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Janssen Pharmaceuticals, Inc. Janssen Pharmaceutica NV,
Janssen Research and Development, LLC,
and Cilag GmbH International

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

MITSUBISHI TANABE PHARMA CORPORATION, JANSSEN PHARMACEUTICALS, INC., JANSSEN PHARMACEUTICA NV, JANSSEN RESEARCH AND DEVELOPMENT, LLC, and CILAG GMBH INTERNATIONAL,

Plaintiffs,

v.

PRINSTON PHARMACEUTICALS, INC., DR. REDDY'S LABORATORIES, INC., DR. REDDY'S LABORATORIES, LTD., HETERO USA, INC., HETERO LABS LIMITED UNIT-V, and HETERO LABS LIMITED,

Defendants.

Civil Action No. _____

COMPLAINT FOR PATENT INFRINGEMENT

(Filed Electronically)

Plaintiffs Mitsubishi Tanabe Pharma Corp. ("MTPC"), Janssen Pharmaceuticals, Inc. ("JPI"), Janssen Pharmaceutica NV ("JNV"), Janssen Research and Development, LLC ("JRD"), and Cilag GmbH International ("Cilag") (collectively, "Plaintiffs"), by their attorneys, for their complaint against Prinston Pharmaceuticals, Inc. ("Prinston"), Dr. Reddy's Laboratories, Inc. ("DRL Inc."), Dr. Reddy's Laboratories, Ltd. ("DRL Ltd.") (DRL Inc. and DRL Ltd. collectively, "DRL"), Hetero USA, Inc. ("Hetero USA"), Hetero Labs Limited Unit-V ("Hetero Unit-V"), Hetero Labs Limited ("Hetero Labs") (Hetero USA, Hetero Unit-V, and Hetero Labs collectively, "Hetero") (collectively, "Defendants") allege as follows:

NATURE OF THE ACTION

1. This is a civil action for infringement of United States Patent Nos. 7,943,582 (the "'582 patent") and 8,513,202 (the "'202 patent") (collectively, the "Patents-in-suit") under the patent laws of the United States, 35 U.S.C. §100, *et seq.* This action arises from Prinston's filing of Abbreviated New Drug Application ("ANDA") No. 210514 ("the Prinston ANDA") with the United States Food and Drug Administration ("FDA") seeking approval to commercially market generic versions of JPI's 100 mg and 300 mg INVOKANA® drug product ("the Prinston ANDA Product"), DRL's filing of ANDA No. 210502 ("the DRL ANDA") with the FDA seeking approval to commercially market generic versions of JPI's 50 mg/500 mg; 50 mg/1 g; 150 mg/500 mg; and 150 mg/1 g INVOKAMET® drug product ("the DRL ANDA Product"), and Hetero USA's filing of ANDA No. 210477 ("the Hetero ANDA") with the FDA seeking approval to commercially market generic versions of JPI's 100 mg and 300 mg INVOKANA® drug product ("the Hetero ANDA Product").

THE PARTIES

2. MTPC is a corporation organized and existing under the laws of Japan, having an office and place of business at 3-2-10, Dosho-machi, Chuo-ku, Osaka 541-8505, Japan.

3. JPI is a corporation organized and existing under the laws of the State of Pennsylvania, having its principal place of business at 1125 Trenton-Harbourton Road, Titusville, New Jersey 08560.

4. JNV is a corporation organized and existing under the laws of Belgium, having its principal place of business at Turnhoutseweg, 30, 2340 Beerse, Belgium.

5. JRD is a corporation organized and existing under the laws of the State of New Jersey, having its principal place of business at 920 Route 202, Raritan, New Jersey 08869.

6. Cilag is a company organized and existing under the laws of Switzerland, having its principal place of business at Gubelstrasse 34, 6300, Zug, Switzerland.

7. On information and belief, defendant Prinston is a corporation organized and existing under the laws of the State of Delaware, having its principal place of business at 2002 Eastpark Boulevard, Cranbury, New Jersey 08512.

8. On information and belief, DRL Inc. is a corporation organized and existing under the laws of the State of New Jersey, having its principal place of business at 107 College Road East, Princeton, New Jersey 08540.

9. On information and belief, defendant DRL Ltd. is an Indian corporation, having its principal place of business at 8-2-337, Road No. 3, Banjara Hills, Hyderabad, Telangana 500034, Andhra Pradesh, India.

10. On information and belief, defendant Hetero USA is a company organized and existing under the laws of Delaware, having its principal place of business at 1035 Centennial Avenue, Piscataway, NJ 08854.

11. On information and belief, defendant Hetero Labs is an Indian corporation, having its principal place of business at 7-2-A2 Hetero Corporate Industrial Estate, Sanath Nagar, Hyderabad 500 018, Telangana, India.

12. On information and belief, defendant Hetero Unit-V is an Indian corporation having its principal place of business at Polepally Village, Jadcherla Mandal, Mahabubnagar 509 301, Andhra Pradesh, India.

THE PATENTS-IN-SUIT

13. On May 17, 2011, the United States Patent and Trademark Office ("USPTO") duly and lawfully issued the '582 patent, entitled "Crystalline form of 1-(β-D-glucopyransoyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate" to MTPC as assignee of inventors Sumihiro Nomura and Eiji Kawanishi. A copy of the '582 patent is attached as Exhibit A.

14. JPI, JRD, and Cilag are exclusive licensees of the '582 patent.

15. JNV is an exclusive sublicensee of the '582 patent.

16. On August 20, 2013, the USPTO duly and lawfully issued the '202 patent, entitled "Crystalline form of 1-(β-D-glucopyransoyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate" to MTPC as assignee of inventors Sumihiro Nomura and Eiji Kawanishi. A copy of the '202 patent is attached as Exhibit B.

17. JPI, JRD, and Cilag are exclusive licensees of the '202 patent.

18. JNV is an exclusive sublicensee of the '202 patent.

THE INVOKANA® AND INVOKAMET® DRUG PRODUCTS

19. JPI holds approved New Drug Application ("NDA") No. 204042 for canagliflozin tablets, which are prescribed and sold under the trademark INVOKANA®. INVOKANA® is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

20. JPI holds approved NDA No. 204353 for canagliflozin and metformin hydrochloride tablets, which are prescribed and sold under the trademark INVOKAMET®. INVOKAMET® is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who are not adequately controlled on a regimen containing metformin or canagliflozin or in patients who are already being treated with both canagliflozin and metformin.

21. The claims of the Patents-in-suit cover, *inter alia*, certain polymorphic forms of canagliflozin.

22. Pursuant to 21 U.S.C. § 355(b)(1), and attendant FDA regulations, the '582 and '202 patents are listed in the FDA publication "Approved Drug Products with Therapeutic Equivalence Evaluations" (the "Orange Book"), with respect to both INVOKANA® and INVOKAMET®.

SUBJECT MATTER JURISDICTION

23. 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.

PERSONAL JURISDICTION AND VENUE OVER PRINSTON

24. This Court has personal jurisdiction over Prinston because, *inter alia*, Prinston has committed an act of patent infringement under 35 U.S.C. § 271(e)(2) and intends a

future course of conduct that includes acts of patent infringement in New Jersey. These acts have led and will lead to foreseeable harm and injury to Plaintiffs in New Jersey. For example, on information and belief, following approval of the Prinston ANDA, Prinston will make, use, import, sell, and/or offer for sale the Prinston ANDA Product in the United States, including in New Jersey, prior to the expiration of the Patents-in-suit.

25. This Court also has personal jurisdiction over Prinston because, *inter alia*, this action arises from actions of Prinston directed toward New Jersey. For example, Prinston's counsel sent a letter dated May 30, 2017 to JPI, a corporation with its principal place of business in this Judicial District stating that Prinston had submitted ANDA No. 210514 seeking approval to commercially manufacture, use, import, offer for sale, and sell the Prinston ANDA Product prior to the expiration of the Patents-in-suit. If Prinston succeeds in obtaining FDA approval, it would sell its Prinston ANDA Product in New Jersey and other states, causing injury to Plaintiffs in New Jersey. On information and belief, Prinston is registered as a wholesaler in the State of New Jersey (No. 5004252). *See* New Jersey Registration and Verification, http://web.doh.state.nj.us/apps2/FoodDrugLicense/fdList.aspx (last visited July 7, 2017).

26. The Court also has personal jurisdiction over Prinston because Prinston has purposefully availed itself of the rights and benefits of New Jersey law by engaging in systematic and continuous contacts with the State of New Jersey. On information and belief, Prinston maintains its principal place of business in the State of New Jersey. On information and belief, Prinston regularly and continuously transacts business within New Jersey, including by selling pharmaceutical products in New Jersey. On information and belief, Prinston derives substantial revenue from the sale of those products in New Jersey and has availed itself of the privilege of conducting business within New Jersey.

27. Prinston states on its website that it engages in "developing, sales & marketing of generic pharmaceutical products in North American markets," and has "launched 10 products in US." Prinston, http://www.prinstonpharm.com (last visited July 7, 2017.)

28. On information and belief, Prinston has continuously placed its products into the stream of commerce for distribution and consumption in the State of New Jersey and throughout the United States, and thus has engaged in the regular conduct of business within this Judicial District.

29. On information and belief, Prinston derives substantial revenue from selling generic pharmaceutical products throughout the United States, including in this Judicial District.

30. On information and belief, Prinston has previously invoked, stipulated and/or consented to personal jurisdiction in this Judicial District in numerous prior patent cases.

31. Prinston has previously been sued in this Judicial District and has availed itself of New Jersey courts through the assertion of counterclaims in suits brought in New Jersey, including in *Sebela International Limited v. Prinston Pharmaceutical Inc., et al.*, Civil Action Nos. 14-7400 (D.N.J.) and 15-5308 (D.N.J.) (consolidated under the lead case *In re Sebela Patent Litigation*, Civil Action No. 14-6414 (D.N.J.)) (not contesting personal jurisdiction or venue and asserting counterclaims), *Boehringer Ingelheim Pharmaceuticals Inc., et al. v. Dr. Reddy's Laboratories, Ltd., et al.*, Civil Action No. 16-2394 (D.N.J.) (not contesting personal jurisdiction or venue and asserting counterclaims), and *AstraZeneca AB, et al. v. Prinston Pharmaceutical Inc.*, Civil Action No. 15-3380 (D.N.J.) (not contesting personal jurisdiction or venue and asserting counterclaims).

32. Venue is proper for Prinston under 28 U.S.C. § 1400(b) because, *inter alia*, Prinston has a regular and established place of business in New Jersey and will commit further acts of infringement in this Judicial District, as set forth in paragraphs 24-25 above.

PERSONAL JURISDICTION AND VENUE OVER DRL

33. On information and belief, DRL Ltd. and DRL Inc. operate as part of a single, integrated generic pharmaceutical manufacturer with DRL Ltd. as the ultimate parent. DRL's website notes that DRL "manage[s] the entire value chain – from producing the active ingredients to developing formulations to distributing them through [its] streamlined supply chain." DRL Generics, http://www.drreddys.com/our-products/business-focus/generics/ (last visited July 9, 2017). DRL also states on its website it has "centers across the USA." DRL Capabilities, http://www.drreddys.com/our-science/capabilities/ (last visited July 9, 2017).

34. On information and belief, DRL Ltd. and DRL Inc. have been, and continue to be, joint and prime actors in the drafting, submission, approval, and maintenance of the DRL ANDA.

35. This Court has personal jurisdiction over DRL Inc. because, *inter alia*, DRL Inc. is a corporation organized and existing under the laws of the State of New Jersey, and DRL Inc. has its principal place of business in this Judicial District.

36. Venue is proper for DRL Inc. under 28 U.S.C. § 1400(b) because, *inter alia*, DRL Inc. is a corporation organized and existing under the laws of the State of New Jersey, and DRL Inc. has its principal place of business in this Judicial District.

37. This Court has personal jurisdiction over DRL Ltd. because, *inter alia*, DRL Ltd. has committed an act of patent infringement under 35 U.S.C. § 271(e)(2) and intends a future course of conduct that includes acts of patent infringement in New Jersey. These acts have led and will lead to foreseeable harm and injury to Plaintiffs in New Jersey. For example,

on information and belief, following approval of the DRL ANDA, DRL Ltd. will work in concert with DRL Inc. to make, use, import, sell, and/or offer for sale the DRL ANDA Product in the United States, including in New Jersey, prior to the expiration of the Patents-in-suit.

38. This Court also has personal jurisdiction over DRL Ltd. because, *inter alia*, this action arises from actions of DRL Ltd. directed toward New Jersey. For example, DRL's counsel sent a letter dated June 2, 2017 to JPI, a corporation with its principal place of business in this Judicial District stating that DRL had submitted ANDA No. 210502 seeking approval to commercially manufacture, use, import, offer for sale, and sell the DRL ANDA Product prior to the expiration of the Patents-in-suit. If DRL succeeds in obtaining FDA approval, DRL Ltd. will work in concert with DRL Inc. to sell its DRL ANDA Product in New Jersey and other states, causing injury to Plaintiffs in New Jersey.

