solvent volume (v/v) ratio. The total volume of the solvent system ranging from about 12 to about 20 ml of the solvent system per gram of the compound. The solvent volume to anti-solvent volume ratio for selected solvent systems is as follows: 1) an ethanol-water solvent system is about 30% to about 40% ethanol to water v/v ratio; 2) a methanol-water solvent system is about 40% to about 50% methanol to water v/v ratio; and 3) an 2 propanol-water solvent system is about 25% to about 35% 2-propanol to water v/v ratio. The preferred solvent system is 2-propanol-water used in about a 30% volume to volume ratio and a total solvent system volume of about 15 ml per gram of the compound.

A process for the crystallization of a compound of the structural formula

4



comprising the steps of:

- (1) mixing about 10% to about 20% by weight of the final amount of (-)-6-chloro-4-cyclopropylethynyl-4-trifluoromethyl-1,4-dihydro-2H-3,1-benzoxazin-2-one in the desired v/v ratio of solvent to anti-solvent at about 20° C. to form the heel or retaining a final slurry from a previous batch;
- (2) adding the solution of solvent and (-)-6-chloro-4-cyclopropylethynyl-4-trifluoromethyl-1,4-dihydro-2H-3,1-benzoxazin-2-one, and anti-solvent to the heel simultaneously at constant rates over about 6 hours maintaining the v/v ratio of solvent to anti-solvent;
- (3) milling the slurry during the addition to reduce the thickness of the slurry;
- (4) cooling the slurry to about 10° C. over about 3 hours and aging slurry until the supernatant concentration reaches equilibrium;
- (5) filtering the milled slurry to isolate a wet cake of the crystalline compound;
- (6) washing the wetcake once with about 1 to about 2 bed volumes of the final crystallization solvent composition and then twice with water using about 5 ml to about 10 ml water per gram of compound; and
- (7) drying the washed wetcake at about 40° C. to about 90° C. under vacuum for about 1 hour to about 3 days, or until the loss on dryness is less than 0.5 weight percent.

The heel crystallization process as recited above wherein the solvent is defined as acetonitrile, dimethyl acetamide, dimethyl formamide or alcohol. A preferred embodiment of the solvents useful in the controlled anti-solvent crystallization process is alcohol, wherein alcohol is defined as (C₁–C₆)-alkanol, such as, methanol, ethanol, and 2 propanol. The preferred alcohol is 2-propanol.

The anti-solvent as recited above is defined as a solvent in which the compound has limited solubility. In the heel crystallization process the preferred anti-solvent is water.

The process as recited above wherein the temperature of the solution during the anti-solvent addition is about 5° C. to about 20° C.

The temperature used during the drying of the washed wetcake is about 40° C. to about 90° C., and preferably about 40° C. to about 60° C.

The solvent system (solvent plus anti-solvent) used ranges from about 30% to about 50% solvent volume to anti-solvent volume (v/v) ratio. The total volume of the solvent system ranging from about 12 to about 20 ml of the solvent system per gram of the compound. The solvent to anti-solvent volume to volume ratio for selected solvent systems is as follows: 1) an ethanol-water solvent system is about 30% to about 40% ethanol to water v/v ratio; 2) a methanol-water solvent system is about 40% to about 50% methanol to water v/v ratio; and 3) an 2-propanol-water solvent

system is about 25% to about 35% 2-propanol to water v/v ratio. The preferred solvent system is 2-propanol-water used in about a 30% volume to volume ratio and a total solvent system volume of about 15 ml per gram of the compound.

FIGS. 3, 4 and 5 are the X-ray powder diffraction (XRPD) patterns for Forms I, II and III, respectively. These XRPD patterns were recorded using an automated X-ray diffractometer APD 3720 with copper K alpha radiation. The crystal forms I and II of (-)-6-chloro-4-cyclopropylethynyl-4-trifluoromethyl-1,4-dihydro-2H-3,1-benzoxazin-2-one which are characterized by the noted X-ray powder diffraction patterns have the following key diffraction peaks (2θ) with intensities (I/I_{max} , %) of 10 or greater:

Form I	Form II	Form III
6.0800	3.6375	7.2150
6.3900	6.3325	10.9675
10.3950	11.0725	13.7275
10.9875	12.7750	14.5325
12.2850	13.3275	16.7275
13.1900	14.2925	19.0675
14.1700	16.1200	19.6550
15.1925	16.8975	20.8250
16.9000	18.5025	21.7450
18.4375	19.1975	22.2825
19.2275	19.6025	22.8475
20.0925	20.6650	23.1750
21.2100	21.3250	23.8850
22.3600	22.6150	24.4900
23.0725	23.1775	24.9075
24.8900	24.4075	25.8200
25.9500	24.9650	27.0325
26.3575	26.0100	27.6050
27.2550	26.8550	29.2975
28.1150	27.6400	30.2600
28.5850	28.3675	30.7300
29.1325	29.1725	31.3125
29.5625	29.6325	33.3975
30.6850	30.5650	38.4325
32.3725	31.8950	39.2100
38.3125	33.8225	

Additionally, these crystal forms are characterized by peaks with varying D-spacings. Form I is characterized by peaks with D-spacings of: 14.5, 8.5, 8.0, 7.2, 6.7, 6.2, 5.2, 4.6, 4.4, 4.2, and 3.6 angstroms. Form II is characterized by peaks with D-spacings of: 24.3, 13.9, 8.0, 6.9, 6.6, 5.5, 4.6, 4.5, 4.3, 4.2, 3.9, 3.6, 3.4, 3.3, and 3.2 angstroms. Form III is characterized by peaks with D-spacings of: 12.2, 8.1, 6.4, 6.1, 4.7, 4.3, 4.1, 4.0, 3.9, 3.8, 3.7, 3.6, 3.3, 3.2, and 3.0 angstroms.

Thermogravimetric analysis results of Form III (FIG. 7) indicated there was no significant weight loss observed from 43° C. to about 137° C. This result is indicative of an anhydrous or unsolvated crystal form.

The differential scanning calorimetry (DSC) results obtained for Form III show an endotherm with an extrapolated onset temperature of 117° C., a peak temperature of 118° C., and an enthalpy of 34 J/g, this is followed by an exotherm with a peak temperature of 120° C. and an enthalpy of 23 J/g. A second endotherm with an extrapolated onset temperature of 138° C., a peak temperature of 139° C., and an enthalpy of 55 J/g is also observed. The first endotherm is associated with the melting of Form III, which subsequently crystallizes to Form I during the exothermic event. The second endothermic event is associated with the melting of Form I.

A process for isolating (-)-6-chloro-4-cyclopropylethynyl-4-trifluoromethyl-1,4-dihydro-2H-3,1-benzoxazin-2-one, the final product from solutions contain-

ing an organic solvent-and water has been developed. In this process water serves as an anti-solvent to produce a solid product from material dissolved in organic solvent. The final solvent composition is chosen to balance yield loss, purification, and slurry handling properties.

For methanol solvent systems about 40% to about 50% volume to volume (v/v) solvent to anti-solvent (water) has been present in the final slurry. Ethanol solvent systems have contained about 30% to about 40% v/v solvent to anti-solvent, and 2-propanol solvent systems have used about 25% to about 35% (v/v) solvent to anti-solvent. The total amount of liquid (alcohol and water) ranges from 12–20 ml/(g solid). The crystallizations are typically performed between 20–25° C., and some slurries have been cooled to 5–10° C. before being filtered. Following the filtration, the wetcake is washed with approximately one bed volume (the approximate volume of the wetcake) of the final crystallization solvent composition. The wetcake is then washed with at least 2 bed volumes of deionized (DI) water.

The rate at which the product is precipitated is controlled by either slowly adding the water to a saturated system following a seed charge (anti-solvent addition) or simultaneously adding the product in alcohol and water at controlled rates to an existing product slurry (heel crystallization).

For the anti-solvent process (FIG. 1), enough water is first added to the organic solvent solution containing the product over 0.5–2 hours to saturate the system in final product. A solid charge of final product is then added to the system as seed (2–10% of the initial amount of product). The seed should be Form I (the crystal form associated with dry final product) for ethanol and methanol systems, and Form II seed (the crystal form generated from a THF/eptane crystallization) is used for 2-propanol systems. The resultant slurry is aged for 0.5–2 hours to establish a seed bed. The remaining water is then added over 2–4 hours in a controlled manner. The slurry is then aged for 2–20 hours and cooled to the desired final temperature during the age, allowing the supernatant to reach equilibrium.

For the heel process (FIG. 2), a slurry at the desired final solvent composition is mixed while adding the product dissolved in alcohol and water at controlled relative rates to maintain a constant solvent ratio. The slurry (the crystalline compound in the final desired solvent system) is often 10–20% of the product from a prior run. The total charge is typically performed over 4–6 hours at 20–25° C. The slurry is then aged for several hours at the desired final temperature before being filtered to allow the supernatant to reach equilibrium. Following the filtration, the wetcake is washed with approximately one bed volume of a clean alcohol/water mixture matching the final crystallization conditions. The wetcake is then washed with at least 2 bed volumes of DI water.

