Title: PROCESS FOR THE PREPARATION OF VOGLIBOSE

Abstract: The invention relates to processes for the preparation of pure voglibose. The invention also relates to the preparation of acid addition salts of voglibose. More particularly, it relates to the preparation of crystalline hydrochloride salt of voglibose. The invention also relates to pharmaceutical compositions that include the pure voglibose or voglibose hydrochloride and use of said compositions for treatment or prevention of hyperglycemic symptoms and various disorders caused by hyperglycemia such as diabetes, obesity, and hyperlipidemia.
PROCESS FOR THE PREPARATION OF VOGLIBOSE

Field of the Invention

The field of the invention relates to processes for the preparation of pure voglibose. The invention also relates to the preparation of acid addition salts of voglibose. More particularly, it relates to the preparation of crystalline hydrochloride salt of voglibose. The invention also relates to pharmaceutical compositions that include the pure voglibose or crystalline voglibose hydrochloride and use of said compositions for treatment or prevention of hyperglycemic symptoms and various disorders caused by hyperglycemia such as diabetes, obesity, adiposity, and hyperlipemia.

Background of the Invention

Chemically, voglibose is (1S)-(1(OH),2,4,5/1,3)-5-[[2-hydroxy-1-(hydroxymethyl) ethyl]amino]-1-C-(hydroxymethyl)-1,2,3,4-cyclohexanetetrol, which has an excellent inhibitory activity against glucoside hydrolase. Several processes have been reported for the preparation of voglibose for example, in U.S. Patent Nos. 4,701,559; 4,824,943; 4,898,986; and 6,150,568; J. Org. Chem., 1992, 57, 3651 and J. Med. Chem., 1986, 29, 1038.

In general, these processes involve the use of ion-exchange chromatographic method using water, followed by concentration of the aqueous solution for isolation of voglibose, and recrystallization from ethanol to obtain pure voglibose. This leads to a difficult isolation procedure due to recovery of large amounts of water requiring prolonged heating and results in a low overall yield of the product. The product, obtained by the reported processes, is initially hygroscopic and converts to sticky oil when exposed to atmosphere. We have found that voglibose, obtained via acid addition salts of voglibose, is pure, stable, non hygroscopic and does not require any chromatographic technique for isolation.

Summary of the Invention

In one general aspect there is provided a pure voglibose.

The pure voglibose may have the X-ray diffraction pattern of Figure IV, infrared spectrum of Figure V, and differential scanning calorimetry plot of Figure VI.

In another general aspect there is provided a process for preparing pure voglibose. The process includes obtaining a solution of voglibose in one or more
solvents; contacting the solution with an acid; isolating voglibose acid addition salt in a solid state; and converting the voglibose acid addition salt into pure voglibose.

The process may include further drying of the product obtained.

In another general aspect there is provided a pharmaceutical composition that includes a therapeutically effective amount of pure voglibose; and one or more pharmaceutically acceptable carriers, excipients or diluents.

In another general aspect there is provided a method for treating or preventing a disease caused by hyperglycemia such as diabetes, obesity, adiposity, and hyperlipemia in a warm-blooded animal, the method comprising providing a pharmaceutical composition to the warm-blooded animal that includes the pure voglibose.

In another general aspect there is provided a crystalline hydrochloride salt of voglibose i.e. voglibose hydrochloride.

The voglibose hydrochloride may have the X-ray diffraction pattern of Figure I, infrared spectrum of Figure II, and differential scanning calorimetry plot of Figure III.

In another general aspect there is provided a process for preparing voglibose hydrochloride. The process includes obtaining a solution of voglibose in one or more solvents; contacting the solution with hydrogen chloride; and isolating the voglibose hydrochloride in the crystalline form.

In another general aspect there is provided a pharmaceutical composition that includes a therapeutically effective amount of crystalline voglibose hydrochloride; and one or more pharmaceutically acceptable carriers, excipients or diluents.

