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UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

NOVEN THERAPEUTICS, LLC Plaintiff, vs. PRINSTON PHARMACEUTICAL INC., SOLCO HEALTHCARE U.S., LLC, AND HUAHAI US INC., Defendants.	Case No. _____

COMPLAINT FOR PATENT INFRINGEMENT

Plaintiff Noven Therapeutics, LLC ("Noven" or "Plaintiff"), in its Complaint of patent infringement against Defendants Prinston Pharmaceutical Inc. ("Prinston"), Solco Healthcare U.S., LLC ("Solco"), and Huahai US Inc. ("Huahai") (collectively, "Defendants"), states as follows:

THE PARTIES

1. Noven is a Delaware limited liability company with a principal place of business at 11960 S.W. 144th Street, Miami, Florida 33186.

2. Upon information and belief, defendant Prinston is a Delaware corporation with a principal place of business at 2002 Eastpark Blvd., Cranbury, New Jersey 08512.

3. Upon information and belief, defendant Prinston is in the business of, among other things, developing, preparing, manufacturing, selling, marketing, and distributing generic pharmaceutical products throughout the United States, including New Jersey.

4. Upon information and belief, defendant Solco is a Delaware corporation with a principal place of business at 2002 Eastpark Blvd., Cranbury, New Jersey 08512.

5. Upon information and belief, defendant Solco is in the business of, among other things, preparing, manufacturing, marketing, and distributing pharmaceutical products, including Prinston's pharmaceutical products, throughout the United States, including New Jersey. According to Prinston's website (http://www.prinstonpharm.com/Subsidiary.html), defendant Solco is the "U.S. sales and marketing division of Prinston Pharmaceutical Inc.," has "FDA-approved manufacturing capabilities," and brings "generic pharmaceutical products to the U.S. market."

6. Upon information and belief, defendant Solco is a wholly-owned subsidiary of Prinston Pharmaceutical Inc.

7. Upon information and belief, defendant Huahai is a New Jersey corporation with a principal place of business at 2002 Eastpark Blvd., Cranbury, New Jersey 08512.

8. Upon information and belief, Zhejiang Huahai Pharmaceutical Co., Ltd. is the ultimate parent company for each of Prinston, Solco and Huahai, each of which share a common place of business in Cranbury, New Jersey.

9. Upon information and belief, defendant Huahai is in the business of, among other things, preparing, manufacturing, marketing, and distributing pharmaceutical products, including Prinston's pharmaceutical products, throughout the United States, including New Jersey. According to Huahai's website (http://www.huahaius.com/history.html), defendant Huahai

provides API for the Zhejiang Huahai Pharmaceutical Co., Ltd. group companies and markets "generic finished dosage products through the subsidiary company, Prinston Pharmaceutical Inc." Further, Huahai has claimed to have "assisted Prinston Pharmaceutical Inc. to get over 15 ANDAs approved by FDA." *See* http://www.huahaius.com/history.html.

NATURE OF THE ACTION

10. This is a civil action for patent infringement of U.S. Patent Nos. 5,874,447 (the "'447 patent"), 7,598,271 (the "'271 patent"), and 8,658,663 (the "'663 patent") (collectively, the "patents-in-suit"), arising under the United States Patent Laws, Title 35, United States Code § 100, *et. seq.*, and in particular under 35 U.S.C. § 271. This action relates to Abbreviated New Drug Application ("ANDA") No. 207188, which Defendants filed or caused to be filed under 21 U.S.C. § 355(j) with the United States Food and Drug Administration ("FDA"), for approval to market a generic copy of Noven's BRISDELLE® product, which is sold in the United States.

JURISDICTION AND VENUE

11. This is a civil action for patent infringement and declaratory judgment arising under the Patent Laws of the United States, including 35 U.S.C. § 271, and the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

12. This Court has subject matter jurisdiction under 28 U.S.C. §§ 1331, 1338(a), 2201, and 2202.

13. This Court has personal jurisdiction over Defendants by virtue of their specific acts in, and their systematic and continuous contacts with the State of New Jersey.

14. Upon information and belief, defendants Prinston, Solco, and Huahai each have their principal place of business at the same location in Cranbury, New Jersey.

15. Upon information and belief, a substantial amount if not all of Defendants' activities relating to the preparation of Defendants' ANDA No. 207188 occurred in the state of New Jersey.