39. This Court also has personal jurisdiction over DRL Ltd. because DRL Ltd. has purposefully availed itself of the rights and benefits of New Jersey law by engaging in systematic and continuous contacts with the State of New Jersey. On information and belief, DRL Ltd. regularly and continuously transacts business within New Jersey, including by making pharmaceutical products for sale in New Jersey and selling pharmaceutical products in New Jersey. On information and belief, DRL Ltd. derives substantial revenue from the sale of those products in New Jersey and has availed itself of the privilege of conducting business within New Jersey. For example, DRL's website states that DRL offers "more than 200 high-quality generic versions of expensive innovator medicines—at a fraction of the cost—in over 80 countries around the world" including, on information and belief, the United States and the State of New Jersey. DRL Generics, http://www.drreddys.com/our-products/business-focus/generics/ (last

visited July 9, 2017). DRL's website also notes that "generics is [its] largest business." DRL Capabilities, http://www.drreddys.com/our-science/capabilities/ (last visited July 9, 2017).

40. On information and belief, DRL Ltd. has continuously placed its products into the stream of commerce for distribution and consumption in the State of New Jersey, and throughout the United States, and thus has engaged in the regular conduct of business within this Judicial District.

41. On information and belief, DRL Ltd. derives substantial revenue from selling generic pharmaceutical products throughout the United States, including in this Judicial District.

42. On information and belief, DRL Ltd. has previously invoked, stipulated, and/or consented to personal jurisdiction in this Judicial District in numerous prior patent cases.

43. DRL Ltd. has previously been sued in this Judicial District and has availed itself of New Jersey courts through the assertion of counterclaims in suits brought in New Jersey, including in *Teva Pharmaceuticals USA, Inc., et al., v. Dr. Reddy's Laboratories, Ltd., et al.*, Civil Action No. 17-517 (not contesting personal jurisdiction and asserting counterclaims), *Celgene Corporation v. Dr. Reddy's Laboratories, Ltd., et al.*, Civil Action No. 16-7704 (D.N.J) (not contesting personal jurisdiction or venue and asserting counterclaims), and *Fresenius Kabi USA, LLC v. Dr. Reddy's Laboratories, Inc., et al.*, Civil Action No. 16-3316 (D.N.J.) (not contesting personal jurisdiction or venue and asserting counterclaims).

44. On information and belief, DRL Inc. is a subsidiary of DRL Ltd. and is controlled and dominated by DRL Ltd.

45. On information and belief, DRL Inc. is in the business, *inter alia*, of developing, manufacturing, and obtaining regulatory approval of generic copies of branded

pharmaceutical products for distribution and sale throughout the United States, including within this Judicial District. On information and belief, DRL Inc. markets, distributes, sells, and/or offers for sale generic drugs throughout the United States and in New Jersey at the direction of, under the control of, and for the direct benefit of DRL Ltd. On information and belief, DRL Inc. is organized and existing under the laws of the State of New Jersey and has its principal place of business in this Judicial District. This Court has jurisdiction over DRL Ltd. because, on information and belief, DRL Ltd. is the parent corporation of DRL Inc.

46. In the alternative, this Court has jurisdiction over DRL Ltd. because the requirements of Federal Rule of Civil Procedure 4(k)(2)(A) are met as (a) Plaintiffs' claims arise under federal law; (b) DRL Ltd. is a foreign defendant not subject to general personal jurisdiction in the courts of any state; and (c) DRL Ltd. has sufficient contacts with the United States as a whole, including, but not limited to, preparing and submitting an ANDA to the FDA and/or manufacturing and/or selling pharmaceutical products distributed throughout the United States, such that this Court's exercise of jurisdiction over DRL Ltd. satisfies due process.

47. Venue is proper for DRL Ltd. under 28 U.S.C. §§ 1391 and/or 1400(b), including because, *inter alia*, DRL Ltd. is subject to personal jurisdiction in this Judicial District, as set forth above, has committed an act of infringement and will commit further acts of infringement in this Judicial District, as set forth in paragraphs 37-38 above, continuously transacts business in this Judicial District, as set forth in paragraph 39 above, and/or has a continuous and permanent presence in this Judicial District through its subsidiary, DRL Inc.

PERSONAL JURISDICTION AND VENUE OVER HETERO

48. On information and belief, Hetero USA, Hetero Unit-V, and Hetero Labs operate as part of a single, integrated generic pharmaceutical manufacturer with Hetero Labs as the ultimate parent. Hetero's website notes that "Hetero's fully vertical integration of products

and services ensures most cost-competitive supply of pharmaceutical APIs and finished dosage products." Hetero, http://heteroworld.com/pages/why-hetero/ (last accessed July 7, 2017). On Hetero's website, Hetero USA is listed as Hetero's USA Marketing Office. Hetero Contact Us, https://heteroworld.com/pages/contactus/ (last visited July 7, 2017). On information and belief, Hetero Labs, Hetero Unit-V, and Hetero USA share common corporate directors.

49. Hetero's website states that it has "a portfolio of more than 200 marketed products and 150 ANDAs filed across major therapeutic areas." Hetero Generics, https://heteroworld.com/pages/business-generics/ (last visited July 9, 2017).

50. On information and belief, Hetero USA, Hetero Unit-V, and Hetero Labs have been, and continue to be, joint and prime actors in the drafting, submission, approval, and maintenance of the Hetero ANDA.

51. Upon information and belief, Hetero USA is the "U.S. Regulatory Agent" with respect to the Hetero ANDA. On information and belief, Hetero USA filed the Hetero ANDA as Hetero Labs's and Hetero Unit-V's agent under Hetero Labs's and Hetero Unit-V's direction and control.

52. On information and belief, Hetero Unit-V is a division of Hetero Labs.

53. This Court has personal jurisdiction over Hetero USA because, *inter alia*, Hetero USA has committed an act of patent infringement under 35 U.S.C. § 271(e)(2) and intends a future course of conduct that includes acts of patent infringement in New Jersey. These acts have led and will lead to foreseeable harm and injury to Plaintiffs in New Jersey. For example, on information and belief, following approval of the Hetero ANDA, Hetero USA will work in concert with Hetero Labs and Hetero Unit-V to make, use, import, sell, and/or offer for

sale the Hetero ANDA Product in the United States, including in New Jersey, prior to the expiration of the Patents-in-suit.

54. This Court also has personal jurisdiction over Hetero USA because, *inter alia*, this action arises from actions of Hetero USA directed toward New Jersey. For example, Hetero's counsel sent a letter dated June 2, 2017 to JPI, a corporation with its principal place of business in this Judicial District stating that Hetero USA had submitted ANDA No. 210477 seeking approval to commercially manufacture, use, import, offer for sale, and sell the Hetero ANDA Product prior to the expiration of the Patents-in-suit. If Hetero USA succeeds in obtaining FDA approval, Hetero USA will work in concert with Hetero Labs and Hetero Unit-V to sell its Hetero ANDA Product in New Jersey and other states, causing injury to Plaintiffs in New Jersey. On information and belief, Hetero USA is registered as a wholesaler in the State of New Jersey (No. 5004050). *See* New Jersey Registration and Verification, http://web.doh.state.nj.us/apps2/FoodDrugLicense/fdList.aspx (last visited July 7, 2017).

55. The Court also has personal jurisdiction over Hetero USA because Hetero USA has purposefully availed itself of the rights and benefits of New Jersey law by engaging in systematic and continuous contacts with the State of New Jersey. On information and belief, Hetero USA maintains its principal place of business in New Jersey and regularly and continuously transacts business within New Jersey, including by selling pharmaceutical products in New Jersey. Hetero lists Hetero USA's address at 1031 Centennial Avenue, Piscataway, New Jersey 08854. Hetero Contact Us, https://heteroworld.com/pages/contactus/ (last visited July 7, 2017). On information and belief, Hetero USA derives substantial revenue from the sale of those products in New Jersey and has availed itself of the privilege of conducting business within New Jersey.

56. On information and belief, Hetero USA has continuously placed its products into the stream of commerce for distribution and consumption in the State of New Jersey, and throughout the United States, and thus has engaged in the regular conduct of business within this Judicial District.

57. On information and belief, Hetero USA derives substantial revenue from selling generic pharmaceutical products throughout the United States, including in this Judicial District.

58. On information and belief, Hetero USA has previously invoked, stipulated, and/or consented to personal jurisdiction in this Judicial District in numerous prior patent cases.

59. Hetero USA has previously been sued in this Judicial District and has availed itself of New Jersey courts through the assertion of counterclaims in suits brought in New Jersey, including in *AstraZeneca AB, et al. v. Hetero USA Inc., et al.*, Civil Action No. 16-2442 (D.N.J.) (not contesting personal jurisdiction or venue and asserting counterclaims), *AstraZeneca AB, et al. v. Hetero Labs Limited, et al.*, Civil Action No. 15-3385 (D.N.J.) (not contesting personal jurisdiction or venue and asserting counterclaims), and *Otsuka Pharmaceutical Co., Ltd. v. Hetero Drugs Limited, et al.*, Civil Action No. 15-161 (D.N.J.) (not contesting personal jurisdiction or venue and asserting counterclaims).

60. Venue is proper for Hetero USA under 28 U.S.C. § 1400(b) because, *inter alia*, Hetero USA has a regular and established place of business in New Jersey and will commit further acts of infringement in this Judicial District, as set forth in paragraphs 53-54 above.

61. This Court has personal jurisdiction over Hetero Unit-V because, *inter alia*, Hetero Unit-V has committed an act of patent infringement under 35 U.S.C. § 271(e)(2) and

intends a future course of conduct that includes acts of patent infringement in New Jersey. These acts have led and will lead to foreseeable harm and injury to Plaintiffs in New Jersey. For example, on information and belief, following approval of the Hetero ANDA, Hetero Unit-V will work in concert with Hetero USA and Hetero Labs to make, use, import, sell, and/or offer for sale the Hetero ANDA Product in the United States, including in New Jersey, prior to the expiration of the Patents-in-suit.

62. This Court also has personal jurisdiction over Hetero Unit-V because, *inter alia*, this action arises from actions of Hetero Unit-V directed toward New Jersey. For example, Hetero's counsel sent a letter dated June 2, 2017 to JPI, a corporation with its principal place of business in this Judicial District stating that Hetero USA, the regulatory agent for Hetero Unit-V, had submitted ANDA No. 210477 seeking approval to commercially manufacture, use, import, offer for sale, and sell the Hetero ANDA Product prior to the expiration of the Patents-in-suit. If Hetero USA succeeds in obtaining FDA approval, Hetero Unit-V will work in concert with Hetero USA and Hetero Labs to sell its Hetero ANDA Product in New Jersey and other states, causing injury to Plaintiffs in New Jersey.

63. This Court also has personal jurisdiction over Hetero Unit-V because Hetero Unit-V has purposefully availed itself of the rights and benefits of New Jersey law by engaging in systematic and continuous contacts with the State of New Jersey. On information and belief, Hetero Unit-V regularly and continuously transacts business within New Jersey, including by making pharmaceutical products for sale in New Jersey and selling pharmaceutical products in New Jersey. On information and belief, Hetero Unit-V derives substantial revenue from the sale of those products in New Jersey and has availed itself of the privilege of conducting business within New Jersey. For example, Hetero's website states it has "a portfolio

of more than 200 marketed products and 150 ANDAs filed across major therapeutic areas." Hetero Generics, https://heteroworld.com/pages/business-generics/ (last visited July 9, 2017).

64. On information and belief, Hetero Unit-V has continuously placed its products into the stream of commerce for distribution and consumption in the State of New Jersey, and throughout the United States, and thus has engaged in the regular conduct of business within this Judicial District.

65. On information and belief, Hetero Unit-V derives substantial revenue from selling generic pharmaceutical products throughout the United States, including in this Judicial District.

66. On information and belief, Hetero Unit-V has previously invoked, stipulated, and/or consented to personal jurisdiction in this Judicial District in numerous prior patent cases.

67. Hetero Unit-V has previously been sued in this Judicial District and has not contested personal jurisdiction or venue, including in *BTG International Ltd., et al. v. Actavis Laboratories FL, Inc., et al.*, Civil Action No. 15-5909 (D.N.J.).

68. On information and belief, Hetero USA is in the business, *inter alia*, of developing, manufacturing, and obtaining regulatory approval of generic copies of branded pharmaceutical products for distribution and sale throughout the United States, including within this Judicial District. On information and belief, Hetero USA markets, distributes, sells, and/or offers for sale generic drugs throughout the United States and in New Jersey at the direction of, under the control of, and for the direct benefit of Hetero Unit-V.

69. In the alternative, this Court has jurisdiction over Hetero Unit-V because the requirements of Federal Rule of Civil Procedure 4(k)(2)(A) are met as (a) Plaintiffs' claims

arise under federal law; (b) Hetero Unit-V is a foreign defendant not subject to general personal jurisdiction in the courts of any state; and (c) Hetero Unit-V has sufficient contacts with the United States as a whole, including, but not limited to, preparing and submitting an ANDA to the FDA and/or manufacturing and/or selling pharmaceutical products distributed throughout the United States, such that this Court's exercise of jurisdiction over Hetero Unit-V satisfies due process.