In another general aspect there is provided a method for treating or preventing a disease caused by hyperglycemia such as diabetes, obesity, adiposity, and hyperlipemia in a warm-blooded animal, the method comprising providing a pharmaceutical composition to the warm-blooded animal that includes the crystalline voglibose hydrochloride.

The details of one or more embodiments of the inventions are set forth in the description below. Other features, objects and advantages of the inventions will be apparent from the description and claims.
Description of the Drawings

Figure I is X-ray powder diffraction pattern of voglibose hydrochloride.

Figure II is an infrared spectrum of voglibose hydrochloride.

Figure III is differential scanning calorimetry plot of voglibose hydrochloride.

Figure IV is X-ray powder diffraction pattern of voglibose.

Figure V is an infrared spectrum of voglibose.

Figure VI is differential scanning calorimetry plot of voglibose.

Detailed Description of the Invention

The inventors have developed a process for the preparation of pure voglibose, by preparing a solution of voglibose in one or more solvents; contacting the solution with an acid; isolating voglibose acid addition salt in a solid state; and converting the voglibose acid addition salt into pure voglibose.

The inventors also have developed pharmaceutical compositions that contain the pure voglibose, in admixture with one or more solid or liquid pharmaceutical diluents, carriers, and/or excipients.

In general, the solution of voglibose may be obtained by dissolving voglibose in a suitable solvent. Alternatively, such a solution may be obtained directly from a reaction in which voglibose is formed. The solvent containing voglibose may be heated to obtain a solution.

The voglibose may be prepared by any of the methods known in the art including those described in U.S. Patent Nos. 4,701,559; 4,824,943; 4,898,986; and 6,150,568; J. Org. Chem., 1992, 57, 3651 and J. Med. Chem., 1986, 29, 1038. The voglibose may contain anti-isomer, polymeric impurities, or any other impurity which may arise during production or storage, such as degradation products.

The term “suitable solvents” includes any solvent or solvent mixture in which voglibose can be solubilized, including, for example, water, alcohols, ketones, nitriles, chlorinated hydrocarbons, dipolar aprotic solvents, esters, cyclic ethers, and mixtures thereof.

A suitable alcohol includes one or more of methanol, ethanol, and isopropanol.

Examples of ketones include acetone and methyl isobutyl ketone. Examples of nitrile
include acetonitrile. A suitable chlorinated hydrocarbon includes one or more of chloroform, dichloromethane, and 1,2-dichloroethane. Examples of dipolar aprotic solvents include solvents such as dimethylsulfoxide and dimethylformamide. Examples of esters include solvents such as methyl acetate, ethyl acetate, and isopropyl acetate. Examples of cyclic ethers include solvents such as dioxane and tetrahydrofuran. Mixtures of all of these solvents are also contemplated.

The solution of voglibose in a solvent can be obtained by dissolving, slurrying, stirring or a combination thereof.

In general, the conversion of voglibose into acid addition salt of voglibose can be carried out by adding organic or an inorganic acid. The acid may be added to a solution of voglibose in a suitable solvent. Alternatively, acid may be added in the last step for the preparation of voglibose and acid addition salt of voglibose may be isolated directly without isolating the voglibose.

Examples of inorganic acids include hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid and nitric acid. Examples of organic acids include formic acid, acetic acid, maleic acid, malic acid, oxalic acid, tartaric acid, citric acid, ascorbic acid, mandelic acid, p-toluenesulfonic acid and methane sulfonic acid.

Isolating the acid addition salt of voglibose includes one or more of distillation, distillation under vacuum, crystallization, precipitation, cooling, filtration, filtration under vacuum, decantation and centrifugation.

The precipitation of acid addition salt of voglibose may be spontaneous, depending upon the solvent and the conditions used. The precipitation may also be facilitated by adding seeds of the desired salt or by adding an anti-solvent, i.e. a solvent in which acid addition salt of voglibose is insoluble or sparingly soluble, to the solvent in which acid addition salt of voglibose is prepared. Alternatively, precipitation may also be induced by distilling off some solvent and/or reducing the temperature.