16. Upon information and belief, Defendants are registered to do business in the state of New Jersey, and purposefully avail themselves of this forum by making, using, importing, selling or offering to sell pharmaceutical products in the state of New Jersey, or causing others to do the same, and therefore, can reasonably expect to be subject to jurisdiction in the New Jersey courts.

17. Upon information and belief, pursuant to Registration No. 5004252, Prinston is registered as a wholesaler in the State of New Jersey under the trade name "Solco Healthcare US LLC."

18. Upon information and belief, defendant Huahai is incorporated under the laws of the state of New Jersey.

19. Upon information and belief, Defendants collectively share common directors, officers, and facilities, operate as agents of each other, and act in concert in the design, development, manufacture, distribution, and sale of pharmaceutical products throughout the United States, including New Jersey.

20. Upon information and belief, Defendants collectively participated in the preparation, development and filing of ANDA No. 207188 and its underlying subject matter, which occurred in the state of New Jersey.

21. Venue is proper in this judicial district under 28 U.S.C. §§ 1391 and 1400(b).

FACTUAL BACKGROUND

22. The '447 patent, entitled "4-Phenylpiperidine Compounds for Treating Depression," was duly and legally issued by the United States Patent and Trademark Office ("USPTO") on February 23, 1999. Noven is the owner of all title, right, and interest in and to the '447 patent by assignment and therefore has the full right to sue and recover for the infringement thereof. A copy of the '447 patent is attached as Exhibit A.

23. The '271 patent, entitled "Crystalline Paroxetine Methane Sulfonate," was duly and legally issued by the USPTO on October 6, 2009 and a certificate of correction was issued on May 17, 2011. Noven is the owner of all title, right, and interest in and to the '271 patent by assignment and therefore has the full right to sue and recover for the infringement thereof. A copy of the '271 patent and certificate of correction is attached as Exhibit B.

24. The '663 patent, entitled "Method of Treating Thermoregulatory Dysfunction With Paroxetine," was duly and legally issued by the USPTO on February 25, 2014 and a certificate of correction was issued on October 7, 2014. Noven is the owner of all title, right, and interest in and to the '663 patent by assignment and therefore has the full right to sue and recover for the infringement thereof. A copy of the '663 patent and certificate of correction is attached as Exhibit C.

25. Noven is the holder of New Drug Application ("NDA") No. 204516 for the manufacture and sale of paroxetine mesylate capsules, which Noven markets and sells under the registered trademark BRISDELLE®. Pursuant to Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 355(b)(1) ("FFD&C Act") and corresponding FDA regulations, Noven has listed the patents-in-suit in the FDA's Orange Book as covering the BRISDELLE® drug and methods for using it.

26. Upon information and belief, pursuant to FFD&C Act 21 U.S.C. § 505(j), Defendants filed ANDA No. 207188 with the FDA. Defendants' ANDA seeks FDA approval to market and sell within the United States a generic 7.5 mg paroxetine mesylate capsule product (the "generic product") prior to the expiration of the patents-in-suit.

27. Upon information and belief, Defendants' ANDA No. 207188 identified Noven's BRISDELLE® product and included a written certification, as required by FFD&C Act 21 U.S.C. § 355(j)(2)(A)(vii)(IV) (the "Paragraph IV certification"), alleging that the claims of the patents-in-suit are invalid or otherwise will not be infringed by Defendants' generic product.

28. On or about October 17, 2014, Noven received a letter from Defendants purporting to be a written notice that Defendants have filed ANDA No. 207188 seeking approval to market their generic product prior to the expiration of the patents-in-suit, pursuant to FFD&C Act 21 U.S.C. § 505(j)(2)(B)(iv) (the "Paragraph IV letter"). The Paragraph IV letter included notice of Defendants' allegations that the patents-in-suit are invalid, unenforceable, and/or not infringed by Defendants' generic product.

29. Defendants' submission of ANDA No. 207188, including the Paragraph IV certification, to the FDA constitutes infringement of the patents-in-suit under 35 U.S.C. § 271(e)(2). Moreover, Defendants' anticipated commercial manufacture, use, sale, offer for sale, or importation of the generic product upon approval and before expiration of the patents-in-suit will infringe at least one claim of each of the patents-in-suit under 35 U.S.C. § 271(a), (b), and/or (c).

30. Noven commenced this action within 45 days of receiving Defendants' Paragraph IV letter.

COUNT I: INFRINGEMENT OF U.S. PATENT NO. 5,874,447

31. Paragraphs 1-30 are incorporated by reference as though fully set forth herein.

32. Defendants' submission of ANDA No. 207188 and its Paragraph IV certification for FDA approval to commercially manufacture, use, sell, offer to sell, or import the generic product prior to the expiration of the '447 patent constitutes infringement under 35 U.S.C. § 271(e)(2).