70. Venue is proper for Hetero Unit-V under 28 U.S.C. §§ 1391 and/or 1400(b), including because, *inter alia*, Hetero Unit-V is subject to personal jurisdiction in this Judicial District, as set forth above, has committed an act of infringement and will commit further acts of infringement in this Judicial District, as set forth in paragraphs 61-62 above, continuously transacts business in this Judicial District, as set forth in paragraph 63 above, and has a continuous and permanent presence in this Judicial District through its subsidiary, Hetero USA.

71. This Court has personal jurisdiction over Hetero Labs because, *inter alia*, Hetero Labs has committed an act of patent infringement under 35 U.S.C. § 271(e)(2) and intends a future course of conduct that includes acts of patent infringement in New Jersey. These acts have led and will lead to foreseeable harm and injury to Plaintiffs in New Jersey. For example, on information and belief, following approval of the Hetero ANDA, Hetero Labs will work in concert with Hetero USA and Hetero Unit-V to make, use, import, sell, and/or offer for sale the Hetero ANDA Product in the United States, including in New Jersey, prior to the expiration of the Patents-in-suit.

72. This Court also has personal jurisdiction over Hetero Labs because, *inter alia*, this action arises from actions of Hetero Labs directed toward New Jersey. For example,

Hetero's counsel sent a letter dated June 2, 2017 to JPI, a corporation with its principal place of business in this Judicial District stating that Hetero USA, the regulatory agent for Hetero Labs, had submitted ANDA No. 210477 seeking approval to commercially manufacture, use, import, offer for sale, and sell the Hetero ANDA Product prior to the expiration of the Patents-in-suit. If Hetero USA succeeds in obtaining FDA approval, Hetero Labs will work in concert with Hetero USA and Hetero Unit-V to sell its Hetero ANDA Product in New Jersey and other states, causing injury to Plaintiffs in New Jersey.

73. This Court also has personal jurisdiction over Hetero Labs because Hetero Labs has purposefully availed itself of the rights and benefits of New Jersey law by engaging in systematic and continuous contacts with the State of New Jersey. On information and belief, Hetero Labs regularly and continuously transacts business within New Jersey, including by making pharmaceutical products for sale in New Jersey and selling pharmaceutical products in New Jersey. On information and belief, Hetero Labs derives substantial revenue from the sale of those products in New Jersey and has availed itself of the privilege of conducting business within New Jersey. For example, Hetero's website states it has "a portfolio of more than 200 marketed products and 150 ANDAs filed across major therapeutic areas." Hetero Generics, https://heteroworld.com/pages/business-generics/ (last accessed July 9, 2017).

74. On information and belief, Hetero Labs has continuously placed its products into the stream of commerce for distribution and consumption in the State of New Jersey, and throughout the United States, and thus has engaged in the regular conduct of business within this Judicial District.

75. On information and belief, Hetero Labs derives substantial revenue from selling generic pharmaceutical products throughout the United States, including in this Judicial District.

76. On information and belief, Hetero Labs has previously invoked, stipulated, and/or consented to personal jurisdiction in this Judicial District in numerous prior patent cases.

77. Hetero Labs has previously been sued in this Judicial District and has availed itself of New Jersey courts through the assertion of counterclaims in suits brought in New Jersey, including in *AstraZeneca AB, et al. v. Hetero USA Inc., et al.*, Civil Action No. 16-2442 (D.N.J.) (not contesting personal jurisdiction or venue and asserting counterclaims), *AstraZeneca AB, et al. v. Hetero Labs Limited, et al.*, Civil Action No. 15-3385 (D.N.J.) (not contesting personal jurisdiction or venue and asserting counterclaims), and *Otsuka Pharmaceutical Co., Ltd. v. Hetero Drugs Limited, et al.*, Civil Action No. 15-161 (D.N.J.) (not contesting personal jurisdiction or venue and asserting counterclaims).

78. On information and belief, Hetero USA and Hetero Unit-V are subsidiaries of Hetero Labs and are controlled and dominated by Hetero Labs. Hetero's website notes that "Hetero's fully vertical integration of products and services ensures most cost-competitive supply of pharmaceutical APIs and finished dosage products." Hetero, http://heteroworld.com/pages/why-hetero/ (last accessed July 7, 2017).

79. On information and belief, Hetero USA is in the business, *inter alia*, of developing, manufacturing, and obtaining regulatory approval of generic copies of branded pharmaceutical products for distribution and sale throughout the United States, including within this Judicial District. On information and belief, Hetero USA markets, distributes, sells, and/or offers for sale generic drugs throughout the United States and in New Jersey at the direction of,

under the control of, and for the direct benefit of Hetero Labs. On information and belief, Hetero USA is based in Piscataway, NJ. This Court has jurisdiction over Hetero Labs because, on information and belief, Hetero Labs is the ultimate parent corporation of Hetero USA.

80. In the alternative, this Court has jurisdiction over Hetero Labs because the requirements of Federal Rule of Civil Procedure 4(k)(2)(A) are met as (a) Plaintiffs' claims arise under federal law; (b) Hetero Labs is a foreign defendant not subject to general personal jurisdiction in the courts of any state; and (c) Hetero Labs has sufficient contacts with the United States as a whole, including, but not limited to, preparing and submitting an ANDA to the FDA and/or manufacturing and/or selling pharmaceutical products distributed throughout the United States, such that this Court's exercise of jurisdiction over Hetero Labs satisfies due process.

81. Venue is proper for Hetero Labs under 28 U.S.C. §§ 1391 and/or 1400(b), including because, *inter alia*, Hetero Labs is subject to personal jurisdiction in this Judicial District, as set forth above, has committed an act of infringement and will commit further acts of infringement in this Judicial District, as set forth in paragraphs 71-72 above, continuously transacts business in this Judicial District, as set forth in paragraph 73 above, and has a continuous and permanent presence in this Judicial District through its subsidiary, Hetero USA.

PRINSTON'S INFRINGING ANDA SUBMISSION

82. On or about June 1, 2017, JPI received from Prinson's counsel a letter, dated May 30, 2017 ("the Prinston May 30 Letter"), stating that Prinston had submitted the Prinston ANDA to the FDA seeking approval to market the Prinston ANDA Product before the expiration of the '582 patent. MTPC received the Prinston May 30 Letter on or about June 5, 2017.

83. Prinston specifically directed the Prinston May 30 Letter to JPI's headquarters in Raritan, New Jersey, within this Judicial District.

84. The Prinston ANDA Product is intended to be a generic version of INVOKANA®.

85. The Prinston May 30 Letter alleges that the Prinston ANDA Product does not infringe the '582 patent. Notwithstanding these allegations, on information and belief, discovery/testing will show that the Prinston ANDA Product infringes the '582 patent.

86. The Prinston May 30 Letter also alleges that the '582 patent is invalid.

87. This action is being commenced before the expiration of 45 days from the date MTPC and JPI received the Prinston May 30 Letter.

DRL'S INFRINGING ANDA SUBMISSION

88. On or about June 5, 2017, JPI received from DRL's counsel a letter, dated June 2, 2017 ("the DRL June 2 Letter"), stating that DRL had submitted the DRL ANDA to the FDA seeking approval to market the DRL ANDA Product before the expiration of the Patents-in-suit. MTPC received the DRL June 2 Letter on or about June 5, 2017.

89. DRL specifically directed the DRL June 2 Letter to JPI's headquarters in Raritan, New Jersey, within this Judicial District.

90. The DRL ANDA Product is intended to be a generic version of INVOKAMET®.

91. The DRL June 2 Letter alleges that the DRL ANDA Product does not infringe the '582 patent or the '202 patent. Notwithstanding these allegations, on information and belief, discovery/testing will show that the DRL ANDA Product infringes the Patents-in-suit.

92. This action is being commenced before the expiration of 45 days from the date MTPC and JPI received the DRL June 2 Letter.

HETERO USA'S INFRINGING ANDA SUBMISSION

93. On or about June 6, 2017, JPI received from Hetero USA's counsel a letter, dated June 2, 2017 ("the Hetero June 2 Letter"), stating that Hetero USA as the U.S. regulatory agent for Hetero Unit-V, a division of Hetero Labs, had submitted the Hetero ANDA to the FDA seeking approval to market the Hetero ANDA Product before the expiration of the Patents-in-suit. MTPC received the Hetero June 2 Letter on or about June 7, 2017.

94. Hetero USA specifically directed the Hetero June 2 Letter to JPI's headquarters in Raritan, New Jersey, within this Judicial District.

95. The Hetero ANDA Product is intended to be a generic version of INVOKANA®.

96. On information and belief, following FDA approval of Hetero USA's ANDA, Hetero USA, Hetero Unit-V, and Hetero Labs will work in concert with one another to make, use, sell, or offer to sell the Hetero ANDA Product throughout the United States, or import such generic products into the United States.

97. The Hetero June 2 Letter alleges that the Hetero ANDA Product does not infringe the '582 patent or the '202 patent. Notwithstanding these allegations, on information and belief, discovery/testing will show that the Hetero ANDA Product infringes the Patents-in-suit.

98. This action is being commenced before the expiration of 45 days from the date MTPC and JPI received the Hetero June 2 Letter.

COUNT I
Infringement of U.S. Patent No. 7,943,582 by Prinston

99. Plaintiffs repeat and reallege paragraphs 1-98 above as if fully set forth herein.

100. By filing its ANDA No. 210514 for the purpose of obtaining approval to engage in the commercial manufacture, use, sale, offer for sale, or importation into the United States of the Prinston ANDA Product before the expiration of the '582 patent, Prinston committed an act of infringement under 35 U.S.C. § 271(e)(2).

101. On information and belief, discovery/testing will show that if Prinston commercially makes, uses, offers to sell, or sells the Prinston ANDA Product within the United States, or imports the Prinston ANDA Product into the United States, or induces or contributes to any such conduct during the term of the '582 patent, it would further infringe at least claims 1, 6, and 7 of the '582 patent under 35 U.S.C. §§ 271(a), (b), and/or (c).

102. Prinston has had knowledge of the '582 patent since at least the date it submitted the Prinston ANDA.

103. Plaintiffs will be irreparably harmed if Prinston is not enjoined from infringing the '582 patent. Plaintiffs do not have an adequate remedy at law.

COUNT II
Infringement of U.S. Patent No. 7,943,582 by DRL

104. Plaintiffs repeat and reallege paragraphs 1-103 above as if fully set forth herein.

105. By filing its ANDA No. 210502 for the purpose of obtaining approval to engage in the commercial manufacture, use, sale, offer for sale, or importation into the United States of the DRL ANDA Product before the expiration of the '582 patent, DRL committed an act of infringement under 35 U.S.C. § 271(e)(2).

106. On information and belief, discovery/testing will show that if DRL commercially makes, uses, offers to sell, or sells the DRL ANDA Product within the United States, or imports the DRL ANDA Product into the United States, or induces or contributes to

any such conduct during the term of the '582 patent, it would further infringe at least claims 1, 6, and 7 of the '582 patent under 35 U.S.C. §§ 271(a), (b), and/or (c).

107. DRL has had knowledge of the '582 patent since at least the date it submitted the DRL ANDA.

108. Plaintiffs will be irreparably harmed if DRL is not enjoined from infringing the '582 patent. Plaintiffs do not have an adequate remedy at law.

COUNT III
Infringement of U.S. Patent No. 8,513,202 by DRL

109. Plaintiffs repeat and reallege paragraphs 1-108 above as if fully set forth herein.

110. By filing its ANDA No. 210502 for the purpose of obtaining approval to engage in the commercial manufacture, use, sale, offer for sale, or importation into the United States of the DRL ANDA Product before the expiration of the '202 patent, DRL committed an act of infringement under 35 U.S.C. § 271(e)(2).

111. On information and belief, discovery/testing will show that if DRL commercially makes, uses, offers to sell, or sells the DRL ANDA Product within the United States, or imports the DRL ANDA Product into the United States, or induces or contributes to any such conduct during the term of the '202 patent, it would further infringe at least claims 1 and 3-5 of the '202 patent under 35 U.S.C. §§ 271(a), (b), and/or (c).

112. DRL has had knowledge of the '202 patent since at least the date it submitted the DRL ANDA.

113. Plaintiffs will be irreparably harmed if DRL is not enjoined from infringing the '202 patent. Plaintiffs do not have an adequate remedy at law.

COUNT IV
Infringement of U.S. Patent No. 7,943,582 by Hetero

114. Plaintiffs repeat and reallege paragraphs 1-113 above as if fully set forth herein.

115. By filing its ANDA No. 210477 for the purpose of obtaining approval to engage in the commercial manufacture, use, sale, offer for sale, or importation into the United States of the Hetero ANDA Product before the expiration of the '582 patent, Hetero USA committed an act of infringement under 35 U.S.C. § 271(e)(2).

116. On information and belief, discovery/testing will show that if Hetero USA, Hetero Unit-V, and/or Hetero Labs commercially makes, uses, offers to sell, or sells the Hetero ANDA Product within the United States, or imports the Hetero ANDA Product into the United States, or induces or contributes to any such conduct during the term of the '582 patent, it would further infringe at least claims 1, 6, and 7 of the '582 patent under 35 U.S.C. §§ 271(a), (b), and/or (c).