The acid addition salt may be recrystallized one or more times before conversion to voglibose, to get higher purity.

Examples of anti-solvents that may be added to precipitate out acid addition salt of voglibose include hydrocarbons such as hexane, cyclohexane, toluene, heptane and octane; lower alkyl ethers such as diethylether and diisopropylether and mixtures thereof.
The conversion of acid addition salts of voglibose to pure voglibose may be achieved by adding a base in a suitable solvent.

The base may be organic or inorganic.

Examples of organic bases include trimethylamine, triethylamine, tributylamine, triisopropylamine, diisopropylethylamine, pyridine, morpholine, DBU (1,8-diazabicyclo-[5.4.0]undec-7-ene), DBN (1,5-diazabicyclo-[4.3.0]non-5-ene), 4-dimethylamino pyridine and mixtures thereof.

Examples of inorganic bases include alkali metal carbonate, bicarbonate, hydroxide and mixtures thereof. Examples of alkali metal carbonate include lithium carbonate, sodium carbonate and potassium carbonate. Examples of alkali metal bicarbonate include sodium bicarbonate and potassium bicarbonate. Examples of alkali metal hydroxide include sodium hydroxide and potassium hydroxide.

The solvents used for the conversion of acid addition salts of voglibose to pure voglibose may be the same as those described above for the preparation of voglibose acid addition salts.

The product obtained may be further or additionally dried to achieve the desired moisture values. For example, the product may be further or additionally dried in a tray drier, dried under vacuum and/or in a Fluid Bed Drier.

The pure voglibose has a purity of more than 99%. More particularly, the purity of voglibose is more than 99.5%, for example more than 99.8%.

The inventors have found a novel crystalline form of voglibose hydrochloride. The crystalline form is characterized by its X-ray powder diffraction pattern as shown in Figure I, infrared spectrum as shown in Figure II, and differential scanning calorimetry plot as shown in Figure III.

In general, the crystalline voglibose hydrochloride may be characterized by X-ray diffraction peaks at about 17.70, 20.20, 22.84 and 26.78 ± 0.2 degrees two-theta. It may be further characterized by X-ray diffraction peaks at about 14.10 15.70, 23.04, 26.02, and 27.54 ± 0.2 degrees two-theta.

The inventors also have developed a process for the preparation of the crystalline form of voglibose hydrochloride, by obtaining a solution of voglibose in one or more solvents; contacting the solution with hydrogen chloride; and isolating the voglibose
hydrochloride in the crystalline form. The inventors also have developed pharmaceutical compositions that contain crystalline voglibose hydrochloride, in admixture with one or more solid or liquid pharmaceutical diluents, carriers, and/or excipients.

The pure voglibose may be obtained from crystalline voglibose hydrochloride in a manner similar to that described above for the preparation of voglibose from acid addition salts of voglibose.

In general, the solution of voglibose may be obtained by dissolving voglibose in one or more solvents. Alternatively, such a solution may be obtained directly from a reaction in which voglibose is formed.

The voglibose may be prepared by any of the methods known in the art including those described in U.S. Patent Nos. 4,701,559; 4,824,943; 4,898,986; and 6,150,568; *J. Org. Chem.*, 1992, 57, 3651 and *J. Med. Chem.*, 1986, 29, 1038. The voglibose may also be obtained as a solution directly from a reaction in which voglibose is formed and used as such without isolation.

The solution of voglibose in a solvent can be obtained by dissolving, slurrying, stirring or a combination thereof.

In general, the hydrogen chloride may be added to a solution of voglibose in a suitable solvent. Alternatively, the hydrogen chloride may be added in the last step for the preparation of voglibose and voglibose hydrochloride in the crystalline form may be isolated directly without isolating the voglibose.