33. Upon information and belief, Defendants will infringe the '447 patent under 35 U.S.C. § 271(a) by making, using, selling, offering to sell, or importing the generic product in the United States upon the FDA's approval of ANDA No. 207188.

34. Upon information and belief, Defendants will induce infringement of the '447 patent under 35 U.S.C. § 271(b) by intentionally encouraging, aiding and abetting acts of direct infringement of the '447 patent, with knowledge of said patent and said infringement, upon the FDA's approval of ANDA No. 207188.

35. Upon information and belief, Defendants will contributorily infringe the '447 patent under 35 U.S.C. § 271(c) by making, using, selling, offering to sell, or importing the generic product in the United States, with knowledge of the '447 patent and that there is no substantial non-infringing use of the generic product, upon the FDA's approval of ANDA No. 207188.

36. Pursuant to 35 U.S.C. § 283 and 35 U.S.C. § 271(e)(4)(B), Noven is entitled to a permanent injunction against further infringement. Noven will be substantially and irreparably harmed if Defendants' direct, induced, and contributory infringement of the '447 patent is not enjoined. Further, Noven does not have an adequate remedy at law.

37. Upon information and belief, Defendants were aware of the '447 patent prior to filing ANDA No. 207188, as well as the statutory provisions and regulations set forth in 21 U.S.C. § 355 and 21 C.F.R. § 314.95, and acted without a reasonable basis for a good faith belief that they would not be liable for infringing the '447 patent.

COUNT II: DECLARATORY JUDGMENT OF INFRINGEMENT OF U.S. PATENT NO. 5,874,447

38. Paragraphs 1-37 are incorporated by reference as though fully set forth herein.

39. This claim arises under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

40. There is an actual case or controversy such that the Court may hear Noven's request for declaratory relief consistent with Article III of the United States Constitution, and that actual case or controversy requires a declaration of rights by this Court.

41. Defendants have made, and will continue to make, substantial preparation in the United States, including New Jersey, to manufacture, use, sell, offer to sell, or import the generic product upon the FDA's approval of ANDA No. 207188.

42. Defendants' anticipated manufacture, use, sale, offer to sell, or importation of the generic product prior to the expiration of the '447 patent will constitute direct, induced, and contributory infringement of said patent.

43. Noven is entitled to a declaratory judgment that Defendants' anticipated manufacture, use, sale, offer to sell, or importation of the generic product prior to the expiration of the '447 patent will constitute direct, induced, and contributory infringement of the '447 patent.

COUNT III: INFRINGEMENT OF U.S. PATENT NO. 7,598,271

44. Paragraphs 1-43 are incorporated by reference as though fully set forth herein.

45. Defendants' submission of ANDA No. 207188 and its Paragraph IV certification for FDA approval to commercially manufacture, use, sell, offer to sell, or import the generic product prior to the expiration of the '271 patent constitutes infringement under 35 U.S.C. § 271(e)(2).

46. Upon information and belief, Defendants will infringe the '271 patent under 35 U.S.C. § 271(a) by making, using, selling, offering to sell, or importing the generic product in the United States upon the FDA's approval of ANDA No. 207188.

47. Upon information and belief, Defendants will induce infringement of the '271 patent under 35 U.S.C. § 271(b) by intentionally encouraging, aiding and abetting acts of direct infringement of the '271 patent, with knowledge of said patent and said infringement, upon the FDA's approval of ANDA No. 207188.

48. Upon information and belief, Defendants will contributorily infringe the '271 patent under 35 U.S.C. § 271(c) by making, using, selling, offering to sell, or importing the generic product in the United States, with knowledge of the '271 patent and that there is no substantial non-infringing use of the generic product, upon the FDA's approval of ANDA No. 207188.

49. Pursuant to 35 U.S.C. § 283 and 35 U.S.C. § 271(e)(4)(B), Noven is entitled to a permanent injunction against further infringement. Noven will be substantially and irreparably harmed if Defendants' direct, induced, and contributory infringement of the '271 patent is not enjoined. Further, Noven does not have an adequate remedy at law.