117. Hetero USA has had knowledge of the '582 patent since at least the date Hetero USA submitted the Hetero ANDA. Hetero Unit-V and Hetero Labs will have knowledge of the '582 patent no later than the date they are served with this complaint.

118. Plaintiffs will be irreparably harmed if Hetero is not enjoined from infringing the '582 patent. Plaintiffs do not have an adequate remedy at law.

COUNT V
Infringement of U.S. Patent No. 8,513,202 by Hetero

119. Plaintiffs repeat and reallege paragraphs 1-118 above as if fully set forth herein.

120. By filing its ANDA No. 210477 for the purpose of obtaining approval to engage in the commercial manufacture, use, sale, offer for sale, or importation into the United

States of the Hetero ANDA Product before the expiration of the '202 patent, Hetero USA committed an act of infringement under 35 U.S.C. § 271(e)(2).

121. On information and belief, discovery/testing will show that if Hetero Labs, Hetero Unit-V, and/or Hetero USA commercially makes, uses, offers to sell, or sells the Hetero ANDA Product within the United States, or imports the Hetero ANDA Product into the United States, or induces or contributes to any such conduct during the term of the '202 patent, it would further infringe at least claims 1 and 3-5 of the '202 patent under 35 U.S.C. §§ 271(a), (b), and/or (c).

122. Hetero USA has had knowledge of the '202 patent since at least the date Hetero USA submitted the Hetero ANDA. Hetero Labs and Hetero Unit-V will have knowledge of the '202 patent no later than the date they are served with this complaint.

123. Plaintiffs will be irreparably harmed if Hetero is not enjoined from infringing the '202 patent. Plaintiffs do not have an adequate remedy at law.

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs respectfully request the following relief:

A. A Judgment that Prinston has infringed one or more claims of the '582 patent by filing ANDA No. 210514;

B. A Judgment that Prinston has infringed, and that Prinston's making, using, selling, offering to sell, or importing the Prinston ANDA Product would constitute infringement of one or more claims of the '582 patent, and/or induce or contribute to the infringement of one or more claims of the '582 patent pursuant to 35 U.S.C. § 271(a), (b) and/or (c);

C. A permanent injunction restraining and enjoining Prinston, and its officers, agents, attorneys, and employees, and those acting in privity or concert with them, from

engaging in the commercial manufacture, use, offer for sale, or sale within the United States, or importation into the United States, of the Prinston ANDA Product until after the expiration of the '582 patent, or any later expiration of exclusivity to which Plaintiffs are or become entitled;

D. An Order that the effective date of any approval of ANDA No. 210514 relating to the Prinston ANDA Product be a date that is not earlier than the expiration date of the '582 patent as extended plus any other regulatory exclusivity to which Plaintiffs are or become entitled;

E. A Judgment that DRL has infringed one or more claims of the '582 patent by filing ANDA No. 210502;

F. A Judgment that DRL has infringed, and that DRL's making, using, selling, offering to sell, or importing the DRL ANDA Product would constitute infringement of one or more claims of the '582 patent, and/or induce or contribute to infringement of one or more claims of the '582 patent pursuant to 35 U.S.C. § 271(a), (b) and/or (c);

G. A permanent injunction restraining and enjoining DRL, and its officers, agents, attorneys, and employees, and those acting in privity or concert with them, from engaging in the commercial manufacture, use, offer for sale, or sale within the United States, or importation into the United States, of the DRL ANDA Product until after the expiration of the '582 patent, or any later expiration of exclusivity to which Plaintiffs are or become entitled;

H. An Order that the effective date of any approval of ANDA No. 210502 relating to the DRL ANDA Product be a date that is not earlier than the expiration date of the '582 patent as extended plus any other regulatory exclusivity to which Plaintiffs are or become entitled;

I. A Judgment that DRL has infringed one or more claims of the ’202 patent by filing ANDA No. 210502;

J. A Judgment that DRL has infringed, and that DRL’s making, using, selling, offering to sell, or importing the DRL ANDA Product would constitute infringement of one or more claims of the ’202 patent, and/or induce or contribute to infringement of one or more claims of the ’202 patent pursuant to 35 U.S.C. § 271(a), (b) and/or (c);

K. A permanent injunction restraining and enjoining DRL, and its officers, agents, attorneys, and employees, and those acting in privity or concert with them, from engaging in the commercial manufacture, use, offer for sale, or sale within the United States, or importation into the United States, of the DRL ANDA Product until after the expiration of the ’202 patent, or any later expiration of exclusivity to which Plaintiffs are or become entitled;

L. An Order that the effective date of any approval of ANDA No. 210502 relating to the DRL ANDA Product be a date that is not earlier than the expiration date of the ’202 patent as extended plus any other regulatory exclusivity to which Plaintiffs are or become entitled;

M. A Judgment that Hetero has infringed one or more claims of the ’582 patent by filing ANDA No. 210477;

N. A Judgment that Hetero has infringed, and that Hetero’s making, using, selling, offering to sell, or importing the Hetero ANDA Product would constitute infringement of one or more claims of the ’582 patent, and/or induce or contribute to infringement of one or more claims of the ’582 patent pursuant to 35 U.S.C. § 271(a), (b) and/or (c);

O. A permanent injunction restraining and enjoining Hetero, and its officers, agents, attorneys, and employees, and those acting in privity or concert with them, from

engaging in the commercial manufacture, use, offer for sale, or sale within the United States, or importation into the United States, of the Hetero ANDA Product until after the expiration of the '582 patent, or any later expiration of exclusivity to which Plaintiffs are or become entitled;

P. An Order that the effective date of any approval of ANDA No. 210477 relating to the Hetero ANDA Product be a date that is not earlier than the expiration date of the '582 patent as extended plus any other regulatory exclusivity to which Plaintiffs are or become entitled;

Q. A Judgment that Hetero has infringed one or more claims of the '202 patent by filing ANDA No. 210477;

R. A Judgment that Hetero has infringed, and that Hetero's making, using, selling, offering to sell, or importing the Hetero ANDA Product would constitute infringement of one or more claims of the '202 patent, and/or induce or contribute to the infringement of one or more claims of the '202 patent pursuant to 35 U.S.C. § 271(a), (b) and/or (c);

S. A permanent injunction restraining and enjoining Hetero, and its officers, agents, attorneys, and employees, and those acting in privity or concert with them, from engaging in the commercial manufacture, use, offer for sale, or sale within the United States, or importation into the United States, of the Hetero ANDA Product until after the expiration of the '202 patent, or any later expiration of exclusivity to which Plaintiffs are or become entitled;

T. An Order that the effective date of any approval of ANDA No. 210477 relating to the Hetero ANDA Product be a date that is not earlier than the expiration date of the '202 patent as extended plus any other regulatory exclusivity to which Plaintiffs are or become entitled; and

U. Such other and further relief as the Court may deem just and proper.

Dated: July 13, 2017

By: s/ Charles M. Lizza

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CERTIFICATION PURSUANT TO LOCAL CIVIL RULES 11.2 & 40.1

I hereby certify that the matter captioned *Mitsubishi Tanabe Pharma Corporation, et al. v. Aurobindo Pharma USA, Inc., et al.*, Civil Action No. 17-5005 (FLW)(DEA) is related to the matter in controversy because the matter in controversy involves the same patents and, in both cases, the defendants are seeking FDA approval to market generic versions of the same 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: July 13, 2017

By: s/ Charles M. Lizza

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EXHIBIT A

US007943582B2

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

(10) **Patent No.: US 7,943,582 B2**
(45) **Date of Patent: May 17, 2011**

(54) **CRYSTALLINE FORM OF 1-(β-D-GLUCOPYRANSOYL)-4-METHYL-3-[5-(4-FLUOROPHENYL)-2-THIENYLMETHYL]BENZENE HEMIHYDRATE**

(75) Inventors: **Sumihiro Nomura**, Osaka (JP); **Eiji Kawanishi**, Osaka (JP)

(73) Assignee: **Mitsubishi Tanabe Pharma Corporation**, Osaka-Shi (JP)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 451 days.

(21) Appl. No.: **11/987,670**

(22) Filed: **Dec. 3, 2007**

(65) **Prior Publication Data**

US 2008/0146515 A1 Jun. 19, 2008

Related U.S. Application Data

(60) Provisional application No. 60/868,426, filed on Dec. 4, 2006.

(30) **Foreign Application Priority Data**

Dec. 4, 2006 (JP) 2006-327019

(51) **Int. Cl.**
A61K 31/7034 (2006.01)
C07H 7/04 (2006.01)

(52) **U.S. Cl.** **514/23**; 536/1.11

(58) **Field of Classification Search** ..... None
See application file for complete search history.

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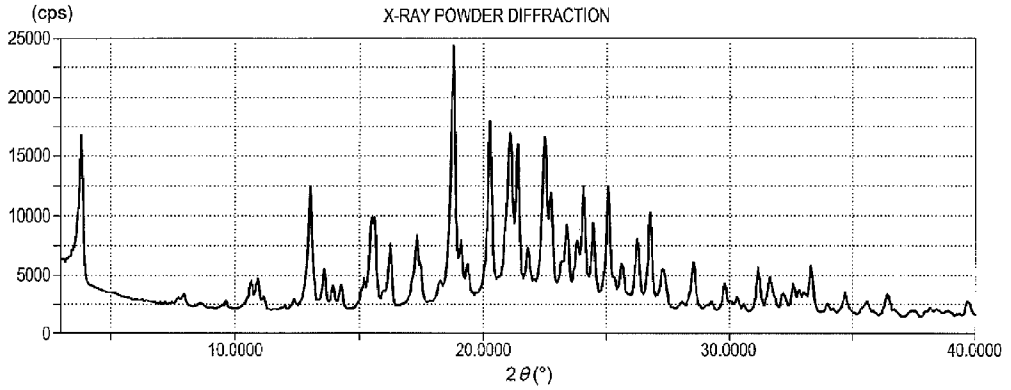
Primary Examiner — Eric S Olson

(74) *Attorney, Agent, or Firm* — Birch, Stewart, Kolasch & Birch, LLP

(57) **ABSTRACT**

A novel crystal form of 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate, and having favorable characteristics, is characterized by its x-ray powder diffraction pattern and/or by its infra-red spectrum.

7 Claims, 2 Drawing Sheets



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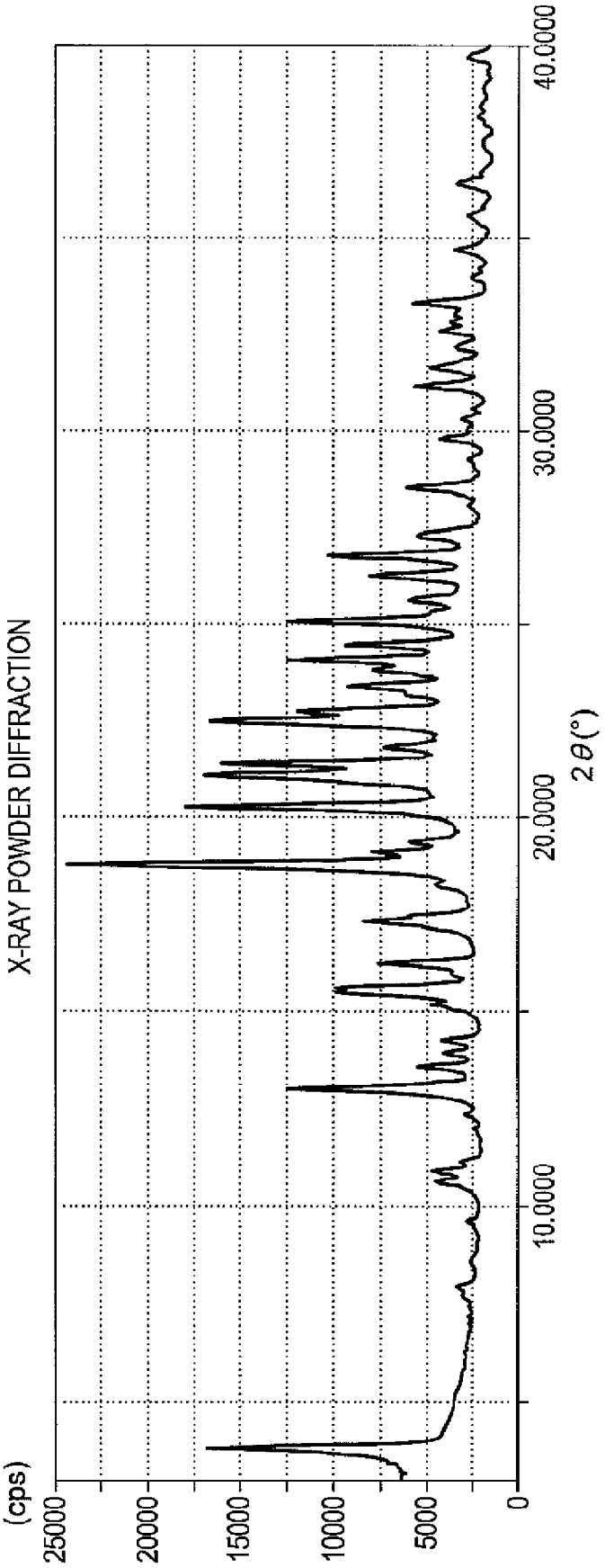
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FIG. 1