Isolating the voglibose hydrochloride in the crystalline form includes one or more of distillation, distillation under vacuum, crystallization, precipitation, cooling, filtration, filtration under vacuum, decantation and centrifugation.

The hydrogen chloride used in the salt formation process may be an aqueous solution or in gaseous form. The aqueous solution of hydrogen chloride is commercially available. The gaseous hydrogen chloride may be obtained commercially or prepared by the methods known in art. The gaseous hydrogen chloride may be dissolved in a suitable solvent.

The solvents used for the preparation of voglibose hydrochloride, may be similar to those used for the preparation of acid addition salts of voglibose as described above.
The product obtained may be further or additionally dried. For example, the product may be further or additionally dried in a tray drier, dried under vacuum and/or in a Fluid Bed Drier.

The resulting crystalline voglibose hydrochloride may be formulated into ordinary dosage forms such as, for example, tablets, capsules, pills, solutions, etc. In these cases, the medicaments can be prepared by conventional methods with conventional pharmaceutical excipients.

The voglibose hydrochloride can be administered for the prevention and treatment of hyperglycemic symptoms and various disorders caused by hyperglycemia such as obesity, adiposity, hyperlipemia (arteriosclerosis), and diabetes in a warm-blooded animal.

For the purpose of this disclosure, a warm-blooded animal is a member of the animal kingdom possessed of a homeostatic mechanism and includes mammals and birds.

The salt is generally administered as part of a pharmaceutical composition with a pharmaceutically acceptable carrier, diluent or excipient and optionally other therapeutic ingredients. The salt may be conventionally formulated into tablets, capsules, suspensions, dispersions, injectables and other pharmaceutical forms. Any suitable route of administration may be employed for example, peroral or parenteral.

The present invention is further illustrated by the following examples which are provided merely to be exemplary of the invention and are not intended to limit the scope of the invention. Certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

Methods

X-Ray Powder Diffraction
X-ray powder diffraction patterns were recorded using the following instrument and parameters:
X-Ray Diffractometer, Rigaku Cooperation, RU-H3R
Goniometer CN2155A3

X-Ray tube with Cu target anode
Divergence slits 1°, receiving slit 0.15mm, Scatter slit 1°
Power: 40 KV, 100 mA
Scanning speed: 2 deg/min step: 0.02 deg
Wave length: 1.5406 A
Infrared Spectra
Infrared spectra were recorded using the following instrument and parameters:

SCAN: 16 scans, 4.0 cm⁻¹

According to the USP 25, general test methods page 1920, infrared absorption spectrum by potassium bromide pellet method.

Differential Scanning Calorimetry

Differential scanning calorimetry plots were recorded using the following instrument and parameters:
DSC821 e, Mettler Toledo
Sample weight: 3-5 mg
Temperature range: 50-250° C

Heating rate: 10° C/min
Nitrogen 80.0 mL/min
Number of holes in the crucible: 1

Example 1: Preparation of tetra-O-benzyl-5-[[2-hydroxy-1-(hydroxymethyl)ethyl]amino]-1-C-(hydroxymethyl)-1,2,3,4-cyclohexanetetrol

2-amino-1,3-propanediol (20.1g, 220 mmol) was added to a solution of tetra-O-benzyl-5-oxo-1-C-(hydroxymethyl)-1,2,3,4-cyclohexanetetrol (35.0 g, 63.4 mmol) in methanol (350 ml) at ambient temperature and stirred for 60 minutes. Sodium cyanoborohydride (14 g, 222 mmol) was then added to the reaction mixture. Concentrated hydrochloric acid was added to adjust pH to about 8.0 and the reaction mixture was stirred overnight. The reaction mixture was partitioned between water and ethyl acetate. Ethyl acetate layer was dried over anhydrous sodium sulfate and concentrated to obtain title compound as pale yellow color syrup.