Further control of the crystal size and slurry viscosity is achieved by using a wet-mill on slurries with excessively long particles and/or extremely thick consistencies. The product typically forms rod shaped crystals which grow much faster in the axial direction than the radial direction. It is understood that the reference to 'thickness' will refer to the crystal size and consistency of the slurry. The mill has been shown to reduce the length of the long crystals and produce a thin slurry from a thick slurry which contains many agglomerates of crystals. On the laboratory scale, the entire slurry can be milled batch-wise when desired. At larger scales, the wet-mill can be used on a recycle loop circulating around the crystallization vessel. An in-line particle size measurement and viscosity measurements could be

coordinated to control the mill. Varying the temperature of the slurry through a range of 5° C. to 50° C. cycles has also been shown to be a useful way of modifying the crystal size and shape.

The solvents useful in this method include alcohol, acetonitrile (heel process only), dimethyl formamide (heel process only), and dimethyl acetamide (heel process only), The preferred solvent is an alcohol selected from methanol, ethanol or 2-propanol.

This crystallization process is advantageous over the prior method. The instant method allows one to isolate a crystalline product with consistent physical properties namely the ability to produce the desired crystal form of the product or convert to Form I with mild drying conditions (heating to about 40 to 60° C.). The alcohol-water crystallizations have also been shown to reject some impurities carried forward from the chemical synthesis. The final product slurry is less viscous and more homogenous with the instant process and is thus easier to mix and handle.

The following examples are meant to be illustrative of the present invention. These examples are presented to exemplify the invention and are not to be construed as limiting the scope of the invention.

EXAMPLE 1

Controlled Anti-Solvent Addition Crystallization Process

400 g of DMP-266 starting material is dissolved in 2.400 L of ethanol. See FIG. 1. The solution is filtered to remove extraneous matter. 2.088 L of deionized (DI) water is added to the solution over 30 to 60 minutes. 20 g of DMP-266 seed is added to the solution. The seed bed is aged for 1 hour. The use of Intermig agitators is preferred to mix the slurry. If required (by the presence of extremely long crystals or a thick slurry), the slurry is wet-milled for 15–60 seconds. 1.512 L of DI water is added to the slurry over 4 to 6 hours. If required (by the presence of extremely long crystals or a thick slurry), the slurry is wet-milled for 15 to about 60 seconds during the addition. The slurry is aged for 1 to 3 hours before being cooled to 10° C. over 3 hours. The slurry is aged for 2 to 16 hours until the product concentration in the supernatant remains constant. The slurry is filtered to isolate a crystalline wet cake. The wet cake is washed with 1 to 2 bed volumes of 40% ethanol in water and then twice with 2 L of DI water each. The washed wet cake is dried under vacuum at 50° C.

EXAMPLE 2

Semi-Continuous Heel Crystallization Process

400 g of DMP-266 starting material is dissolved in 2,400 L of ethanol. See FIG. 2. A heel slurry is produced by mixing 20 g of DMP-266 in 0.3 L of 40% (v/v) ethanol in water. The dissolved batch and 3.6 L of DI water are simultaneously charged to the heel slurry at constant rates over 6 hours to maintain a constant solvent composition in the crystallizer. Use of Intermig agitators during the crystallization is preferred. During this addition the slurry is wet-milled when the crystal lengths become excessively long or the slurry becomes too thick. The slurry is cooled to about 10° C. over 3 hours. The slurry is aged for 2 to 16 hours until the product concentration in the supernatant remains constant. The slurry is filtered to isolate a crystalline wet cake. The wet cake is washed with 1 to 2 bed volumes of 40% ethanol in water and then twice with 2 L of DI water each. The washed wet cake is dried under vacuum at 50° C.

EXAMPLES 3–8

Following the crystallization procedures described in Examples 1 and 2 above using the solvents noted in the table below in the amounts recited DMP-266 can be crystallized.

Ex #:	Solvent	ml solvent per g. DMP-266*	ml H ₂ O per g. DMP-266*	Anti-solvent Process	Heel Process
EX. 3:	Acetonitrile	3.6–8.0	7.2–14	—	X
EX. 4:	Dimethyl acetamide	3.6–8.0	7.2–14	—	X
EX. 5:	Dimethyl formamide	3.6–8.0	7.2–14	—	X
EX. 6:	Ethanol	3.6–8.0	7.2–14	X	X
EX. 7:	Methanol	4.8–10	5.4–12	X	X
EX. 8:	2-Propanol	3.0–7.0	7.8–15	X	X

*The sum of the amounts of solvent and water should be at least 12 ml/g.

The currently preferred concentration is 15 ml/g.

— method did not work.

X method worked.

EXAMPLE 9

Crystallization of DMP-266 from 30% 2-Propanol in Water Using a Ratio of 15 ml Solvent per Gram DMP-266 Using Controlled Anti-Solvent Addition on a 400 g Scale

400 g. of DMP-266 starting material is dissolved in 1.8 L of 2-propanol. The solution is filtered to remove extraneous matter. 1.95 L of deionized (DI) water is added to the solution over 30 to 60 minutes. 10 g. to 20 g. of DMP-266 seed (Form II wetcake) is added to the solution. The seed bed is aged for 1 hour. The use of Intermig agitators is preferred to mix the slurry. If required (by the presence of extremely long crystals or a thick slurry), the slurry is wet-milled for 15–60 seconds. 2.25 L of DI water is added to the slurry over 4 to 6 hours. If required (by the presence of extremely long crystals or a thick slurry), the slurry is wet-milled for 15–60 seconds during the addition. The slurry is aged for 2 to 16 hours until the product concentration in the supernatant remains constant. The slurry is filtered to isolate a crystalline wet cake. The wet cake is washed with 1 to 2 bed volumes of 30% 2-propanol in water and then twice with 1 bed volume of DI water each. The washed wet cake is dried under vacuum at 50° C.

EXAMPLE 10

Crystallization of DMP-266 from 30% 2-Propanol in Water Using a Ratio of 15 ml Solvent per Gram DMP-266 Using a Semi-Continuous Process on a 400 g Scale.

400 g. of DMP-266 starting material is dissolved in 1.8 L of 2-propanol. A heel slurry is produced by mixing 20 g. of Form II DMP-266 in 0.3 L of 30% (v/v) 2-propanol in water or retaining part of a slurry from a previous crystallization in the crystallizer. The dissolved batch and 4.2 L of DI water are simultaneously charged to the heel slurry at constant rates over 6 hours to maintain a constant solvent composition in the crystallizer. Use of Intermig agitators during the crystallization is preferred. During this addition the slurry is wet-milled when the crystal lengths become excessively long or the slurry becomes too thick. The slurry is aged for 2 to 16 hours until the product concentration in the supernatant remains constant. The slurry is filtered to isolate a

crystalline wet cake. The wet cake is washed with 1 to 2 bed volumes of 30% 2-propanol in water and then twice with 1 bed volume of DI water each. The washed wet cake is dried under vacuum at 50° C.

What is claimed is:

1. Form I of (-)-6-chloro-4-cyclopropylethynyl-4-trifluoromethyl-1,4-dihydro-2H-3,1-benzoxazin-2-one which is characterized by an X-ray powder diffraction pattern as exhibited in FIG. 3.

2. Form II of (-)-6-chloro-4-cyclopropylethynyl-4-trifluoromethyl-1,4-dihydro-2H-3,1-benzoxazin-2-one which is characterized by an X-ray powder diffraction pattern as exhibited in FIG. 4.

3. Form III of (-)-6-chloro-4-cyclopropylethynyl-4-trifluoromethyl-1,4-dihydro-2H-3,1-benzoxazin-2-one which is characterized by an X-ray powder diffraction pattern as exhibited in FIG. 5.

4. Form III of (-)-6-chloro-4-cyclopropylethynyl-4-trifluoromethyl-1,4-dihydro-2H-3,1-benzoxazin-2-one as recited in claim 3, which is further characterized by a DSC curve as exhibited in FIG. 6.

5. Form III of (-)-6-chloro-4-cyclopropylethynyl-4-trifluoromethyl-1,4-dihydro-2H-3,1-benzoxazin-2-one as recited in claim 4, which is further characterized by a TG analysis as exhibited in FIG. 7.

6. Form I of (-)-6-chloro-4-cyclopropylethynyl-4-trifluoromethyl-1,4-dihydro-2H-3,1-benzoxazin-2-one characterized by crystallographic D-spacings of 14.5, 8.5, 8.0, 7.2, 6.7, 6.2, 5.2, 4.6, 4.4, 4.2 and 3.6 Angstroms.

7. Form I according to claim 6, having no detectable peaks for Form II or Form III in its X-ray powder diffraction pattern.

8. Form II of (-)-6-chloro-4-cyclopropylethynyl-4-trifluoromethyl-1,4-dihydro-2H-3,1-benzoxazin-2-one characterized by crystallographic D-spacings of 24.3, 13.9, 8.0, 6.9, 6.6, 5.5, 4.6, 4.5, 4.3, 4.2, 3.9, 3.6, 3.4, 3.3 and 3.2 Angstroms.