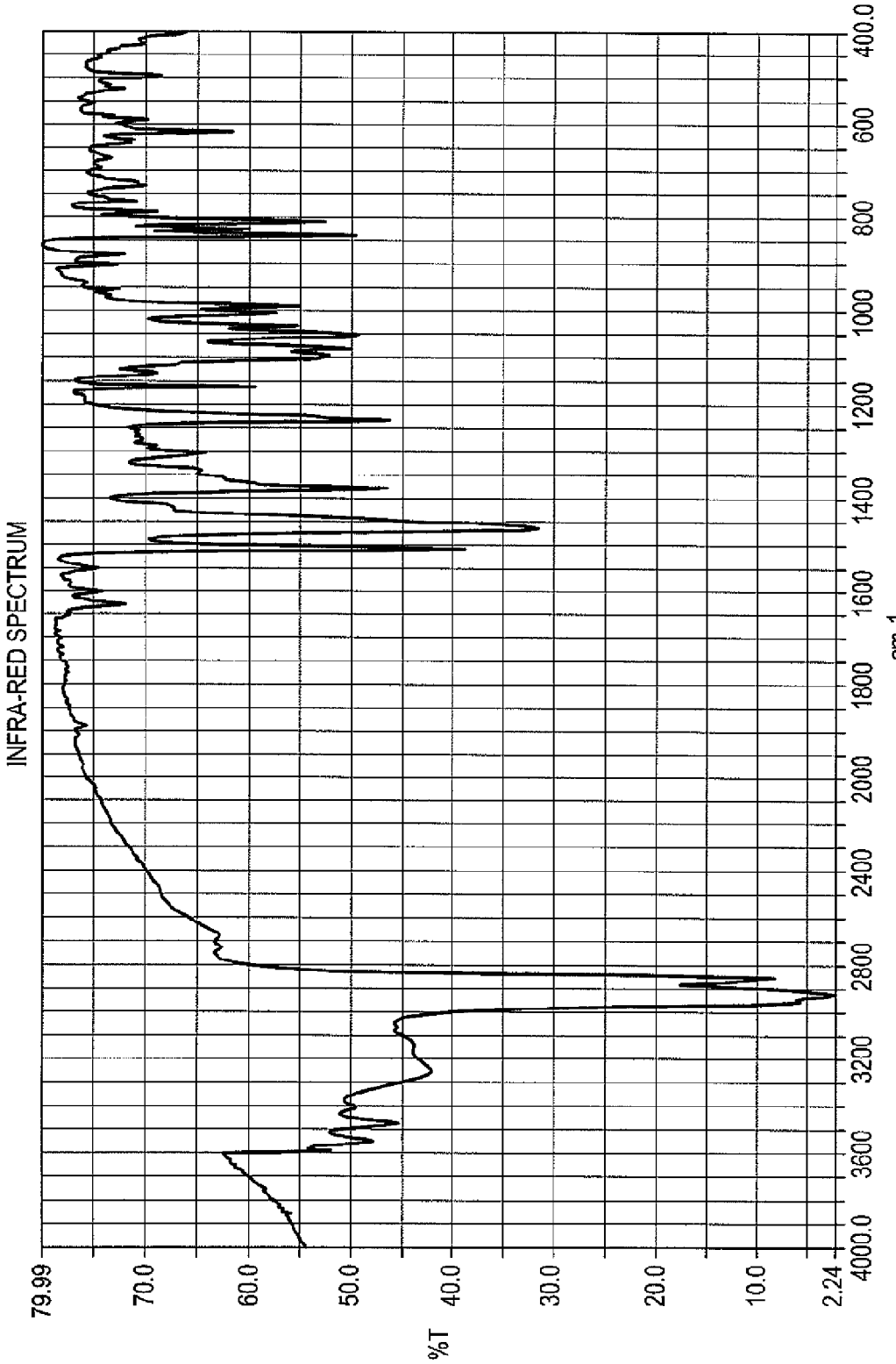
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FIG.2

CRYSTALLINE FORM OF 1-(β-D-GLUCOPYRANSOYL)-4-METHYL-3-[5-(4-FLUOROPHENYL)-2-THIENYLMETHYL]BENZENE HEMIHYDRATE

BACKGROUND OF THE INVENTION

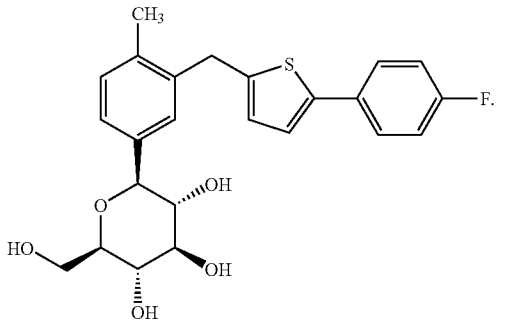
1. Field of the Invention

This invention relates to a crystalline form of 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate useful as an inhibitor of sodium-dependent glucose transporter, to methods for its preparation and isolation, to pharmaceutical compositions which include the compound and a pharmaceutically acceptable carrier, and to pharmaceutical methods of treatment.

2. Description of the Related Art

WO 2005/012326 pamphlet discloses a class of compounds that are inhibitors of sodium-dependent glucose transporter (SGLT) and thus of therapeutic use for treatment of diabetes, obesity, diabetic complications, and the like. There is described in WO 2005/012326 pamphlet 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene of formula (I):

(I)



In general, for commercial use it is important that a product should have good handling qualities. Additionally, there is a need to produce the product in a pure and crystalline form to enable formulations to meet exacting pharmaceutical requirements and specifications.

And it is desirable that the product should be in a form that is readily filterable and easily dried.

Additionally, it is economically desirable that the product be stable for extended periods of time without the need for specialized storage conditions.

But there have been difficulties in obtaining a crystal form of the compound of formula (I) from organic solvents.

It has now been discovered that the compound of formula (I) hemihydrate can be produced in a crystalline form in a manner reproducible on a commercial scale.

SUMMARY OF THE INVENTION

The present invention provides a crystalline form of hemihydrate of the compound of formula (I) as a novel material, in particular in pharmaceutically acceptable form.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1**:

X-ray powder diffraction pattern of the crystalline of hemihydrate of the compound of formula (I).

FIG. **2**:

Infra-red spectrum of the crystalline of hemihydrate of the compound of formula (I).

DETAILED DESCRIPTION OF THE INVENTION

The inventors of the present invention have found that the compounds of formula (I) can be crystallized from a water-containing solvent and the crystalline form of hemihydrate of the compounds (I) have good handling qualities and characteristics.

Accordingly, the present invention is directed to:

1. A crystalline of hemihydrate of 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene.
2. A crystalline of hemihydrate of 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene characterized by a powder x-ray diffraction pattern comprising the following 2θ values measured using CuK_α radiation: 4.36±0.2, 13.54±0.2, 16.00±0.2, 19.32±0.2, 20.80±0.2.
3. A crystalline of hemihydrate of 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene, having substantially the same X-ray powder diffraction pattern as set out in FIG. **1**.
4. A crystalline of hemihydrate of 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene, having substantially the same IR spectrum, as set out in FIG. **2**.
5. A process for the preparation of a crystalline of hemihydrate of 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene, which comprises forming a solution of 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene and crystallizing said hemihydrate from the solution by precipitation or recrystallization.
6. A pharmaceutical composition comprising an effective amount of a crystalline of hemihydrate of 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene and a pharmaceutically acceptable carrier.
7. A method for treatment or delaying the progression or onset of diabetes mellitus, diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, delayed wound healing, insulin resistance, hyperglycemia, hyperinsulinemia, elevated blood levels of fatty acids, elevated blood levels of glycerol, hyperlipidemia, obesity, hypertriglyceridemia, Syndrome X, diabetic complications, atherosclerosis, or hypertension, which comprises administering a therapeutically effective amount of a crystalline of hemihydrate of 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene.

As discussed, the present invention includes a certain solid state crystalline form. Several methods for characterizing such forms exist, and the invention should not be limited by the methods chosen or the instrumentation used in characterizing the compounds of the present invention. For example, with regard to x-ray diffraction patterns, the diffraction peak intensities in the experimental patterns can vary, as is known in the art, primarily due to preferred orientation (non-random orientation of the crystals) in the prepared sample. As such, the scope of the present invention must be considered in light of the variability of characterization that is appreciated by those skilled in the art.

X-Ray Powder Diffraction

The crystalline form of the present invention (I) is characterized by its X-ray powder diffraction pattern. The X-ray diffraction pattern of the crystalline of hemihydrate of the compound (I) was measured on an X-ray diffractometer

(RINT-TTR III, Rigaku, Tokyo, Japan) with measured using CuK_α radiation. Methodology of X-ray powder diffraction is as follows:

Scanning rate: 2.00 degree/minute.

Target: CuK_α.

Voltage: 50 kV.

Current: 300 mA.

Scan range: from 3 to 40.0 degree.

Sampling width: 0.0200 degree.

Infra-Red Spectrum

The infra-red spectrum of the crystalline form of the present invention in mineral oil comprises the following main peaks: 1626, 1600, 1549, and 1507 cm^{-1}.

The infra-red spectrum of crystalline compound (I) hemihydrate is shown in the accompanying drawing in which the ordinate is the transmittance in % and the abscissa is the wavenumber in cm^{-1}.

Thermogravimetric Analysis

The crystalline form of the present invention has been observed to exist in a hemihydrate form. The theoretical water content of the crystalline of the present invention is 1.98%. The thermogravimetric analysis for the crystalline of the present invention shows a mass loss of 1.705%.

Methodology of thermogravimetric analysis is as follows: about 8 mg of compound (I) hemihydrate is weighed and transferred in an aluminum cell holder for TG-50 (Shimadzu, Japan), and then, the thermogravimetric (TG) thermal curve of crystalline compound (I) hemihydrate is determined at a heat rate of 5° C./minute. Typical measuring range is from ambient to 150° C.

The present invention also provides a process for producing the crystalline form of hemihydrate of the compound (I) which comprises forming a solution of compound (I) and precipitating the crystalline form from solution.

Typically, the crystalline of hemihydrate of the compound (I) may be obtained from a mixture of the compound of formula (I), a good solvent and water, optionally containing a poor solvent.

Sometimes some impurities may act as crystallization inhibitors, and impurities need to be removed using a conventional manner, such as silica gel column chromatography. However, the crystalline of hemihydrate of the compound of formula (I) can even be obtained from relatively impure compound (I).

The present invention also provides a pharmaceutical composition comprising the crystalline of hemihydrate of the compound (I) and a pharmaceutically acceptable carrier.

The crystalline compound of the present invention possesses activity as inhibitors of sodium-dependent glucose transporters, and show excellent blood glucose lowering effect.

The crystalline form of the present invention are expected to be useful in the treatment, prevention or delaying the progression or onset of diabetes mellitus (type 1 and type 2 diabetes mellitus, etc.), diabetic complications (such as diabetic retinopathy, diabetic neuropathy, diabetic nephropathy), postprandial hyperglycemia, delayed wound healing, insulin resistance, hyperglycemia, hyperinsulinemia, elevated blood levels of fatty acids, elevated blood levels of glycerol, hyperlipidemia, obesity, hypertriglyceridemia, Syndrome X, atherosclerosis, or hypertension.

The crystalline form of the present invention or a pharmaceutically acceptable salt thereof may be administered either orally or parenterally, and can be used in the form of a suitable pharmaceutical preparation. Suitable pharmaceutical preparations for oral administration include, for example, solid preparations such as tablets, granules, capsules, and powders,

or solution preparations, suspension preparations, emulsion preparations, and the like. Suitable pharmaceutical preparations for parenteral administration include, for example, suppositories; injection preparations or intravenous drip preparations, using distilled water for injection, physiological saline solution or aqueous glucose solution; and inhalant preparations.

The pharmaceutical compositions herein will contain, per dosage unit, e.g., tablet, capsule, powder, injection, suppository, teaspoonful and the like, from about 0.01 mg/kg to about 100 mg/kg body weight (preferably from about 0.01 mg/kg to about 50 mg/kg; and, more preferably, from about 0.01 mg/kg to about 30 mg/kg) of the active ingredient, and may be given at a dosage of from about 0.01 mg/kg/day to about 100 mg/kg/day (preferably from about 0.01 mg/kg/day to about 50 mg/kg/day and more preferably from about 0.01 mg/kg/day to about 30 mg/kg/day). The method of treating a disorder described in the present invention may also be carried out using a pharmaceutical composition comprising the crystalline form as defined herein and a pharmaceutical acceptable carrier. The dosage form will contain from about 0.01 mg/kg to about 100 mg/kg (preferably from about 0.01 mg/kg to about 50 mg/kg; and, more preferably, from about 0.01 mg/kg to about 30 mg/kg) of the active ingredient, and may be constituted into any form suitable for the mode of administration selected. The dosages, however, may be varied depending upon administration routes, the requirement of the subjects, the severity of the condition being treated and the compound being employed. The use of either daily administration or post-periodic dosing may be employed.