Yield: 38.6 g

HPLC Purity: 90.0%
^1HNMR (CDCl₃), δ: 1.60 (1H, dd, J=2.1, 15Hz), 1.92 (1H, dd, J=2.7, 15Hz), 2.75 (1H, m), 3.20 (1H, d, J=8.4Hz), 3.44 (1H, m), 3.50 – 3.69 (7H, m), 4.10 (1H, m), 4.39 (2H, s), 4.56 – 4.94 (6H, m), 7.22 – 7.36 (20H, m)

Example 2: Preparation of voglibose hydrochloride

5% palladium carbon (13 g) and 4% hydrogen chloride solution (20 ml) were added to a solution of tetra-O-benzyl-5-[[2-hydroxy-1-(hydroxymethyl)ethyl]amino]-1-C-(hydroxymethyl)-1,2,3,4-cyclohexanetetrol (13.0 g, 20.73 mmol) in methanol and tetrahydrofuran (1:1, 260 ml) and the mixture was hydrogenated with shaking for 3 hours at 3.0 – 3.5 Kg/cm² at room temperature. The solid was removed by filtration and washed with methanol. The combined filtrate and washings were concentrated. Ethanol was then added to the residue so obtained and solvent was recovered completely. This was repeated several times to remove traces of water. Methanol (35 ml) was then added and stirred at room temperature for 1 hour. The product was filtered to obtain voglibose hydrochloride as a white crystalline solid.

Yield: 5.0 g

^1HNMR (D₂O), δ: 1.94 (1H, d, J=3.0, 16.2Hz), 2.33 (1H, d, J=2.1, 16.2Hz), 3.60 – 3.70 (4H, m), 3.80 – 4.0 (7H, m)

XRD pattern, IR spectrum and DSC graph were similar to those shown in Figure I, II and III, respectively.

Example 3: Preparation of voglibose

20% triethylamine in methanol was added to a suspension of voglibose hydrochloride (5.0 g, 16.47 mmol) in 40 ml methanol to adjust pH to about 8.8 – 9.0. The suspension became clear, and then free base crystallized out. It was stirred for 1 hour, filtered and washed with methanol to give voglibose as a white crystalline solid, which was recrystallized from methanol.

Yield: 3.0 g

HPLC Purity: 99.9%
$^1$HNMR (D$_2$O), δ: 1.55 (1H, dd, J=2.1, 15Hz), 2.10 (1H, dd, J=2.7, 15Hz), 2.9 (1H, m), 3.40 – 3.55 (2H, m), 3.59 (2H, m), 3.64 – 3.80 (5H, m), 3.88 (1H, t, J=9.6Hz)

XRD pattern, IR spectrum and DSC graph were similar to those shown in Figure IV, V and VI, respectively.

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are included within the scope of the present invention.
We Claim:

1. A process for the preparation of pure voglibose, the process comprising,
   obtaining a solution of voglibose in one or more solvents;
   contacting the solution with an acid;
   isolating voglibose acid addition salt in a solid state; and
   converting the voglibose acid addition salt into pure voglibose.

2. The process of claim 1, wherein the voglibose is obtained as a solution directly
   from a reaction mixture.

3. The process of claim 1, wherein the solvent comprises one or more of ketones,
   alcohols, esters, nitriles, chlorinated hydrocarbons, cyclic ethers, dipolar aprotic
   solvents, or mixtures thereof.

4. The process of claim 4, wherein the ketone comprises one or both of acetone and
   methyl isobutyl ketone.

5. The process of claim 4, wherein the alcohol comprises one or more of methanol,
   ethanol, and isopropanol.

6. The process of claim 4, wherein the ester comprises one or more of methyl acetate,
   ethyl acetate and isopropyl acetate.

7. The process of claim 4, wherein the nitrile is acetonitrile.

8. The process of claim 4, wherein the chlorinated hydrocarbon comprises one or
   more of chloroform, dichloromethane, and 1,2-dichloroethane.