9. Form II according to claim 8, having no detectable peaks for Form I or Form III in its X-ray powder diffraction pattern.

10. Form III of (-)-6-chloro-4-cyclopropylethynyl-4-trifluoromethyl-1,4-dihydro-2H-3,1-benzoxazin-2-one characterized by crystallographic D-spacings of 12.2, 8.1, 6.4, 6.1, 4.7, 4.3, 4.1, 4.0, 3.9, 3.8, 3.7, 3.6, 3.3, 3.2 and 3.0 Angstroms.

11. Form III according to claim 10, having no detectable peaks for Form I or Form II in its X-ray powder diffraction pattern.

* * * * *

EXHIBIT B



US006939964B2

(12) **United States Patent**
Crocker et al.

(10) **Patent No.:** **US 6,939,964 B2**
(45) **Date of Patent:** ***Sep. 6, 2005**

(54) **CRYSTAL FORMS OF (-)-6-CHLORO-4-CYCLOPROPYLETHYNYL-4-TRIFLUOROMETHYL-1,4-DIHYDRO-2H-3,1-BENZOXAZIN-2-ONE**

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(75) Inventors: **Louis S. Crocker**, Belle Mead, NJ (US); **Joseph L. Kukura, II**, Somerset, NJ (US); **Andrew S. Thompson**, Mountainside, NJ (US); **Christine Stelmach**, Westfield, NJ (US); **Steven D. Young**, Lansdale, PA (US)

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WO	WO 98/45278	10/1998
WO	WO 99/64405	12/1999

(73) Assignee: **Merck & Co., Inc.**, Rahway, NJ (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

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* cited by examiner

(21) Appl. No.: **10/891,749**

(22) Filed: **Jun. 24, 2004**

(65) **Prior Publication Data**

US 2004/0259872 A1 Dec. 23, 2004

Related U.S. Application Data

(60) Continuation of application No. 10/447,690, filed on May 29, 2003, now abandoned, which is a continuation of application No. 10/000,537, filed on Oct. 19, 2001, now Pat. No. 6,639,071, which is a continuation of application No. 09/282,744, filed on Mar. 31, 1999, now abandoned, which is a division of application No. 09/008,824, filed on Jan. 20, 1998, now Pat. No. 5,965,729.

(60) Provisional application No. 60/037,385, filed on Feb. 5, 1997, and provisional application No. 60/042,807, filed on Apr. 8, 1997.

(51) **Int. Cl.⁷** **C07D 265/18**

(52) **U.S. Cl.** **544/92**

(58) **Field of Search** 544/92

(56) **References Cited**

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Primary Examiner—Richard L. Raymond

(74) *Attorney, Agent, or Firm*—Kenneth R. Walton; Valerie J. Camara

(57) **ABSTRACT**

The instant invention describes a method for crystallizing (-)-6-chloro-4-cyclopropylethynyl-4-trifluoromethyl-1,4-dihydro-2H-3,1-benzoxazin-2-one from a solvent and anti-solvent solvent system and producing the crystalline product. The desired final crystal form, Form I, can be produced when using methanol or ethanol. Form II is isolated from 2-propanol and can be converted to the desired crystal form at low drying temperatures, such as between about a temperature of 40° C. and 50° C.