50. Upon information and belief, Defendants were aware of the '271 patent prior to filing ANDA No. 207188, as well as the statutory provisions and regulations set forth in 21

U.S.C. § 355 and 21 C.F.R. § 314.95, and acted without a reasonable basis for a good faith belief that they would not be liable for infringing the '271 patent.

COUNT IV: DECLARATORY JUDGMENT OF INFRINGEMENT OF U.S. PATENT NO. 7,598,271

51. Paragraphs 1-50 are incorporated by reference as though fully set forth herein.

52. This claim arises under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

53. There is an actual case or controversy such that the Court may hear Noven's request for declaratory relief consistent with Article III of the United States Constitution, and that actual case or controversy requires a declaration of rights by this Court.

54. Defendants have made, and will continue to make, substantial preparation in the United States, including New Jersey, to manufacture, use, sell, offer to sell, or import the generic product upon the FDA's approval of ANDA No. 207188.

55. Defendants' anticipated manufacture, use, sale, offer to sell, or importation of the generic product prior to the expiration of the '271 patent will constitute direct, induced, and contributory infringement of said patent.

56. Noven is entitled to a declaratory judgment that Defendants' anticipated manufacture, use, sale, offer to sell, or importation of the generic product prior to the expiration of the '271 patent will constitute direct, induced, and contributory infringement of the '271 patent.

COUNT V: INFRINGEMENT OF U.S. PATENT NO. 8,658,663

57. Paragraphs 1-56 are incorporated by reference as though fully set forth herein.

58. Defendants' submission of ANDA No. 207188 and its Paragraph IV certification for FDA approval to commercially manufacture, use, sell, offer to sell, or import the generic

product prior to the expiration of the '663 patent constitutes infringement under 35 U.S.C. § 271(e)(2).

59. Upon information and belief, Defendants will infringe the '663 patent under 35 U.S.C. § 271(a) by making, using, selling, offering to sell, or importing the generic product in the United States upon the FDA's approval of ANDA No. 207188.

60. Upon information and belief, Defendants will induce infringement of the '663 patent under 35 U.S.C. § 271(b) by intentionally encouraging, aiding and abetting acts of direct infringement of the '663 patent, with knowledge of said patent and said infringement, upon the FDA's approval of ANDA No. 207188.

61. Upon information and belief, Defendants will contributorily infringe the '663 patent under 35 U.S.C. § 271(c) by making, using, selling, offering to sell, or importing the generic product in the United States, with knowledge of the '663 patent and that there is no substantial non-infringing use of the generic product, upon the FDA's approval of ANDA No. 207188.

62. Pursuant to 35 U.S.C. § 283 and 35 U.S.C. § 271(e)(4)(B), Noven is entitled to a permanent injunction against further infringement. Noven will be substantially and irreparably harmed if Defendants' direct, induced, and contributory infringement of the '663 patent is not enjoined. Further, Noven does not have an adequate remedy at law.

63. Upon information and belief, Defendants were aware of the '663 patent prior to filing ANDA No. 207188, as well as the statutory provisions and regulations set forth in 21 U.S.C. § 355 and 21 C.F.R. § 314.95, and acted without a reasonable basis for a good faith belief that they would not be liable for infringing the '663 patent.

COUNT VI: DECLARATORY JUDGMENT OF INFRINGEMENT OF U.S. PATENT NO. 8,658,663

64. Paragraphs 1-63 are incorporated by reference as though fully set forth herein.

65. This claim arises under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

66. There is an actual case or controversy such that the Court may hear Noven's request for declaratory relief consistent with Article III of the United States Constitution, and that actual case or controversy requires a declaration of rights by this Court.

67. Defendants have made, and will continue to make, substantial preparation in the United States, including New Jersey, to manufacture, use, sell, offer to sell, or import the generic product upon the FDA's approval of ANDA No. 207188.

68. Defendants' anticipated manufacture, use, sale, offer to sell, or importation of the generic product prior to the expiration of the '663 patent will constitute direct, induced, and contributory infringement of said patent.

69. Noven is entitled to a declaratory judgment that Defendants' anticipated manufacture, use, sale, offer to sell, or importation of the generic product prior to the expiration of the '663 patent will constitute direct, induced, and contributory infringement of the '663 patent.