The crystalline form of the present invention may be used, if necessary, in combination with one or more of other antidiabetic agents, antihyperglycemic agents and/or agents for treatment of other diseases. The present compounds and these other agents may be administered in the same dosage form, or in a separate oral dosage form or by injection.

The dosage of those agents may vary according to, for example, ages, body weight, conditions of patients, administration routes, and dosage forms.

These pharmaceutical compositions may be orally administered to mammalian species including human beings, apes, and dogs, in the dosage form of, for example, tablet, capsule, granule or powder, or parenterally administered in the form of injection preparation, or intranasally, or in the form of transdermal patch.

The crystalline form of hemihydrate of the compound of formula (I) can be prepared from a mixture of the compound (I), a good solvent and water, optionally containing a poor solvent.

Examples of good solvents which have been found suitable include ketones (e.g., acetone, 2-butanone), esters (e.g., ethyl acetate, methyl acetate), alcohols (e.g., methanol, ethanol, i-propanol), and a mixture of these solvents. Examples of poor solvents include alkanes (e.g., hexane, heptane), aromatic hydrocarbons (e.g., benzene, toluene), ethers (e.g., diethyl ether, dimethyl ether, diisopropyl ether) and a mixture of these solvents.

One preferred preparation of the crystalline form of hemihydrate of the compound of formula (I) typically involves dissolving in a good solvent (e.g., ketones or esters) crude or amorphous compound of formula (I) prepared in accordance with the procedures described in WO 2005/012326 pamphlet, and adding water and a poor solvent (e.g., alkanes or ethers) to the resulting solution, followed by filtration.

In case that a good solvent is soluble in water, a poor solvent needs not be used and water may be added to the

solution of the compound of formula (I) in the good solvent so the solubility of the compound of formula (I) can be decreased in the solution.

In case that a poor solvent is used, water is preferably used in amount of 1 to 10 molar equivalents to the compound of formula (I), the good solvent is preferably used in amount of 10 to 100 times of volume of water, and the poor solvent is preferably used in amount of 0.1 to 10 times of volume of the good solvent.

The precise conditions under which the crystalline of hemihydrate of the compound (I) is formed may be empirically determined.

Under these conditions, crystallization can preferably be carried out at a lowered, ambient or elevated temperature.

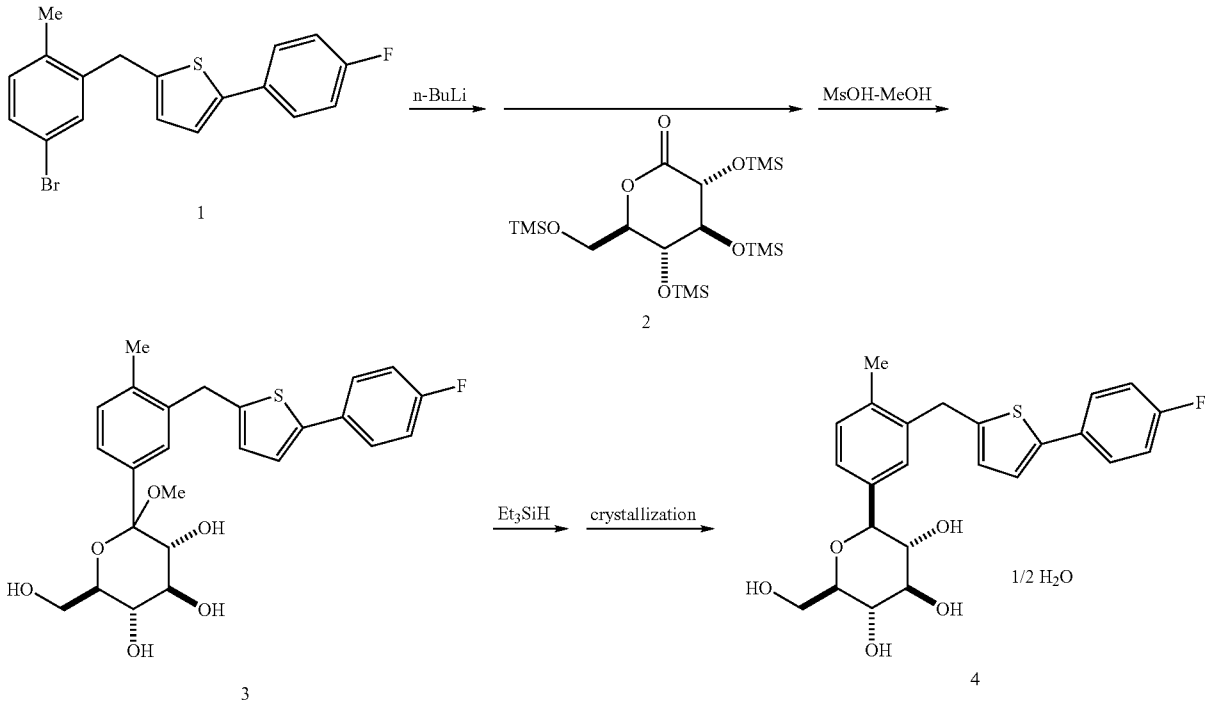
The crystalline form of hemihydrate of the compound of formula (I) is significantly easier to isolate than amorphous form of the compound and can be filtered from the crystallization medium after cooling, and washed and dried. Also, the crystalline form of the present invention is more stable than the amorphous form of the compound of formula (I).

EXAMPLES

Example 1

Crystalline 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate

1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene was prepared in a similar manner as described in WO 2005/012326.



(1) To a solution of 5-bromo-1-[5-(4-fluorophenyl)-2-thienylmethyl]-2-methylbenzene (1, 28.9 g) in tetrahydrofuran (480 ml) and toluene (480 ml) was added n-butyllithium (1.6M hexane solution, 50.0 ml) dropwise at −67 to −70° C. under argon atmosphere, and the mixture was stirred for 20 minutes at the same temperature. Thereto was added a solution of 2 (34.0 g) in toluene (240 ml) dropwise at the same temperature, and the mixture was further stirred for 1 hour at the same temperature. Subsequently, thereto was added a solution of methanesulfonic acid (21.0 g) in methanol (480 ml) dropwise, and the resulting mixture was allowed to warm to room temperature and stirred for 17 hours. The mixture was cooled under ice—water cooling, and thereto was added a saturated aqueous sodium hydrogen carbonate solution. The mixture was extracted with ethyl acetate, and the combined organic layer was washed with brine and dried over magnesium sulfate. The insoluble was filtered off and the solvent was evaporated under reduced pressure. The residue was triturated with toluene (100 ml)—hexane (400 ml) to give 1-(1-methoxyglucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]-benzene (3) (31.6 g). APCI-Mass m/Z 492 ($M+NH_4$).

(2) A solution of 3 (63.1 g) and triethylsilane (46.4 g) in dichloromethane (660 ml) was cooled by dry ice-acetone bath under argon atmosphere, and thereto was added dropwise boron trifluoride•ethyl ether complex (50.0 ml), and the mixture was stirred at the same temperature. The mixture was allowed to warm to 0° C. and stirred for 2 hours. At the same temperature, a saturated aqueous sodium hydrogen carbonate solution (800 ml) was added, and the mixture was stirred for 30 minutes. The organic solvent was evaporated under reduced pressure, and the residue was poured into water and extracted with ethyl acetate twice. The organic layer was washed with water twice, dried over magnesium sulfate and treated with activated carbon. The insoluble was filtered off and the solvent was evaporated under reduced pressure. The residue was dissolved in ethyl acetate (300 ml), and thereto were added diethyl ether (600 ml) and H_2O (6 ml). The mixture was stirred at room temperature overnight, and the

precipitate was collected, washed with ethyl acetate-diethyl ether (1:4) and dried under reduced pressure at room temperature to give 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate (33.5 g) as colorless crystals. mp 98-100° C. APCI-Mass m/Z 462 ($M+NH_4$). ^{1}H-NMR (DMSO-d_6) δ 2.26 (3H, s), 3.13-3.28 (4H, m), 3.44 (1H, m), 3.69 (1H, m), 3.96 (1H, d, J=9.3 Hz), 4.10, 4.15 (each 1H, d, J=16.0 Hz), 4.43 (1H, t, J=5.8 Hz), 4.72 (1H, d, J=5.6 Hz), 4.92 (2H, d, J=4.8 Hz), 6.80 (1H, d, J=3.5 Hz), 7.11-7.15 (2H, m), 7.18-7.25 (3H, m), 7.28 (1H, d, J=3.5 Hz), 7.59 (2H, dd, J=8.8, 5.4 Hz). Anal. Calcd. for $C_{24}H_{25}FO_5S.0.5H_2O$: C, 63.56; H, 5.78; F, 4.19; S, 7.07. Found: C, 63.52; H, 5.72; F, 4.08; S, 7.00.

Example 2

An amorphous powder of 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene (1.62 g) was dissolved in acetone (15 ml), and thereto were added H_2O (30 ml) and a crystalline seed. The mixture was stirred at room temperature for 18 hours, and the precipitate was collected, washed with acetone—H_2O (1:4, 30 ml) and dried under reduced pressure at room temperature to give 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate (1.52 g) as colorless crystals. mp 97-100° C.

The invention claimed is:

1. A crystalline form of 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate.

2. A crystalline form of 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate of claim **1**, having a powder x-ray diffraction pattern comprising the following 2θ values measured using CuK_α radiation: 4.36±0.2, 13.54±0.2, 16.00±0.2, 19.32±0.2, and 20.80±0.2.

3. A crystalline form of 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate of claim **1**, having substantially the same X-ray diffraction pattern as set out in FIG. **1**.

4. A crystalline form of 1-(β-D-glucopyranosyl)-4-methyl-3[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate of claim **1**, having substantially the same IR spectrum, as set out in FIG. **2**.

5. A process for the preparation of a crystalline form of 1-(β-D-glucopyranosyl) -4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate of claim **1**, which comprises forming a solution of 1-(β-D-glucopyranosyl)-4-methyl-3[5-(4-fluoro-phenyl) -2-thienylmethyl]benzene and crystallizing said hemihydrate from the solution by precipitation or recrystallization.

6. A pharmaceutical composition comprising an effective amount of a crystalline form of 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate of claim **1** and a pharmaceutically acceptable carrier.

7. A method for treatment or delaying the progression or onset of diabetes mellitus, diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, delayed wound healing, insulin resistance, hyperglycemia, hyperinsulinemia, elevated blood levels of fatty acids, elevated blood levels of glycerol, hyperlipidemia, obesity, hypertriglyceridemia, Syndrome X, diabetic complications, atherosclerosis, or hypertension, which comprises administering a therapeutically effective amount of a crystalline form of 1-(β-D-glucopyranosyl)-4-methyl-3[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate of claim **1** to a subject in need thereof.

* * * * *

EXHIBIT B

US008513202B2

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

(10) **Patent No.: US 8,513,202 B2**
(45) **Date of Patent: *Aug. 20, 2013**

(54) **CRYSTALLINE FORM OF 1-(β-D-GLUCOPYRANOSYL)-4-METHYL-3-[5-(4-FLUOROPHENYL)-2-THIENYL-METHYL]BENZENE HEMIHYDRATE**

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(73) Assignee: **Mitsubishi Tanabe Pharma Corporation**, Osaka-Shi (JP)

(*) 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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(51) **Int. Cl.**
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C07H 7/04 (2006.01)

(52) **U.S. Cl.**
CPC ***A61K 31/7034*** (2013.01); ***C07H 7/04*** (2013.01)
USPC **514/23**; 536/122

(58) **Field of Classification Search**
None
See application file for complete search history.

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(57) **ABSTRACT**

A novel crystal form of 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate, and having favorable characteristics, is characterized by its x-ray powder diffraction pattern and/or by its infra-red spectrum.