14 Claims, 7 Drawing Sheets

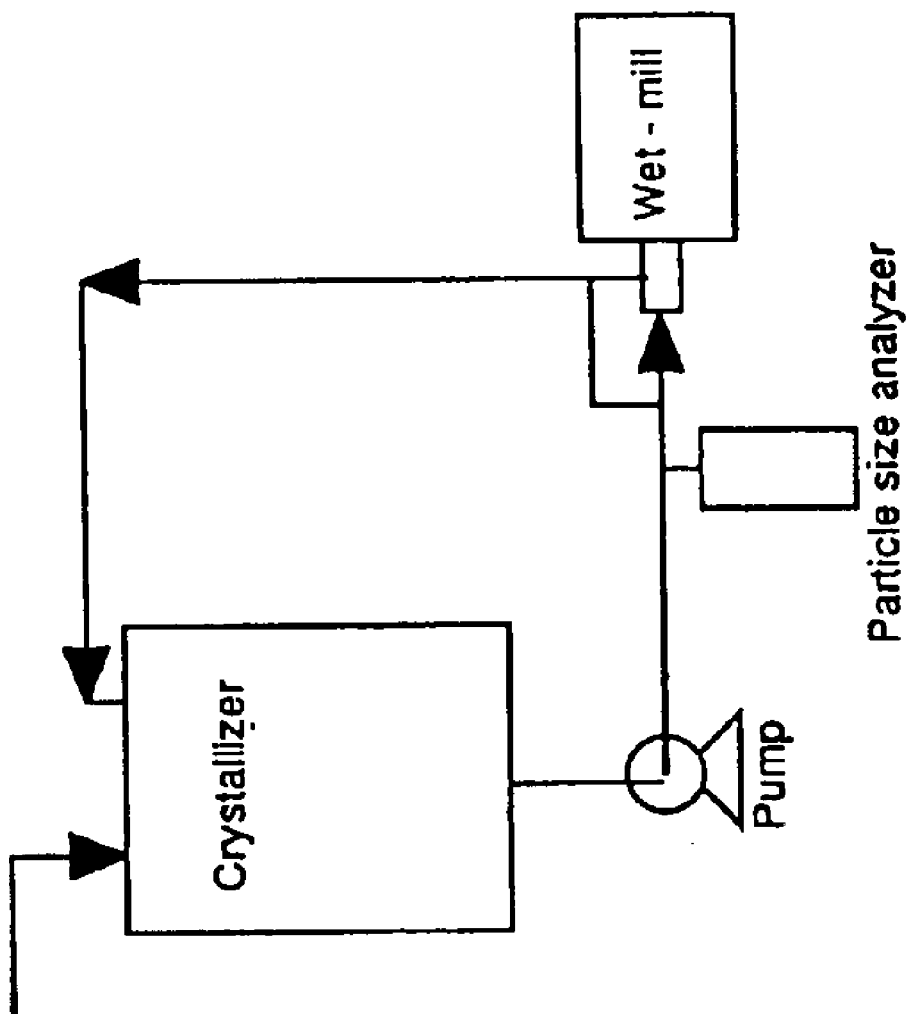


Figure 1 Controlled Anti-solvent Addition

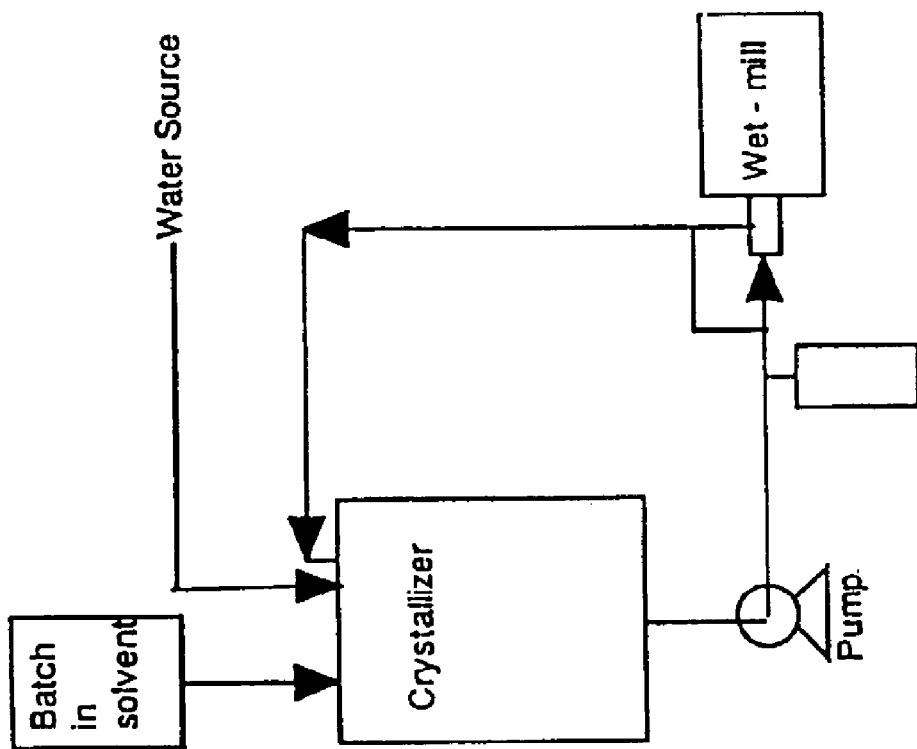


Figure 2 Heel Crystallization
Particle size analyzer

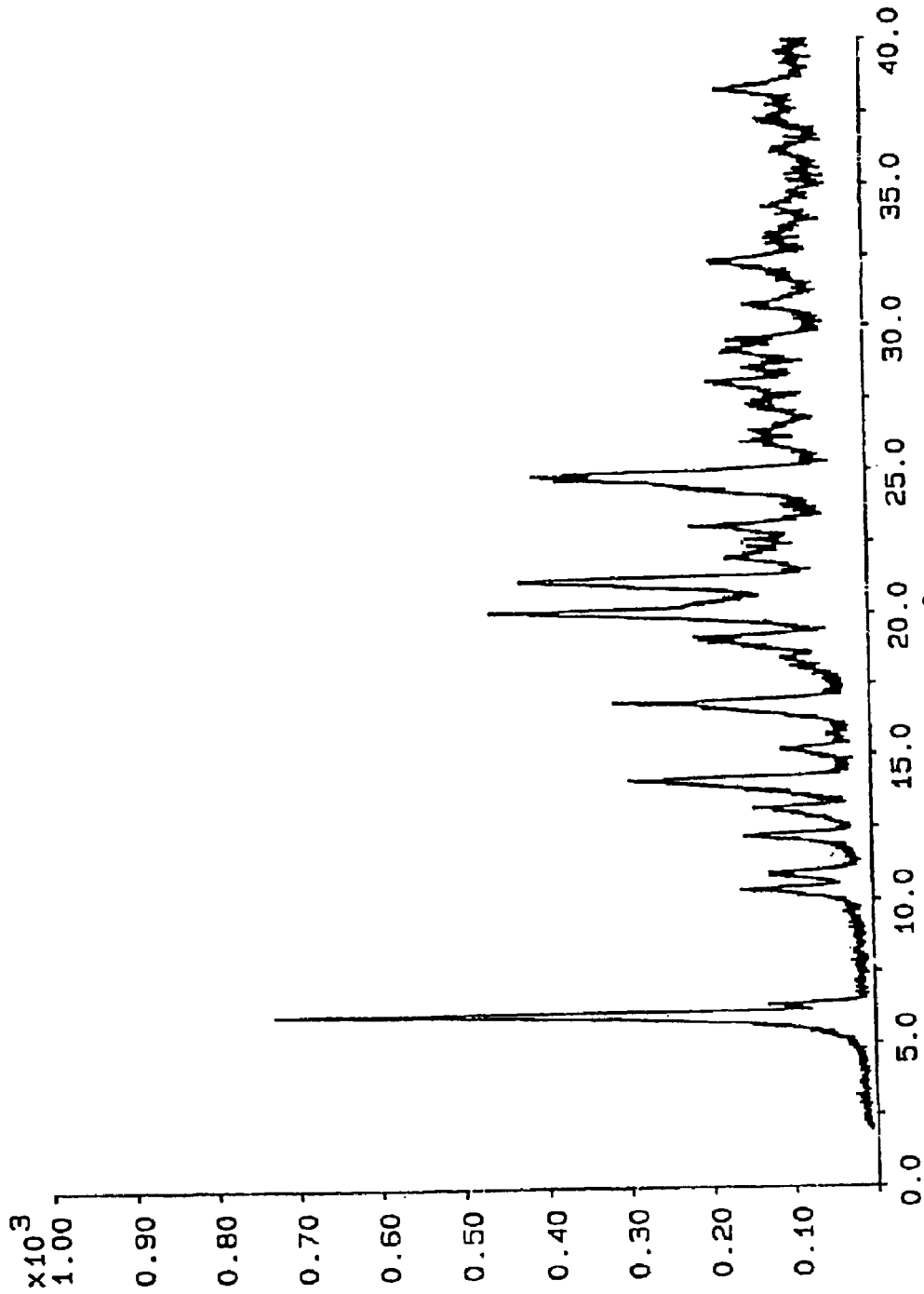


Figure 3

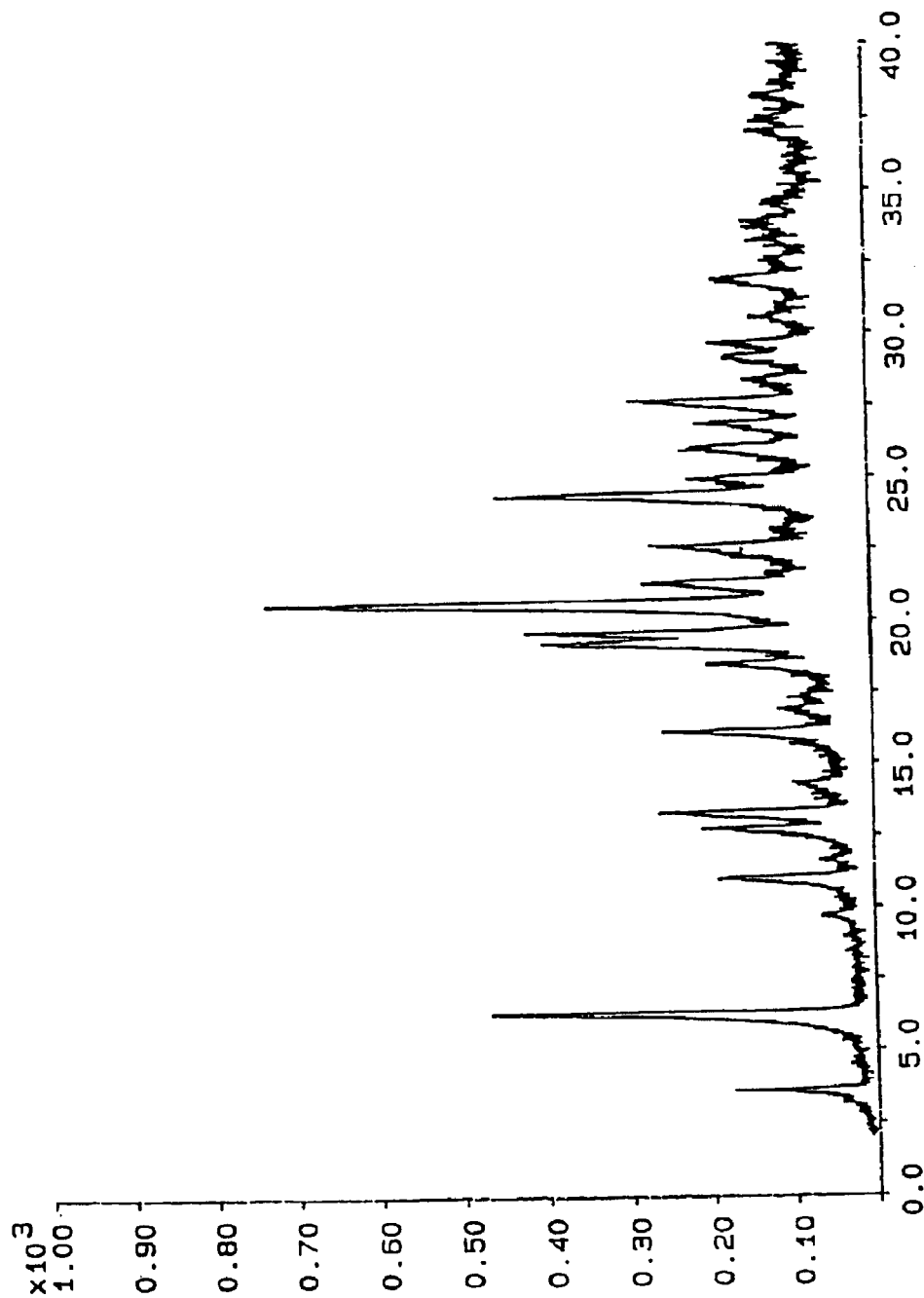


Figure 4

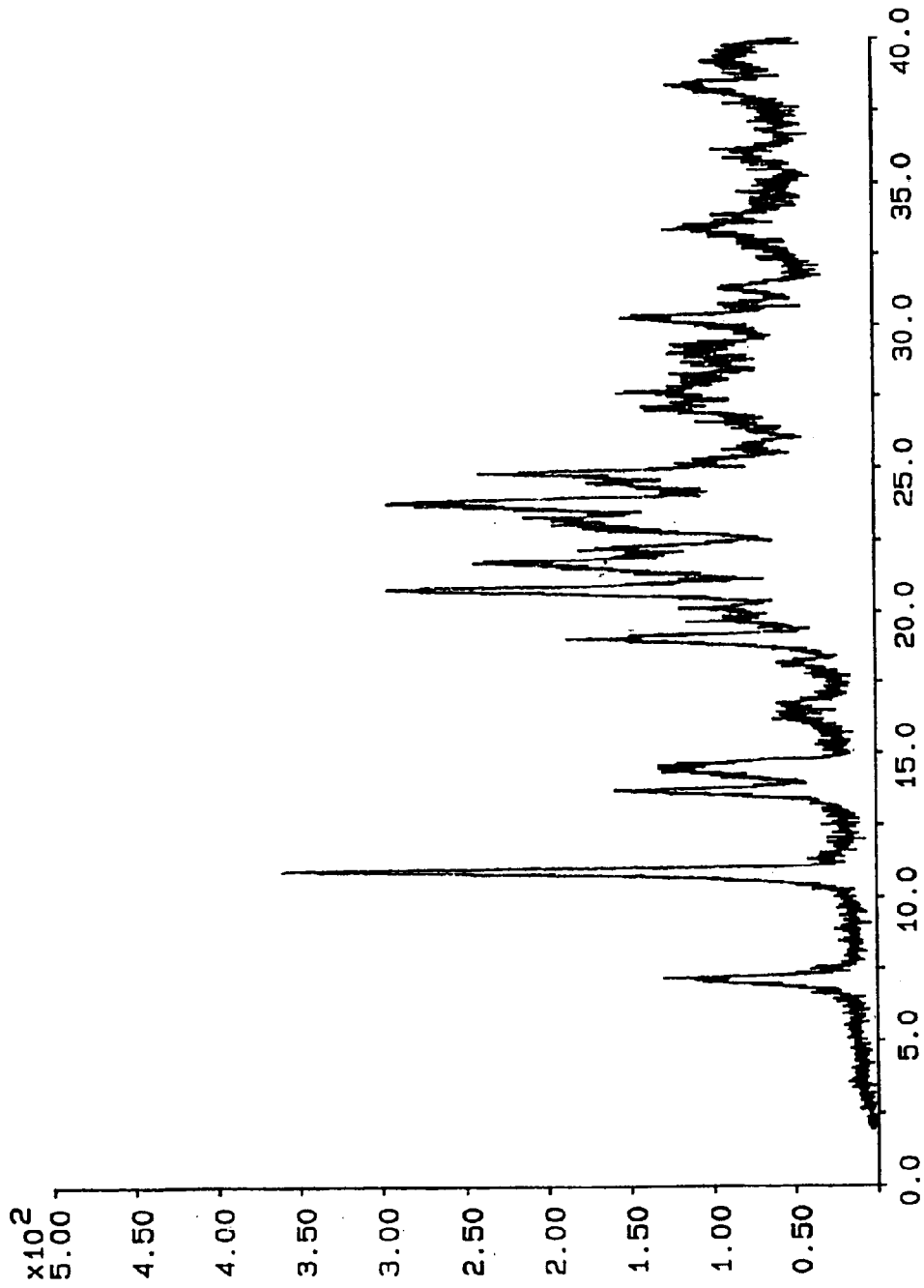


Figure 5

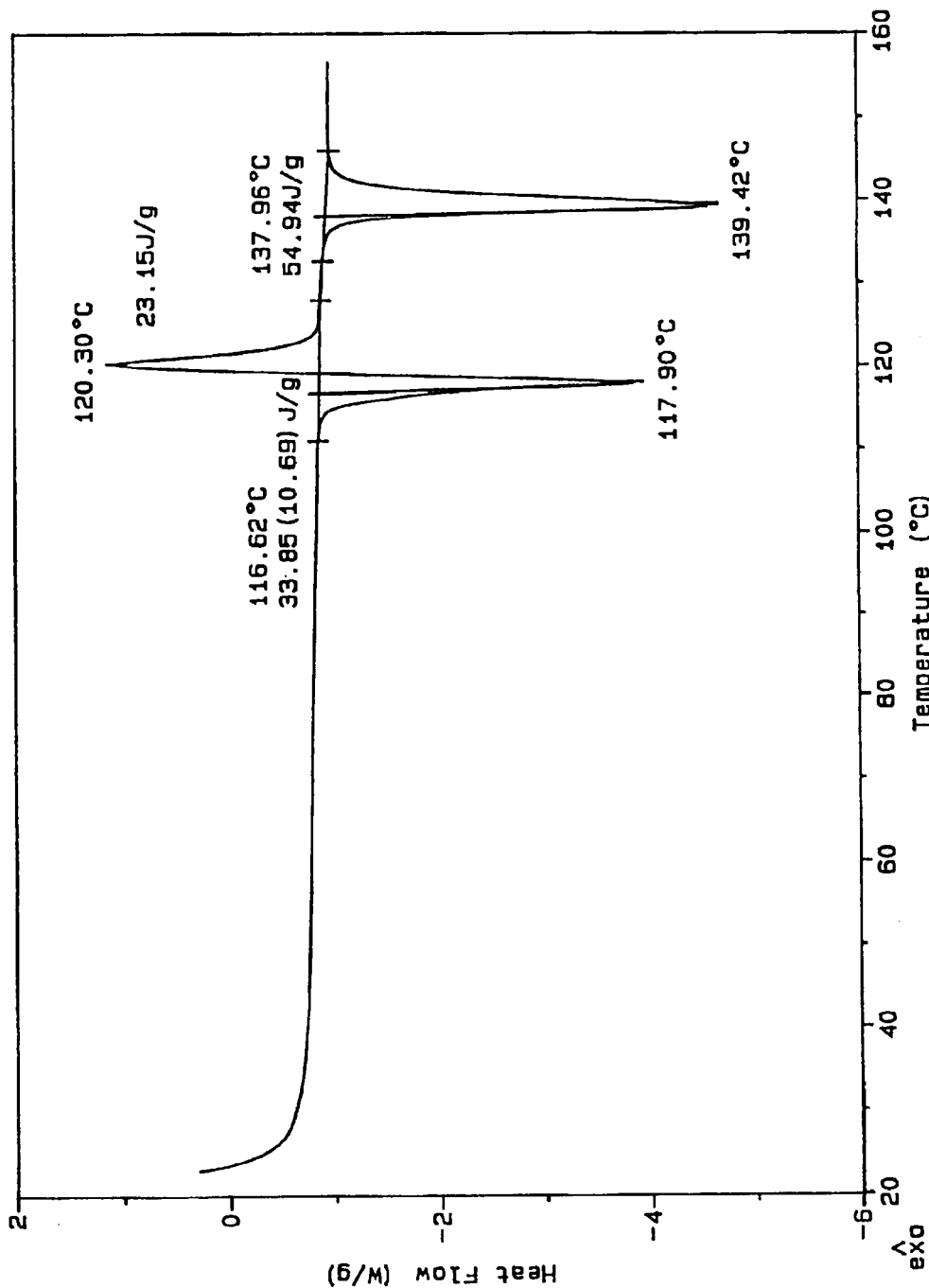


Figure 6

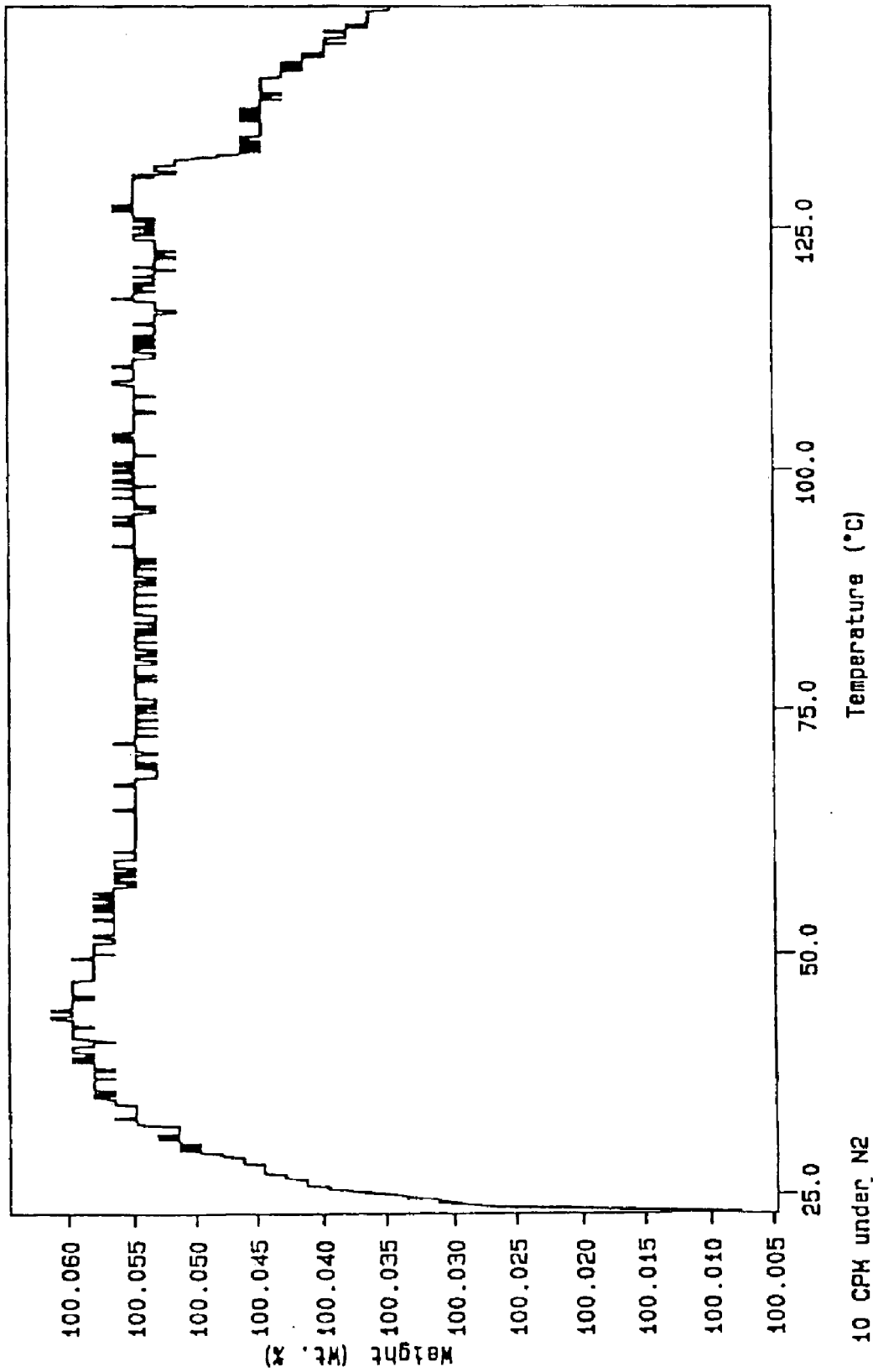


Figure 7

1

CRYSTAL FORMS OF (-)-6-CHLORO-4-CYCLOPROPYLETHYNYL-4-TRIFLUOROMETHYL-1,4-DIHYDRO-2H-3,1-BENZOXAZIN-2-ONE

This application is a continuation of U.S. application Ser. No. 10/447,690, filed May 29, 2003, abandoned; which is a continuation of U.S. application Ser. No. 10/000,537, filed Oct. 19, 2001, now U.S. Pat. No. 6,639,071; which is a continuation of U.S. application Ser. No. 09/282,744, filed Mar. 31, 1999, abandoned; which is a divisional of U.S. application Ser. No. 09/008,824, filed Jan. 20, 1998, now U.S. Pat. No. 5,965,729; which claims the benefit of U.S. provisional application Ser. Nos. 60/037,385, filed Feb. 5, 1997 and 60/042,807, filed Apr. 8, 1997.

BACKGROUND OF THE INVENTION

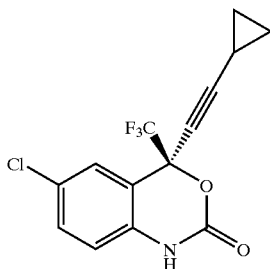
The synthesis of the reverse transcriptase inhibitor (RTI), (-)-6-chloro-4-cyclopropylethynyl-4-trifluoromethyl-1,4-dihydro-2H-3,1-benzoxazin-2-one, also known as DMP-266 has been described in U.S. Pat. No. 5,519,021 issued on May 21, 1996 and the corresponding PCT International Patent Application WO 95/20389, which published on Aug. 3, 1995. Additionally, the asymmetric synthesis of an enantiomeric benzoxazinone by a highly enantioselective acetylide addition and cyclization sequence has been described by Thompson, et al., *Tetrahedron Letters* 1995, 36, 937-940, as well as the PCT publication, WO 96/37457, which published on Nov. 28, 1996.

The compound was previously crystallized from a heptane-tetrahydrofuran (THF) solvent system. The crystallization procedure required the use of high temperatures (about 90° C.) to dissolve the final product. Crystals formed by nucleation during the cooling process. The crystals which were produced were Form II and are converted to the desired Form I while drying under vacuum at 90° C. This crystallization provided minimal purification and produced material with inconsistent physical properties. The final product slurry was extremely difficult to mix and handle due to its high viscosity and heterogeneous nature.

The instant invention describes a method for crystallizing (-)-6-chloro-4-cyclopropylethynyl-4-trifluoromethyl-1,4-dihydro-2H-3,1-benzoxazin-2-one from a solvent and anti-solvent solvent system and producing the crystalline product. The desired final crystal form, Form I, can be produced when using methanol or ethanol. Form II is isolated from 2-propanol and can be converted to the desired crystal form at low drying temperatures, as low as 40° C.