PRAYER FOR RELIEF

WHEREFORE, Noven respectfully prays for:

A. A judgment that Defendants have infringed the patents-in-suit under 35 U.S.C. § 271(e)(2)(A) by submitting ANDA No. 207188 under the FFD&C Act, and that the commercial manufacture, use, sale, offer for sale, and/or importation of the generic product before the expiration of the patents-in-suit will constitute acts of infringement of each of the patents-in-suit;

B. An order pursuant to 35 U.S.C. § 271(e)(4)(A) that the effective date of any approval of ANDA No. 207188 shall be no earlier than the date on which the '447, '271, and '663 patents expire, including any regulatory extensions;

C. An injunction under 35 U.S.C. § 271(e)(4)(B) and/or 35 U.S.C. § 283, permanently enjoining Defendants, their officers, agents, servants, employees, licensees, representatives, attorneys, and all other persons acting or attempting to act in active concert or participation with them or acting on their behalf, from engaging in the commercial manufacture, use, sale, offer to sell, and/or importation within the United States, of any pharmaceutical product covered by any of the patents-in-suit;

D. A declaration under 28 U.S.C. § 2201 that if Defendants, their officers, agents, servants, employees, licensees, representatives, attorneys, and all other persons acting or attempting to act in active concert or participation with them or acting on their behalf, engage in the commercial manufacture, use, sale, offer to sell, and/or importation within the United States, of the generic products prior to the expiration of the patents-in-suit, such acts will constitute direct and/or indirect infringement of each of the patents-in-suit;

E. An award of damages or other monetary relief under 35 U.S.C. § 271(e)(4)(C) and/or § 284 as appropriate;

F. A finding that this is an exceptional case under 35 U.S.C. § 285, and that Noven be awarded reasonable attorneys' fees and costs; and

G. An award of any such other and further relief as the Court may deem just and proper.

Dated: November 26, 2014

Respectfully submitted,

By: /s/ Anne B. Sekel

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CERTIFICATION PURSUANT TO LOCAL CIVIL RULE 11.2

Pursuant to Local Civil Rule 11.2, I hereby certify that the matter in controversy is related to the subject matter of the following action currently pending in the U.S. District Court for the District of New Jersey: *Noven Therapeutics, LLC v. Actavis Laboratories FL, Inc., Actavis Pharma, Inc., Andrx Corp., and Actavis Inc.*, Case No. 2:14-cv-06414-FSH-MAH. The foregoing case involves BRISDELLE® (paroxetine mesylate capsules), a product marketed by Noven. The foregoing BRISDELLE® matter has been assigned to Hon. Faith S. Hochberg and Plaintiffs respectfully request that this case also be assigned to Judge Hochberg.

November 26, 2014

Respectfully submitted,

By: /s/ Anne B. Sekel

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Attorneys for Plaintiff Noven Therapeutics, LLC

EXHIBIT A

US005874447A

United States Patent [19]

Benneker et al.

[11] **Patent Number: 5,874,447**

[45] **Date of Patent: Feb. 23, 1999**

[54] **4-PHENYLPIPERIDINE COMPOUNDS FOR TREATING DEPRESSION**

[75] Inventors: **Franciscus Bernardus Gemma Benneker**, Nijmegan; **Frans Van Dalen**, Neunen; **Jacobus Maria Lemmens**, Mook; **Theodorus Hendricus Antonium Peters**, Arnhem, all of Netherlands; **Frantisek Picha**, Brno, Czechoslovakia

[73] Assignee: **Synthon B. V.**, Nijmegen, Netherlands

[21] Appl. No.: **872,023**

[22] Filed: **Jun. 10, 1997**

[51] **Int. Cl.**[6] **A61K 31/445**; C07D 405/12

[52] **U.S. Cl.** **514/321**; 514/317; 514/319; 546/197; 546/198; 546/205; 546/206; 546/236

[58] **Field of Search** 546/197, 198, 546/205, 206, 236; 814/317, 319; 514/321

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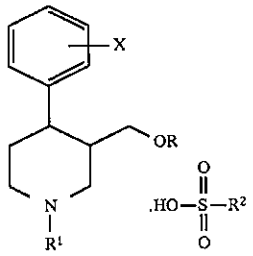
Primary Examiner—Ceila Chang
Attorney, Agent, or Firm—Howrey & Simon

[57] **ABSTRACT**

The invention relates to a compound, and pharmaceutically acceptable salts, having the formula I:



wherein:

R represents an alkyl or alkynyl group having 1–4 carbon atoms, or a phenyl group optionally substituted by C_{1-4} alkyl, alkylthio, alkoxy, halogen, nitro, acylamino, methylsulfonyl or methylenedioxy, or represents tetrahydronaphthyl,