5 Claims, 2 Drawing Sheets

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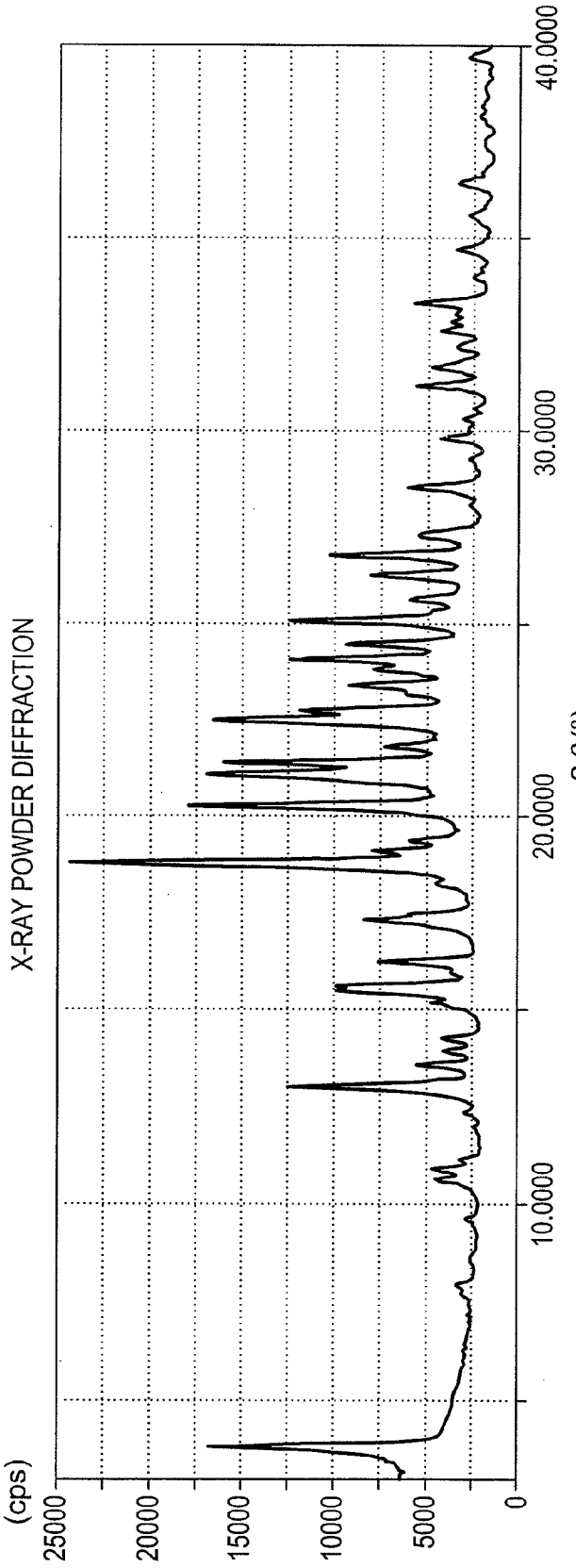
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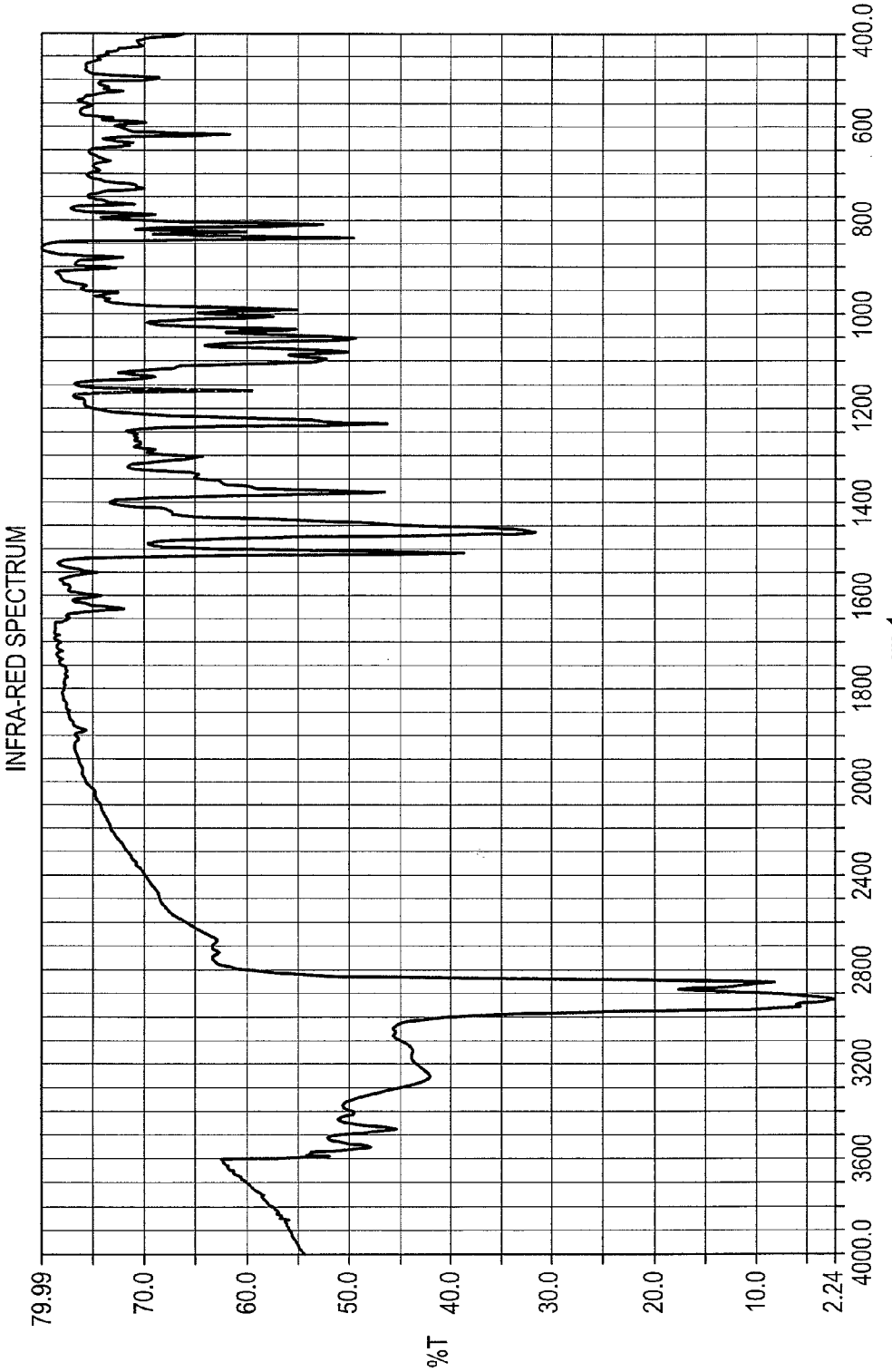
FIG. 1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cm-1

FIG.2

CRYSTALLINE FORM OF 1-(β-D-GLUCOPYRANOSYL)-4-METHYL-3-[5-(4-FLUOROPHENYL)-2-THIENYL-METHYL]BENZENE HEMIHYDRATE

This application is a Continuation of U.S. application Ser. No. 11/987,670 filed Dec. 3, 2007, which issued as U.S. Pat. No. 7,943,582 on May 17, 2011, which claims the benefit of priority under 35 U.S.C. §119(e) of U.S. Application No. 60/868,426, filed Dec. 4, 2006. U.S. application Ser. No. 11/987,670 also claims the benefit of priority of JP 2006-327019, filed Dec. 4, 2006. The entire content of each of the above-identified applications is hereby incorporated by reference.

BACKGROUND OF THE INVENTION

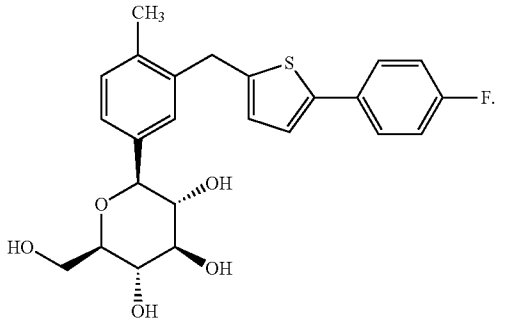
1. Field of the Invention

This invention relates to a crystalline form of 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate useful as an inhibitor of sodium-dependent glucose transporter, to methods for its preparation and isolation, to pharmaceutical compositions which include the compound and a pharmaceutically acceptable carrier, and to pharmaceutical methods of treatment.

2. Description of the Related Art

WO 2005/012326 pamphlet discloses a class of compounds that are inhibitors of sodium-dependent glucose transporter (SGLT) and thus of therapeutic use for treatment of diabetes, obesity, diabetic complications, and the like. There is described in WO 2005/012326 pamphlet 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene of formula (I):

(I)



In general, for commercial use it is important that a product should have good handling qualities. Additionally, there is a need to produce the product in a pure and crystalline form to enable formulations to meet exacting pharmaceutical requirements and specifications.

And it is desirable that the product should be in a form that is readily filterable and easily dried. Additionally, it is economically desirable that the product be stable for extended periods of time without the need for specialized storage conditions.

But there have been difficulties in obtaining a crystal form of the compound of formula (I) from organic solvents.

It has now been discovered that the compound of formula (I) hemihydrate can be produced in a crystalline form in a manner reproducible on a commercial scale.

SUMMARY OF THE INVENTION

The present invention provides a crystalline form of hemihydrate of the compound of formula (I) as a novel material, in particular in pharmaceutically acceptable form.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1**:

X-ray powder diffraction pattern of the crystalline of hemihydrate of the compound of formula (I).

FIG. **2**:

Infra-red spectrum of the crystalline of hemihydrate of the compound of formula (I).

DETAILED DESCRIPTION OF THE INVENTION

The inventors of the present invention have found that the compounds of formula (I) can be crystallized from a water-containing solvent and the crystalline form of hemihydrate of the compounds (I) have good handling qualities and characteristics.

Accordingly, the present invention is directed to:

1. A crystalline of hemihydrate of 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene.

2. A crystalline of hemihydrate of 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene characterized by a powder x-ray diffraction pattern comprising the following 2θ values measured using CuK_α radiation: 4.36±0.2, 13.54±0.2, 16.00±0.2, 19.32±0.2, 20.80±0.2.

3. A crystalline of hemihydrate of 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene, having substantially the same X-ray powder diffraction pattern as set out in FIG. **1**.

4. A crystalline of hemihydrate of 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene, having substantially the same IR spectrum, as set out in FIG. **2**.

5. A process for the preparation of a crystalline of hemihydrate of 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene, which comprises forming a solution of 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene and crystallizing said hemihydrate from the solution by precipitation or recrystallization.

6. A pharmaceutical composition comprising an effective amount of a crystalline of hemihydrate of 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl] benzene and a pharmaceutically acceptable carrier.

7. A method for treatment or delaying the progression or onset of diabetes mellitus, diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, delayed wound healing, insulin resistance, hyperglycemia, hyperinsulinemia, elevated blood levels of fatty acids, elevated blood levels of glycerol, hyperlipidemia, obesity, hypertriglyceridemia, Syndrome X, diabetic complications, atherosclerosis, or hypertension, which comprises administering a therapeutically effective amount of a crystalline of hemihydrate of 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene.

As discussed, the present invention includes a certain solid state crystalline form. Several methods for characterizing such forms exist, and the invention should not be limited by the methods chosen or the instrumentation used in characterizing the compounds of the present invention. For example, with regard to x-ray diffraction patterns, the diffraction peak intensities in the experimental patterns can vary, as is known in the art, primarily due to preferred orientation (non-random

orientation of the crystals) in the prepared sample. As such, the scope of the present invention must be considered in light of the variability of characterization that is appreciated by those skilled in the art.

X-Ray Powder Diffraction

The crystalline form of the present invention (I) is characterized by its X-ray powder diffraction pattern. The X-ray diffraction pattern of the crystalline of hemihydrate of the compound (I) was measured on an X-ray diffractometer (RINT-TTR III, Rigaku, Tokyo, Japan) with measured using $CuK_{\square}$ radiation. Methodology of X-ray powder diffraction is as follows:

Scanning rate: 2.00 degree/minute.

Target: $CuK_{\square}$.

Voltage: 50 kV.

Current: 300 mA.

Scan range: from 3 to 40.0 degree.

Sampling width: 0.0200 degree.

Infra-Red Spectrum

The infra-red spectrum of the crystalline form of the present invention in mineral oil comprises the following main peaks: 1626, 1600, 1549, and 1507 cm^{-1}.

The infra-red spectrum of crystalline compound (I) hemihydrate is shown in the accompanying drawing in which the ordinate is the transmittance in % and the abscissa is the wavenumber in cm^{-1}.

Thermogravimetric Analysis

The crystalline form of the present invention has been observed to exist in a hemihydrate form. The theoretical water content of the crystalline of the present invention is 1.98%. The thermogravimetric analysis for the crystalline of the present invention shows a mass loss of 1.705%.

Methodology of thermogravimetric analysis is as follows: about 8 mg of compound (I) hemihydrate is weighed and transferred in an aluminum cell holder for TG-50 (Shimadzu, Japan), and then, the thermogravimetric (TG) thermal curve of crystalline compound (I) hemihydrate is determined at a heat rate of 5° C./minute. Typical measuring range is from ambient to 150° C.

The present invention also provides a process for producing the crystalline form of hemihydrate of the compound (I) which comprises forming a solution of compound (I) and precipitating the crystalline form from solution.

Typically, the crystalline of hemihydrate of the compound (I) may be obtained from a mixture of the compound of formula (I), a good solvent and water, optionally containing a poor solvent.

Sometimes some impurities may act as crystallization inhibitors, and impurities need to be removed using a conventional manner, such as silica gel column chromatography. However, the crystalline of hemihydrate of the compound of formula (I) can even be obtained from relatively impure compound (I).

The present invention also provides a pharmaceutical composition comprising the crystalline of hemihydrate of the compound (I) and a pharmaceutically acceptable carrier.

The crystalline compound of the present invention possesses activity as inhibitors of sodium-dependent glucose transporters, and show excellent blood glucose lowering effect.