SUMMARY OF THE INVENTION

A process for the crystallization of a compound of the structural formula



comprising the use of a solvent to effect the dissolution of the compound followed by the addition of an anti-solvent to initiate the crystallization.

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BRIEF DESCRIPTION OF THE FIGURES

FIG. 1. Flowsheet of the controlled anti-solvent addition crystallization method.

FIG. 2. Flowsheet of the heel crystallization method.

FIG. 3. X-ray powder diffraction pattern for Form I of (-)-6-chloro-4-cyclopropylethynyl-4-trifluoromethyl-1,4-dihydro-2H-3,1-benzoxazin-2-one.

FIG. 4. X-ray powder diffraction pattern for Form II of (-)-6-chloro-4-cyclopropylethynyl-4-trifluoromethyl-1,4-dihydro-2H-3,1-benzoxazin-2-one.

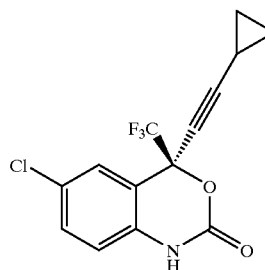
FIG. 5. X-ray powder diffraction pattern for Form III of (-)-6-chloro-4-cyclopropylethynyl-4-trifluoromethyl-1,4-dihydro-2H-3,1-benzoxazin-2-one.

FIG. 6. DSC curve for Form III of (-)-6-chloro-4-cyclopropylethynyl-4-trifluoromethyl-1,4-dihydro-2H-3,1-benzoxazin-2-one.

FIG. 7. TG analysis for Form III of (-)-6-chloro-4-cyclopropylethynyl-4-trifluoromethyl-1,4-dihydro-2H-3,1-benzoxazin-2-one.

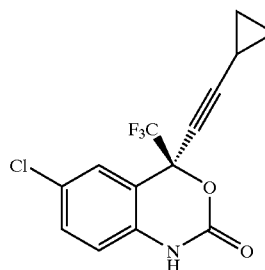
DETAILED DESCRIPTION OF THE INVENTION

A process for the crystallization of a compound of the structural formula



comprising the use of a solvent to effect the dissolution of the compound followed by the addition of an anti-solvent to initiate crystallization.

A process for the crystallization of a compound of the structural formula



comprising the steps of:

- (1) dissolving the compound in a solvent in a ratio of about 3.0 ml to about 10.0 ml of solvent to 1 gram of the compound;
- (2) filtering the solution of the compound to remove any particulate matter;
- (3) adding the anti-solvent to the stirring solution at room temperature over a period of about 30 minutes to about an hour to reach the saturation point of the solution containing the compound;

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- (4) adding to the solution a solid seed charge of the compound in the amount of about 2 to about 10 percent by weight to form a slurry;
- (5) milling the slurry to reduce the thickness of the slurry;
- (6) adding the remaining water to reach the desired solvent composition of about 30% to about 50% and milling the slurry as needed during the addition;
- (7) slowly cooling the slurry to about 5° C. to about 20° C.;
- (8) aging for about 2 to about 16 hours until the supernatant concentration reaches equilibrium;
- (9) milling the slurry, as needed, to reduce the thickness of the slurry;
- (10) filtering the milled slurry to isolate a wet cake of the crystalline compound;