R^1 represents hydrogen, trifluoro (C_{1-4}) alkyl, alkyl or alkynyl,

X represents hydrogen, alkyl having 1–4 carbon atoms, alkoxy, trifluoroalkyl, hydroxy, halogen, methylthio or aralkoxy,

R^2 represents:

a C1–C10 alkyl group,

a phenyl group optionally substituted by one or more of the following groups:

a C1–C10 alkyl group,

a halogen group,

a nitro group,

hydroxy group,

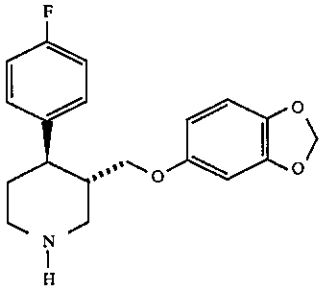
and/or an alkoxy group.

29 Claims, No Drawings

4-PHENYLPIPERIDINE COMPOUNDS FOR TREATING DEPRESSION

The present invention relates to a group of tri-substituted, 4-phenylpiperidines, to a process for preparing such compounds, to a medicament comprising such compounds, and to the use of such compounds for the manufacture of a medicament.

The compound paroxetine, trans-4-(4'-fluorophenyl)-3-(3',4'-methylene dioxyphenoxymethyl) piperidine having the formula below:



is known and has been used in medicaments for treating, amongst other ailments, depression.

Paroxetine has been used as a therapeutic agent in the form of a salt with pharmaceutically acceptable acids. The first clinical trials were conducted with the acetate salt.

A known useful salt of paroxetine is the hydrochloride. This salt is considered to be the active substance in several marketed pharmaceutical products, e.g. Paxil or Seroxat. A number of forms of paroxetine hydrochloride have been described:

- the anhydrous form in several crystalline modifications (PCT Appl. WO 96/24595);
- the hydrated form—a hemihydrate (EP 223403) and in the solvated forms.

The comparison of behaviour between anhydrous and hydrated form of paroxetine hydrochloride is described in the Intl. Journal of Pharmaceutics 42, 135–143 (1988).

EP 223403 discloses paroxetine hydrochloride hemihydrate and pharmaceutical compositions based thereon.

Most of these known salts of paroxetine have unsuitable physico-chemical characteristics for ensuring safe and efficient handling during production thereof and formulation into final forms, since they are unstable (acetate, maleate) and possess undesirable hygroscopicity.

Furthermore their formation by crystallization from both aqueous or non-aqueous solvents is generally low-yielded and troublesome as they usually contain an undefined and unpredicted amount of bound solvent which is difficult to remove.

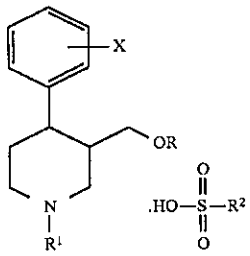
The crystalline paroxetine hydrochloride hemihydrate approaches these problems, but as stated in WO 95/16448, its limited photostability causes undesired colouration during classical wet tabletting procedure.

Moreover, crystalline paroxetine hydrochloride hemihydrate exhibits only limited solubility in water.

It has been generally suggested that where the aqueous solubility is low, for example less than 3 mg/ml, the dissolution rate at in vivo administration could be rate-limiting in the absorption process. The aqueous solubility of the paroxetine hemihydrate at room temperature exceeds this threshold by a relatively small margin.

An object of the present invention is to provide a compound with improved characteristics.

According to a first aspect, the present invention comprises a compound, and pharmaceutically acceptable salts, having the formula I:



R represents an alkyl or alkynyl group having 1–4 carbon atoms, or a phenyl group optionally substituted by C_{1-4} alkyl, alkylthio, alkoxy, halogen, nitro, acylamino, methylsulfonyl or methylenedioxy, or represents tetrahydronaphthyl,

R^1 represents hydrogen, trifluoro (C_{1-4}) alkyl, alkyl or alkynyl,

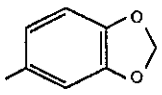
X represents hydrogen, alkyl having 1–4 carbon atoms, alkoxy, trifluoroalkyl, hydroxy, halogen, methylthio or aralkoxy,

R^2 represents:

- a C1–C10 alkyl group,
- a phenyl group optionally substituted by one or more of the following groups:
  - a C1–C10 alkyl group,
  - a halogen group,
  - a nitro group,
  - hydroxy group,
  - and/or an alkoxy group.

The inventors have found that these compounds exhibit good stability and very high solubility. This yields the advantage that high concentrations of the compound are obtainable in small volumes.