9. The process of claim 4, wherein the cyclic ether comprises one or both of dioxane
   and tetrahydrofuran.

10. The process of claim 4, wherein the polar aprotic solvent comprises one or both of
    dimethylformamide and dimethylsulfoxide.

11. The process of claim 1, wherein the acid is an organic or inorganic.

12. The process of claim 11, wherein the inorganic acid comprises one or more of
    hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid and nitric acid.
The process of claim 11, wherein the organic acid comprises one or more of acetic acid, maleic acid, malic acid, oxalic acid, tartaric acid, citric acid, ascorbic acid, mandelic acid, p-toluenesulfonic acid and methane sulfonic acid.

The process of claim 1, further comprising adding an anti-solvent to precipitate the acid addition salt of voglibose.

The process of claim 14, wherein the anti-solvent comprises one or more of lower alkyl ethers, hydrocarbons and mixtures thereof.

The process of claim 15, wherein the alkyl ether comprises one or both of diethylether and diisopropylether.

The process of claim 15, wherein the hydrocarbon comprises one or more of hexane, cyclohexane, toluene, heptane and octane.

The process of claim 1, wherein the conversion of acid addition salts of voglibose to pure voglibose is achieved by addition of an organic or inorganic base.

The process of claim 18, wherein the organic base comprises one or more of trimethylamine, triethylamine, tributylamine, triisopropylamine, diisopropylethylamine, pyridine, morpholine, DBU (1,8-diazabicyclo-[5.4.0]-undec-7-ene), DBN (1,5-diazabicyclo-[4.3.0]-non-5-ene), 4-dimethylamino pyridine and mixtures thereof.

The process of claim 18, wherein the inorganic base comprises one or more of alkali metal carbonate, alkali metal bicarbonate and alkali metal hydroxide.

The process of claim 20, wherein the alkali metal carbonate comprises one or more of lithium carbonate, sodium carbonate and potassium carbonate.

The process of claim 20, wherein the alkali metal bicarbonate comprises one or both of sodium bicarbonate and potassium bicarbonate.

The process of claim 20, wherein the alkali metal hydroxide comprises one or both of sodium hydroxide and potassium hydroxide.

The process of claim 1, further comprising additional drying of the product obtained.
25. The process of claim 1, further comprising forming the product obtained into a finished dosage form.

26. A method of treating or preventing a disease caused by hyperglycemia in a warm-blooded animal, the method comprising providing a dosage form to the warm-blooded animal that includes voglibose obtained by the process of claim 1.

27. The method of claim 26, wherein the disease is diabetes, obesity, adiposity, and hyperlipemia.

28. Voglibose having a purity of more than 99.5% by HPLC.

29. Voglibose having a purity of more than 99.8% by HPLC.

30. The pure voglibose of claim 29, wherein the voglibose has the X-ray diffraction pattern of Figure IV.

31. The pure voglibose of claim 29, wherein the voglibose has an infrared spectrum of Figure V.

32. The pure voglibose of claim 29, wherein the voglibose has the differential scanning calorimetry plot of Figure VI.

33. A pharmaceutical composition comprising a therapeutically effective amount of pure voglibose, and one or more pharmaceutically acceptable carriers, excipients or diluents.

34. A method of treating or preventing a disease caused by hyperglycemia in a warm-blooded animal, the method comprising providing a dosage form to the warm-blooded animal that includes pure voglibose.

35. The method of claim 34, wherein the disease is diabetes, obesity, adiposity, and hyperlipemia.

36. Crystalline hydrochloride salt of voglibose

37. The crystalline hydrochloride salt of voglibose of claim 36, wherein the voglibose has the X-ray diffraction pattern of Figure I.

38. The crystalline hydrochloride salt of voglibose of claim 36, wherein the voglibose has the infrared spectrum of Figure II.
39. The crystalline hydrochloride salt of voglibose of claim 36, wherein the voglibose has the differential scanning calorimetry plot of Figure III.