- (11) washing the wetcake once with about 1 to about 2 bed volumes of the final crystallization solvent composition and then twice with water using about 5–10 ml water per gram of compound; and
- (12) drying the washed wetcake at about 40° C. to about 90° C. under vacuum for about 1 hour to about 3 days, or until the loss on dryness is less than 0.5 weight percent.

The controlled anti-solvent crystallization process as recited above wherein the solvent is defined as alcohol, wherein alcohol is a straight or branched chain (C₁–C₆)-alkanol. A preferred embodiment of the solvents useful in the controlled anti-solvent crystallization process is (C₁–C₆)-alkanol, such as, methanol, ethanol, and 2-propanol. The preferred alcohol is 2-propanol.

The preferred alcohol is 2-propanol for reasons relating to obtaining consistent crystal forms. Although methanol and ethanol solvent systems have been shown to be capable of producing the desired Form I crystal structure, a slight contamination of Form III crystals in a crystallization slurry in these systems can convert the entire slurry to containing exclusively Form III crystals, which are relatively difficult to convert to the desired Form I structure. Any known crystal structure of this compound placed in an about 25% to 35% (v/v) 2-propanol-water solvent system has been shown to quickly convert to the Form II crystal structure, which can readily convert to the desired Form I crystal structure during drying.

The anti-solvent as recited above is defined as a solvent in which the compound has limited solubility. In the instant process, the preferred anti-solvent is water.

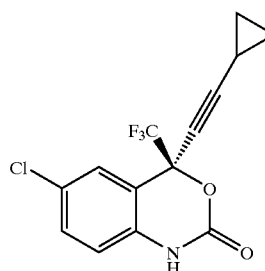
The temperature of the solution during the anti-solvent addition (Step 3) was about 20° C. to about 25° C. The temperature of the slurry being about 5° C. to about 20° C., and preferably at about 10° C.

The temperature used during the drying of the washed wetcake (Step 12) is about 40° C. to about 90° C., and preferably about 40° C. to about 60° C.

The solvent system (solvent plus anti-solvent) used ranged from about 30% to about 50% solvent volume to anti-solvent volume (v/v) ratio. The total volume of the solvent system ranging from about 12 to about 20 ml of the solvent system per gram of the compound. The solvent volume to anti-solvent volume ratio for selected solvent systems is as follows: 1) an ethanol-water solvent system is about 30% to about 40% ethanol to water v/v ratio; 2) a methanol-water solvent system is about 40% to about 50% methanol to water v/v ratio; and 3) an 2-propanol-water solvent system is about 25% to about 35% 2-propanol to water v/v ratio. The preferred solvent system is 2-propanol-water used in about a 30% volume to volume ratio and a total solvent system volume of about 15 ml per gram of the compound.