The R group is preferably the 3,4 methylenedioxyphenyl group of the formula:



The X group is preferably a fluorine group attached to position 4 in the phenyl ring.

The R^2 group preferably represents a C1–C4 alkyl group, and most preferably represents a C1–C2 alkyl group in order to provide an optimum solubility.

The compounds can have a solubility at about 20° C. of at least about 10 mg/ml water, preferably having a solubility in water of at least 100, for example 500 and most preferably of at least 1000 mg/ml water.

According to a second aspect of the present invention, there is provided a process for preparing a compound as above, comprising the steps of mixing together a 4 phenylpiperidine compound, a salt and/or a base thereof having the formula II:

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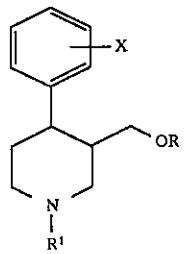


wherein:

R represents an alkyl or alkynyl group having 1–4 carbon atoms, or a phenyl group optionally substituted by C_{1-4} alkyl, alkylthio, alkoxy, halogen, nitro, acylamino, methylsulfonyl or methylenedioxy, or represents tetrahydronaphthyl,

R_1 represents hydrogen, trifluoro (C_{1-4}) alkyl, alkyl or alkynyl,

X represents hydrogen, alkyl having 1–4 carbon atoms, alkoxy, trifluoroalkyl, hydroxy, halogen, methylthio or aralkoxy,

with a sulfonic acid of the general formula R_2-SO_3H, wherein R_2 represents:

a C1–C10 alkyl group,

a phenyl group optionally substituted by one or more of he following groups:

a C1–C10 alkyl group,

a halogen group,

a nitro group,

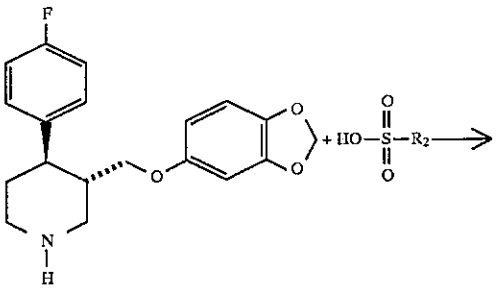
a hydroxy group, and/or

an alkoxy group,

to form a solution, followed by separating the compound formed from this solution.

The compounds of the invention can be prepared from the free base of the 4 phenylpiperidine, having the formula II, this preferably being paroxetine, by treatment with a sulfonic acid as defined above in a suitable solvent to form a solution of the desired acid addition salt, whereafter this is precipitated out of the solution.

The equation for paroxetine free base and sulfonic acids is as follows:



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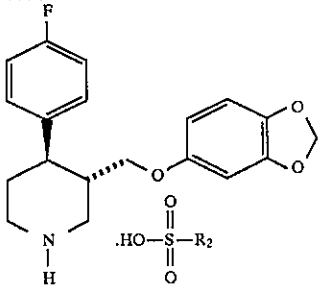
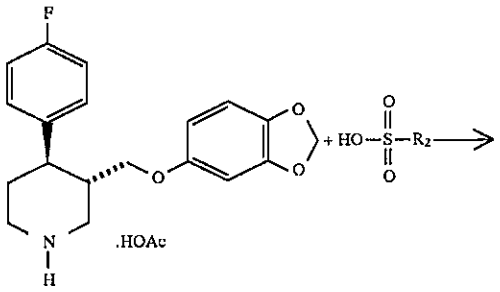


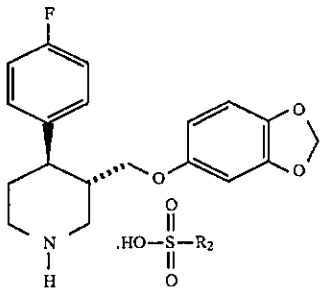
The forming of a solution may preferably proceed at temperatures from about 0° C. to the boiling point of the solvent.

Optionally, the solution may be purified by treatment of activated charcoal, silica gel, kieselguhr or other suitable materials.

Alternatively, the solution of a salt of the invention can be formed by dissolution of a salt of 4 phenyl piperidine having the formula II with an organic sulfonic acid.