40. A crystalline hydrochloride salt of voglibose characterized by X-ray diffraction pattern having peaks at about 17.70, 20.20, 22.84 and 26.78 ± 0.2 degrees two-theta.

41. The crystalline hydrochloride salt of voglibose of claim 40 further characterized by X-ray diffraction peaks at about 14.10, 15.70, 23.04, 26.02, and 27.54 ± 0.2 degrees two-theta.

42. A pharmaceutical composition comprising a therapeutically effective amount of crystalline hydrochloride salt of voglibose; and one or more pharmaceutically acceptable carriers, excipients or diluents.

43. A process for the preparation of crystalline voglibose hydrochloride, the process comprising:

obtaining a solution of voglibose in one or more solvents;

contacting the solution with hydrogen chloride; and

isolating the voglibose hydrochloride in the crystalline form.

44. The process of claim 43, wherein the voglibose is obtained as a solution directly from a reaction in which voglibose is formed.

45. The process of claim 43, wherein the solvent comprises one or more of ketones, alcohols, esters, nitriles, chlorinated hydrocarbons, cyclic ethers, dipolar aprotic solvents and mixtures thereof.

46. The process of claim 45, wherein the ketone comprises one or both of acetone and methyl isobutyl ketone.

47. The process of claim 45, wherein the alcohol comprises one or more of methanol, ethanol, and isopropanol.

48. The process of claim 45, wherein the ester comprises one or more of methyl acetate, ethyl acetate and isopropyl acetate.

49. The process of claim 45, wherein the nitrile is acetonitrile.
50. The process of claim 45, wherein the chlorinated hydrocarbon comprises one or more of chloroform, dichloromethane, and 1,2-dichloroethane.

51. The process of claim 45, wherein the cyclic ether comprises one or both of dioxane and tetrahydrofuran.

52. The process of claim 45, wherein the polar aprotic solvent comprises one or both of dimethylformamide and dimethylsulfoxide.

53. The process of claim 43, wherein isolating the voglibose hydrochloride in crystalline form comprises one or more of distillation, distillation under vacuum, crystallization, precipitation, cooling, filtration, filtration under vacuum, decantation, and centrifugation.

54. The process of claim 43, further comprising additional drying of the product obtained.

55. The process of claim 43, further comprising forming the product obtained into a finished dosage form.

56. A method of treating or preventing a disease caused by hyperglycemia in a warm-blooded animal, the method comprising providing a dosage form to the warm-blooded animal that includes a crystalline form of voglibose hydrochloride obtained by the process of claim 43.

57. The method of claim 56, wherein the disease is diabetes, obesity, adiposity, and hyperlipemia.
### INTERNATIONAL SEARCH REPORT

**INTERNATIONAL SEARCH REPORT**

**International Application No: PCT/IB2004/003120**

**A. CLASSIFICATION OF SUBJECT MATTER**


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

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols):

- IPC 7: C07C

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

- Electronic database consulted during the international search (name of database and, where practicable, search terms used):
  - EPO-Internal, CHEM ABS Data, WPI Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
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<td>US 4 898 986 A (HORII ET AL) 6 February 1990 (1990-02-06) cited in the application example 16</td>
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**X** Patent family members are listed in annex.

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

**Date of the actual completion of the international search:** 10 February 2005

**Date of mailing of the international search report:** 23/02/2005

**Name and mailing address of the ISA:**

European Patent Office, P.B. 5818 Patentlaan 2, NL-2280 HV Rijswijk
Tel. (+31-70) 940-2040, Tx. 31 651 epo nl, Fax. (+31-70) 940-3016

**Authorized officer:**

Cooper, S
INTERNATIONAL SEARCH REPORT

Box II  Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. X Claims Nos.:  
   because they relate to subject matter not required to be searched by this Authority, namely:  
   Although claims 26,27,34,35,56 and 57 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2.  
   because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3.  
   because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III  Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1.  
   As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2.  
   As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3.  
   As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4.  
   No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
- No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (2)) (January 2004)
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