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A process for the crystallization of a compound of the structural formula



comprising the steps of:

- (1) mixing about 10% to about 20% by weight of the final amount of (-)-6-chloro-4-cyclopropylethynyl-4-trifluoromethyl-1,4-dihydro-2H-3,1-benzoxazin-2-one in the desired v/v ratio of solvent to anti-solvent at about 20° C. to form the heel or retaining a final slurry from a previous batch;
- (2) adding the solution of solvent and (-)-6-chloro-4-cyclopropylethynyl-4-trifluoromethyl-1,4-dihydro-2H-3,1-benzoxazin-2-one, and anti-solvent to the heel simultaneously at constant rates over about 6 hours maintaining the v/v ratio of solvent to anti-solvent;
- (3) milling the slurry during the addition to reduce the thickness of the slurry;
- (4) cooling the slurry to about 10° C. over about 3 hours and aging slurry until the supernatant concentration reaches equilibrium;
- (5) filtering the milled slurry to isolate a wet cake of the crystalline compound;
- (6) washing the wetcake once with about 1 to about 2 bed volumes of the final crystallization solvent composition and then twice with water using about 5 ml to about 10 ml water per gram of compound; and
- (7) drying the washed wetcake at about 40° C. to about 90° C. under vacuum for about 1 hour to about 3 days, or until the loss on dryness is less than 0.5 weight percent.

The heel crystallization process as recited above wherein the solvent is defined as acetonitrile, dimethyl acetamide, dimethyl formamide or alcohol. A preferred embodiment of the solvents useful in the controlled anti-solvent crystallization process is alcohol, wherein alcohol is defined as (C₁–C₆)-alkanol, such as, methanol, ethanol, and 2-propanol. The preferred alcohol is 2-propanol.

The anti-solvent as recited above is defined as a solvent in which the compound has limited solubility. In the heel crystallization process the preferred anti-solvent is water.

The process as recited above wherein the temperature of the solution during the anti-solvent addition is about 5° C. to about 20° C.

The temperature used during the drying of the washed wetcake is about 40° C. to about 90° C., and preferably about 40° C. to about 60° C.

The solvent system (solvent plus anti-solvent) used ranges from about 30% to about 50% solvent volume to anti-solvent volume (v/v) ratio. The total volume of the solvent system ranging from about 12 to about 20 ml of the solvent system per gram of the compound. The solvent to anti-solvent volume to volume ratio for selected solvent systems is as follows: 1) an ethanol-water solvent system is about 30% to about 40% ethanol to water v/v ratio; 2) a methanol-

water solvent system is about 40% to about 50% methanol to water v/v ratio; and 3) an 2-propanol-water solvent system is about 25% to about 35% 2-propanol to water v/v ratio. The preferred solvent system is 2-propanol-water used in about a 30% volume to volume ratio and a total solvent system volume of about 15 ml per gram of the compound.

FIGS. 3, 4 and 5 are the X-ray powder diffraction (XRPD) patterns for Forms I, II and III, respectively. These XRPD patterns were recorded using an automated X-ray diffractometer APD 3720 with copper K alpha radiation. The crystal forms I and II of (-)-6-chloro-4-cyclopropylethynyl-4-trifluoromethyl-1,4-dihydro-2H-3,1-benzoxazin-2-one which are characterized by the noted X-ray powder diffraction patterns have the following key diffraction peaks (2 θ) with intensities (I/I_{max} , %) of 10 or greater:

Form I	Form II	Form III
6.0800	3.6375	7.2150
6.3900	6.3325	10.9675
10.3950	11.0725	13.7275
10.9875	12.7750	14.5325
12.2850	13.3275	16.7275
13.1900	14.2925	19.0675
14.1700	16.1200	19.6550
15.1925	16.8975	20.8250
16.9000	18.5025	21.7450
18.4375	19.1975	22.2825
19.2275	19.6025	22.8475
20.0925	20.6650	23.1750
21.2100	21.3250	23.8850
22.3600	22.6150	24.4900
23.0725	23.1775	24.9075
24.8900	24.4075	25.8200
25.9500	24.9650	27.0325
26.3575	26.0100	27.6050
27.2550	26.8550	29.2975
28.1150	27.6400	30.2600
28.5850	28.3675	30.7300
29.1325	29.1725	31.3125
29.5625	29.6325	33.3975
30.6850	30.5650	38.4325
32.3725	31.8950	39.2100
38.3125	33.8225	

Additionally, these crystal forms are characterized by peaks with varying D-spacings. Form I is characterized by peaks with D-spacings of: 14.5, 8.5, 8.0, 7.2, 6.7, 6.2, 5.2, 4.6, 4.4, 4.2, and 3.6 angstroms. Form II is characterized by peaks with D-spacings of: 24.3, 13.9, 8.0, 6.9, 6.6, 5.5, 4.6, 4.5, 4.3, 4.2, 3.9, 3.6, 3.4, 3.3, and 3.2 angstroms. Form III is characterized by peaks with D-spacings of: 12.2, 8.1, 6.4, 6.1, 4.7, 4.3, 4.1, 4.0, 3.9, 3.8, 3.7, 3.6, 3.3, 3.2, and 3.0 angstroms.

Thermogravimetric analysis results of Form III (FIG. 7) indicated there was no significant weight loss observed from 43° C. to about 137° C. This result is indicative of an anhydrous or unsolvated crystal form.

The differential scanning calorimetry (DSC) results obtained for Form III show an endotherm with an extrapolated onset temperature of 117° C., a peak temperature of 118° C., and an enthalpy of 34 J/g, this is followed by an exotherm with a peak temperature of 120° C. and an enthalpy of 23 J/g. A second endotherm with an extrapolated onset temperature of 138° C., a peak temperature of 139° C., and an enthalpy of 55 J/g is also observed. The first endotherm is associated with the melting of Form III, which subsequently crystallizes to Form I during the exothermic event. The second endothermic event is associated with the melting of Form I.

A process for isolating (-)-6-chloro-4-cyclopropylethynyl-4-trifluoromethyl-1,4-dihydro-2H-3,1-

benzoxazin-2-one, the final product from solutions containing an organic solvent and water has been developed. In this process water serves as an anti-solvent to produce a solid product from material dissolved in organic solvent. The final solvent composition is chosen to balance yield loss, purification, and slurry handling properties.

For methanol solvent systems about 40% to about 50% volume to volume (v/v) solvent to anti-solvent (water) has been present in the final slurry. Ethanol solvent systems have contained about 30% to about 40% v/v solvent to anti-solvent, and 2-propanol solvent systems have used about 25% to about 35% (v/v) solvent to anti-solvent. The total amount of liquid (alcohol and water) ranges from 12–20 ml/(g solid). The crystallizations are typically performed between 20–25° C., and some slurries have been cooled to 5–10° C. before being filtered. Following the filtration, the wetcake is washed with approximately one bed volume (the approximate volume of the wetcake) of the final crystallization solvent composition. The wetcake is then washed with at least 2 bed volumes of deionized (DI) water.

The rate at which the product is precipitated is controlled by either slowly adding the water to a saturated system following a seed charge (anti-solvent addition) or simultaneously adding the product in alcohol and water at controlled rates to an existing product slurry (heel crystallization).

For the anti-solvent process (FIG. 1), enough water is first added to the organic solvent solution containing the product over 0.5–2 hours to saturate the system in final product. A solid charge of final product is then added to the system as seed (2–10% of the initial amount of product). The seed should be Form I (the crystal form associated with dry final product) for ethanol and methanol systems, and Form II seed (the crystal form generated from a THF/heptane crystallization) is used for 2-propanol systems. The resultant slurry is aged for 0.5–2 hours to establish a seed bed. The remaining water is then added over 2–4 hours in a controlled manner. The slurry is then aged for 2–20 hours and cooled to the desired final temperature during the age, allowing the supernatant to reach equilibrium.

For the heel process (FIG. 2), a slurry at the desired final solvent composition is mixed while adding the product dissolved in alcohol and water at controlled relative rates to maintain a constant solvent ratio. The slurry (the crystalline compound in the final desired solvent system) is often 10–20% of the product from a prior run. The total charge is typically performed over 4–6 hours at 20–25° C. The slurry is then aged for several hours at the desired final temperature before being filtered to allow the supernatant to reach equilibrium. Following the filtration, the wetcake is washed with approximately one bed volume of a clean alcohol/water mixture matching the final crystallization conditions. The wetcake is then washed with at least 2 bed volumes of DI water.