The crystalline form of the present invention are expected to be useful in the treatment, prevention or delaying the progression or onset of diabetes mellitus (type 1 and type 2 diabetes mellitus, etc.), diabetic complications (such as diabetic retinopathy, diabetic neuropathy, diabetic nephropathy), postprandial hyperglycemia, delayed wound healing, insulin resistance, hyperglycemia, hyperinsulinemia, elevated blood levels of fatty acids, elevated blood levels of glycerol, hyperlipidemia, obesity, hypertriglyceridemia, Syndrome X, atherosclerosis, or hypertension.

The crystalline form of the present invention or a pharmaceutically acceptable salt thereof may be administered either orally or parenterally, and can be used in the form of a suitable pharmaceutical preparation. Suitable pharmaceutical preparations for oral administration include, for example, solid preparations such as tablets, granules, capsules, and powders, or solution preparations, suspension preparations, emulsion preparations, and the like. Suitable pharmaceutical preparations for parenteral administration include, for example, suppositories; injection preparations or intravenous drip preparations, using distilled water for injection, physiological saline solution or aqueous glucose solution; and inhalant preparations.

The pharmaceutical compositions herein will contain, per dosage unit, e.g., tablet, capsule, powder, injection, suppository, teaspoonful and the like, from about 0.01 mg/kg to about 100 mg/kg body weight (preferably from about 0.01 mg/kg to about 50 mg/kg; and, more preferably, from about 0.01 mg/kg to about 30 mg/kg) of the active ingredient, and may be given at a dosage of from about 0.01 mg/kg/day to about 100 mg/kg/day (preferably from about 0.01 mg/kg/day to about 50 mg/kg/day and more preferably from about 0.01 mg/kg/day to about 30 mg/kg/day). The method of treating a disorder described in the present invention may also be carried out using a pharmaceutical composition comprising the crystalline form as defined herein and a pharmaceutical acceptable carrier. The dosage form will contain from about 0.01 mg/kg to about 100 mg/kg (preferably from about 0.01 mg/kg to about 50 mg/kg; and, more preferably, from about 0.01 mg/kg to about 30 mg/kg) of the active ingredient, and may be constituted into any form suitable for the mode of administration selected. The dosages, however, may be varied depending upon administration routes, the requirement of the subjects, the severity of the condition being treated and the compound being employed. The use of either daily administration or post-periodic dosing may be employed.

The crystalline form of the present invention may be used, if necessary, in combination with one or more of other antidiabetic agents, antihyperglycemic agents and/or agents for treatment of other diseases. The present compounds and these other agents may be administered in the same dosage form, or in a separate oral dosage form or by injection.

The dosage of those agents may vary according to, for example, ages, body weight, conditions of patients, administration routes, and dosage forms.

These pharmaceutical compositions may be orally administered to mammalian species including human beings, apes, and dogs, in the dosage form of, for example, tablet, capsule, granule or powder, or parenterally administered in the form of injection preparation, or intranasally, or in the form of transdermal patch.

The crystalline form of hemihydrate of the compound of formula (I) can be prepared from a mixture of the compound (I), a good solvent and water, optionally containing a poor solvent.

Examples of good solvents which have been found suitable include ketones (e.g., acetone, 2-butanone), esters (e.g., ethyl acetate, methyl acetate), alcohols (e.g., methanol, ethanol, i-propanol), and a mixture of these solvents. Examples of poor solvents include alkanes (e.g., hexane, heptane), aromatic hydrocarbons (e.g., benzene, toluene), ethers (e.g., diethyl ether, dimethyl ether, diisopropyl ether) and a mixture of these solvents.

One preferred preparation of the crystalline form of hemihydrate of the compound of formula (I) typically involves dissolving in a good solvent (e.g., ketones or esters) crude or amorphous compound of formula (I) prepared in accordance with the procedures described in WO 2005/012326 pamphlet, and adding water and a poor solvent (e.g., alkanes or ethers) to the resulting solution, followed by filtration.

In case that a good solvent is soluble in water, a poor solvent needs not be used and water may be added to the solution of the compound of formula (I) in the good solvent so the solubility of the compound of formula (I) can be decreased in the solution.

In case that a poor solvent is used, water is preferably used in amount of 1 to 10 molar equivalents to the compound of formula (I), the good solvent is preferably used in amount of 10 to 100 times of volume of water, and the poor solvent is preferably used in amount of 0.1 to 10 times of volume of the good solvent.

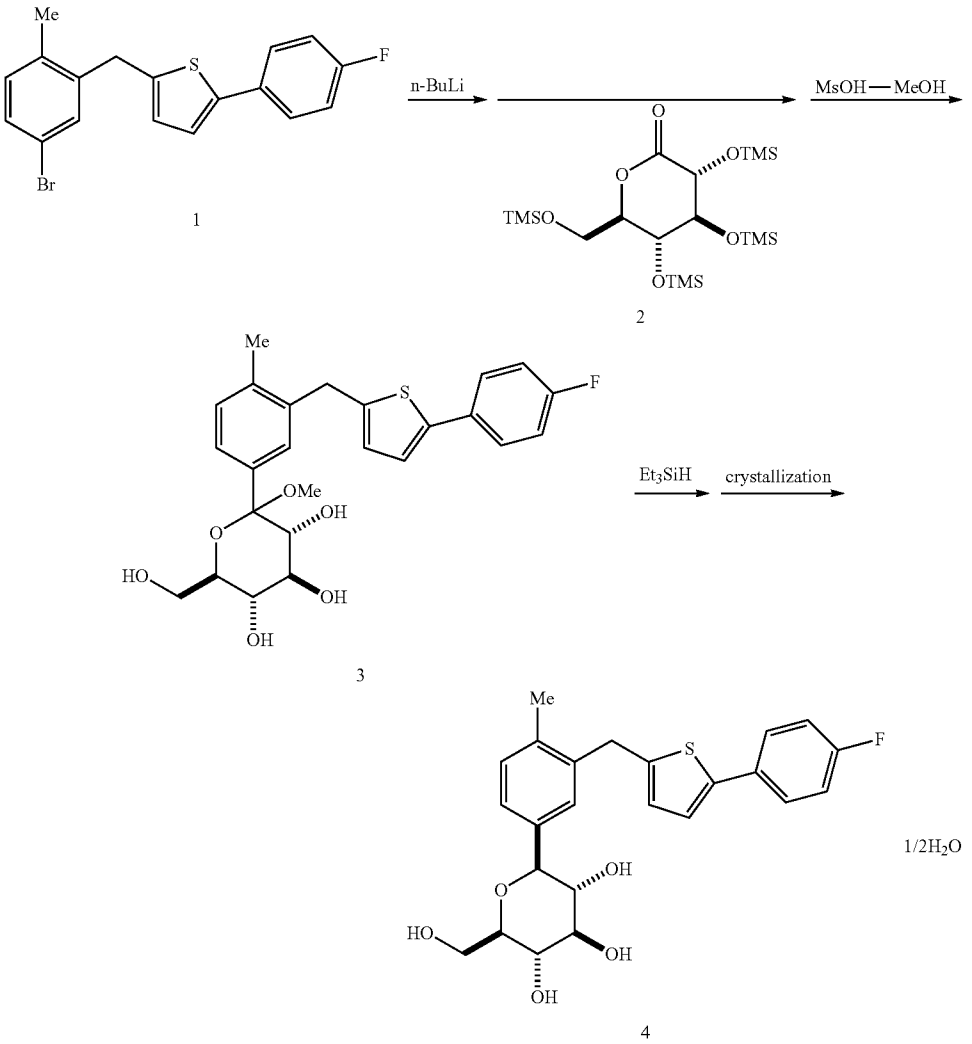
The crystalline form of hemihydrate of the compound of formula (I) is significantly easier to isolate than amorphous form of the compound and can be filtered from the crystallization medium after cooling, and washed and dried. Also, the crystalline form of the present invention is more stable than the amorphous form of the compound of formula (I).

EXAMPLES

Example 1

Crystalline 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate

1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene was prepared in a similar manner as described in WO 2005/012326.



The precise conditions under which the crystalline of hemihydrate of the compound (I) is formed may be empirically determined.

Under these conditions, crystallization can preferably be carried out at a lowered, ambient or elevated temperature.

(1) To a solution of 5-bromo-1-[5-(4-fluorophenyl)-2-thienylmethyl]-2-methylbenzene (1, 28.9 g) in tetrahydrofuran (480 ml) and toluene (480 ml) was added n-butyllithium (1.6M hexane solution, 50.0 ml) dropwise at −67 to −70° C. under argon atmosphere, and the mixture was stirred for 20

minutes at the same temperature. Thereto was added a solution of 2 (34.0 g) in toluene (240 ml) dropwise at the same temperature, and the mixture was further stirred for 1 hour at the same temperature. Subsequently, thereto was added a solution of methanesulfonic acid (21.0 g) in methanol (480 ml) dropwise, and the resulting mixture was allowed to warm to room temperature and stirred for 17 hours. The mixture was cooled under ice—water cooling, and thereto was added a saturated aqueous sodium hydrogen carbonate solution. The mixture was extracted with ethyl acetate, and the combined organic layer was washed with brine and dried over magnesium sulfate. The insoluble was filtered off and the solvent was evaporated under reduced pressure. The residue was triturated with toluene (100 ml)—hexane (400 ml) to give 1-(1-methoxyglucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]-benzene (3) (31.6 g). APCI-Mass m/Z 492 ($M+NH_4$).

(2) A solution of 3 (63.1 g) and triethylsilane (46.4 g) in dichloromethane (660 ml) was cooled by dry ice—acetone bath under argon atmosphere, and thereto was added dropwise boron trifluoride.ethyl ether complex (50.0 ml), and the mixture was stirred at the same temperature. The mixture was allowed to warm to 0° C. and stirred for 2 hours. At the same temperature, a saturated aqueous sodium hydrogen carbonate solution (800 ml) was added, and the mixture was stirred for 30 minutes. The organic solvent was evaporated under reduced pressure, and the residue was poured into water and extracted with ethyl acetate twice. The organic layer was washed with water twice, dried over magnesium sulfate and treated with activated carbon. The insoluble was filtered off and the solvent was evaporated under reduced pressure. The residue was dissolved in ethyl acetate (300 ml), and thereto were added diethyl ether (600 ml) and H_2O (6 ml). The mixture was stirred at room temperature overnight, and the precipitate was collected, washed with ethyl acetate—diethyl ether (1:4) and dried under reduced pressure at room temperature to give 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate (33.5 g) as colorless crystals. mp 98-100° C. APCI-Mass m/Z 462 ($M+NH_4$). ^{1}H-NMR (DMSO-d_6) δ 2.26 (3H, s), 3.13-3.28 (4H, m), 3.44 (1H, m), 3.69 (1H, m), 3.96 (1H, d, J=9.3 Hz), 4.10, 4.15 (each 1H, d, J=16.0 Hz), 4.43 (1H, t, J=5.8 Hz), 4.72 (1H, d, J=5.6 Hz), 4.92 (2H, d, J=4.8 Hz), 6.80 (1H, d, J=3.5 Hz), 7.11-7.15 (2H, m), 7.18-7.25 (3H, m), 7.28 (1H, d, J=3.5 Hz), 7.59 (2H, dd, J=8.8, 5.4 Hz). Anal. Calcd. for $C_{24}H_{25}FO_5S.0.5H_2O$: C, 63.56; H, 5.78; F, 4.19; S, 7.07. Found: C, 63.52; H, 5.72; F, 4.08; S, 7.00.

Example 2

An amorphous powder of 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene (1.62 g) was dissolved in acetone (15 ml), and thereto were added H_2O (30 ml) and a crystalline seed. The mixture was stirred at room temperature for 18 hours, and the precipitate was collected, washed with acetone—H_2O (1:4, 30 ml) and dried under reduced pressure at room temperature to give 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate (1.52 g) as colorless crystals. mp 97-100° C.

The invention claimed is:

1. A crystalline form of 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate having an infra-red spectrum in mineral oil comprising the following main peaks: 1626, 1600, 1549, and 1507 cm^{-1}.

2. A process for the preparation of a crystalline form of 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate of claim **1**, which comprises forming a solution of 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluoro-phenyl)-2-thienylmethyl]benzene and crystallizing said hemihydrate from the solution by precipitation or recrystallization.

3. A pharmaceutical composition comprising an effective amount of a crystalline form of 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate of claim **1** and a pharmaceutically acceptable carrier.

4. A method for treatment or delaying the progression or onset of diabetes mellitus, diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, delayed wound healing, insulin resistance, hyperglycemia, hyperinsulinemia, elevated blood levels of fatty acids, elevated blood levels of glycerol, hyperlipidemia, obesity, hypertriglyceridemia, Syndrome X, diabetic complications, atherosclerosis, or hypertension, which comprises administering a therapeutically effective amount of a crystalline form of 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate of claim **1** to a subject in need thereof.

5. A method for inhibiting a sodium-dependent glucose transporter in a mammal in need thereof, comprising administering to said mammal a therapeutically effective amount of the crystalline form of hemihydrate of 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene of claim **1**.

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