Further control of the crystal size and slurry viscosity is achieved by using a wet-mill on slurries with excessively long particles and/or extremely thick consistencies. The product typically forms rod shaped crystals which grow much faster in the axial direction than the radial direction. It is understood that the reference to 'thickness' will refer to the crystal size and consistency of the slurry. The mill has been shown to reduce the length of the long crystals and produce a thin slurry from a thick slurry which contains many agglomerates of crystals. On the laboratory scale, the entire slurry can be milled batch-wise when desired. At larger scales, the wet-mill can be used on a recycle loop circulating around the crystallization vessel. An in-line par-

ticle size measurement and viscosity measurements could be coordinated to control the mill. Varying the temperature of the slurry through a range of 5° C. to 50° C. cycles has also been shown to be a useful way of modifying the crystal size and shape.

The solvents useful in this method include alcohol, acetonitrile (heel process only), dimethyl formamide (heel process only), and dimethyl acetamide (heel process only). The preferred solvent is an alcohol selected from methanol, ethanol or 2-propanol.

This crystallization process is advantageous over the prior method. The instant method allows one to isolate a crystalline product with consistent physical properties namely the ability to produce the desired crystal form of the product or convert to Form I with mild drying conditions (heating to about 40 to 60° C.). The alcohol-water crystallizations have also been shown to reject some impurities carried forward from the chemical synthesis. The final product slurry is less viscous and more homogenous with the instant process and is thus easier to mix and handle.

The following examples are meant to be illustrative of the present invention. These examples are presented to exemplify the invention and are not to be construed as limiting the scope of the invention.

EXAMPLE 1

Controlled Anti-Solvent Addition Crystallization Process

400 g of DMP-266 starting material is dissolved in 2.400 L of ethanol. See FIG. 1. The solution is filtered to remove extraneous matter. 2.088 L of deionized (DI) water is added to the solution over 30 to 60 minutes. 20 g of DMP-266 seed is added to the solution. The seed bed is aged for 1 hour. The use of Intermig agitators is preferred to mix the slurry. If required (by the presence of extremely long crystals or a thick slurry), the slurry is wet-milled for 15–60 seconds. 1.512 L of DI water is added to the slurry over 4 to 6 hours. If required (by the presence of extremely long crystals or a thick slurry), the slurry is wet-milled for 15 to about 60 seconds during the addition. The slurry is aged for 1 to 3 hours before being cooled to 10° C. over 3 hours. The slurry is aged for 2 to 16 hours until the product concentration in the supernatant remains constant. The slurry is filtered to isolate a crystalline wet cake. The wet cake is washed with 1 to 2 bed volumes of 40% ethanol in water and then twice with 2 L of DI water each. The washed wet cake is dried under vacuum at 50° C.

EXAMPLE 2

Semi-Continuous Heel Crystallization Process

400 g of DMP-266 starting material is dissolved in 2.400 L of ethanol. See FIG. 2. A heel slurry is produced by mixing 20 g of DMP-266 in 0.3 L of 40% (v/v) ethanol in water. The dissolved batch and 3.6 L of DI water are simultaneously charged to the heel slurry at constant rates over 6 hours to maintain a constant solvent composition in the crystallizer. Use of Intermig agitators during the crystallization is preferred. During this addition the slurry is wet-milled when the crystal lengths become excessively long or the slurry becomes too thick. The slurry is cooled to about 10° C. over 3 hours. The slurry is aged for 2 to 16 hours until the product concentration in the supernatant remains constant. The slurry is filtered to isolate a crystalline wet cake. The wet cake is washed with 1 to 2 bed volumes of 40% ethanol in water and then twice with 2 L of DI water each. The washed wet cake is dried under vacuum at 50° C.

EXAMPLES 3–8

Following the crystallization procedures described in Examples 1 and 2 above using the solvents noted in the table below in the amounts recited DMP-266 can be crystallized.

Ex #:	Solvent	ml solvent per g. DMP-266*	ml H ₂ O per g. DMP-266*	Anti-solvent Process	Heel Process
10	EX. 3: Acetonitrile	3.6–8.0	7.2–14	—	X
	EX. 4: Dimethyl acetamide	3.6–8.0	7.2–14	—	X
	EX. 5: Dimethyl formamide	3.6–8.0	7.2–14	—	X
15	EX. 6: Ethanol	3.6–8.0	7.2–14	X	X
	EX. 7: Methanol	4.8–10	5.4–12	X	X
	EX. 8: 2-Propanol	3.0–7.0	7.8–15	X	X

*The sum of the amounts of solvent and water should be at least 12 ml/g. The currently preferred concentration is 15 ml/g.

20 — method did not work.

X method worked.

EXAMPLE 9

25 Crystallization of DMP-266 from 30% 2-Propanol in Water using a ratio of 15 ml solvent per gram DMP-266 Using Controlled Anti-Solvent Addition on a 400 g Scale

400 g. of DMP-266 starting material is dissolved in 1.8 L of 2-propanol. The solution is filtered to remove extraneous matter. 1.95 L of deionized (DI) water is added to the solution over 30 to 60 minutes. 10 g. to 20 g. of DMP-266 seed (Form II wetcake) is added to the solution. The seed bed is aged for 1 hour. The use of Intermig agitators is preferred to mix the slurry. If required (by the presence of extremely long crystals or a thick slurry), the slurry is wet-milled for 15–60 seconds. 2.25 L of DI water is added to the slurry over 4 to 6 hours. If required (by the presence of extremely long crystals or a thick slurry), the slurry is wet-milled for 15–60 seconds during the addition. The slurry is aged for 2 to 16 hours until the product concentration in the supernatant remains constant. The slurry is filtered to isolate a crystalline wet cake. The wet cake is washed with 1 to 2 bed volumes of 30% 2-propanol in water and then twice with 1 bed volume of DI water each. The washed wet cake is dried under vacuum at 50° C.

EXAMPLE 10

50 Crystallization of DMP-266 from 30% 2-Propanol in Water using a ratio of 15 ml solvent per gram DMP-266 Using a Semi-Continuous Process on a 400 g Scale

400 g. of DMP-266 starting material is dissolved in 1.8 L of 2-propanol. A heel slurry is produced by mixing 20 g. of Form II DMP-266 in 0.3 L of 30% (v/v) 2-propanol in water or retaining part of a slurry from a previous crystallization in the crystallizer. The dissolved batch and 4.2 L of DI water are simultaneously charged to the heel slurry at constant rates over 6 hours to maintain a constant solvent composition in the crystallizer. Use of Intermig agitators during the crystallization is preferred. During this addition the slurry is wet-milled when the crystal lengths become excessively long or the slurry becomes too thick. The slurry is aged for 2 to 16 hours until the product concentration in the supernatant remains constant. The slurry is filtered to isolate a crystalline wet cake. The wet cake is washed with 1 to 2 bed volumes of 30% 2-propanol in water and then twice with 1 bed volume of DI water each. The washed wet cake is dried under vacuum at 50° C.

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What is claimed is:

1. Form I of (-)-6-chloro-4-cyclopropylethynyl-4-trifluoromethyl-1,4-dihydro-2H-3,1-benzoxazin-2-one, which is characterized by crystallographic D-spacings of 14.5, 8.5 and 7.2 Angstroms.

2. Form I according to claim 1, characterized by crystallographic D-spacings of 14.5, 8.5, 7.2, 6.2, 4.4 and 4.2 Angstroms.

3. Form I according to claim 2, characterized by crystallographic D-spacings of 14.5, 8.5, 8.0, 7.2, 6.7, 6.2, 4.4 and 4.2 Angstroms.

4. Form I according to claim 1, having no detectable peaks for Form II or Form III in its X-ray powder diffraction pattern.

5. Form II of (-)-6-chloro-4-cyclopropylethynyl-4-trifluoromethyl-1,4-dihydro-2H-3,1-benzoxazin-2-one, characterized by crystallographic D-spacings of 24.3, 6.9 and 5.5 Angstroms.

6. Form II according to claim 5, characterized by crystallographic D-spacings of 24.3, 13.9, 6.9, 6.6, 5.5 and 4.3 Angstroms.

7. Form II according to claim 6, characterized by crystallographic D-spacings of 24.3, 13.9, 8.0, 6.9, 6.6, 5.5, 4.5, 4.3, and 3.6 Angstroms.

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8. Form II according to claim 5, having no detectable peaks for Form I or Form III in its X-ray powder diffraction pattern.

9. Form III of (-)-6-chloro-4-cyclopropylethynyl-4-trifluoromethyl-1,4-dihydro-2H-3,1-benzoxazin-2-one, characterized by crystallographic D-spacings of 12.2, 6.1 and 4.3 Angstroms.

10. Form III according to claim 9, characterized by crystallographic D-spacings of 12.2, 8.1, 6.1, 4.7, 4.3 and 4.1 Angstroms.

11. Form III according to claim 10, characterized by crystallographic D-spacings of 12.2, 8.1, 6.4, 6.1, 4.7, 4.3, 4.1, 3.7 and 3.6 Angstroms.

12. Form III according to claim 9, having no detectable peaks for Form I or Form II in its X-ray powder diffraction pattern.

13. Form III according to claim 9, which is further characterized by a DSC curve with a peak temperature of about 118° C. and an enthalpy of 34 J/g.

14. Form III according to claim 13, which is further characterized by a thermogravimetric analysis indicating no significant weight loss from 43° C. to 137° C.

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