For example the compounds of the invention may be prepared from a paroxetine C1–C5 carboxylate, such as the acetate, by addition of corresponding organic sulfonic acid to the solution of the said carboxylate, as follows:



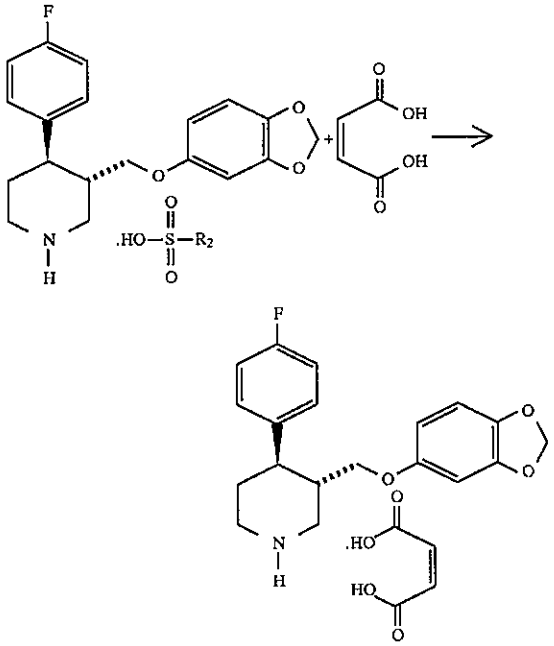


According to a third aspect of the present invention, there is provided a compound obtainable by this process.

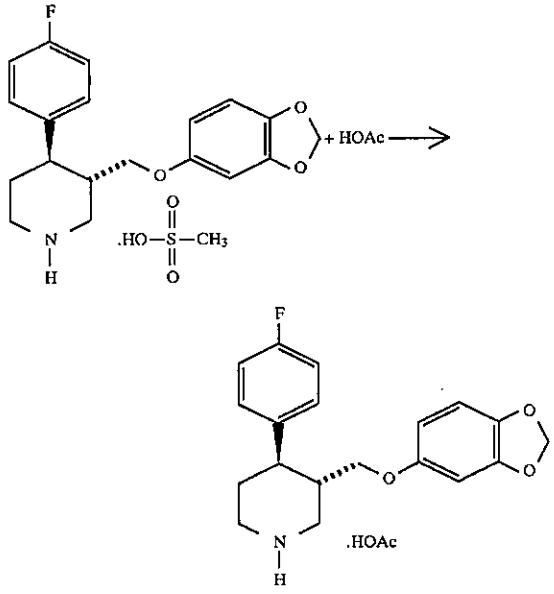
According to a fourth aspect of the present invention there is provided the above compound for use as a medicament and, according to a fifth aspect, a medicament comprising this compound, and to the use thereof for treating depressions, obsessive compulsive disorders, panic disorders, bulimia, anorexia, pain, obesity, senile demential, migraine, anorexia, social phobia, depressions arising from pre-menstrual tension.

According to a sixth aspect of the present invention, there is provided the use of a compound of the invention as a reagent in further syntheses. More specifically, the compounds of the present invention can be used as a start reagent for forming further acid addition salts, for example for

providing further paroxetine acid addition salts, by reacting with a suitable regent, i.e. with a corresponding acid. For example, the formation of paroxetine maleate according to the present invention proceeds by the following equation:

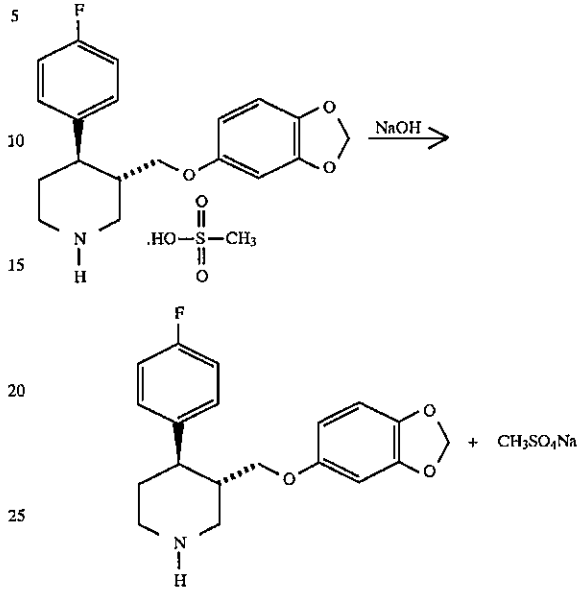


and the formation of paroxetine acetate proceeds as follows:



This is an advantageous route, since by using the substantially pure sulfonic acid salts according to the present invention as a start reagent, the preparation of a further salt, as above, results in this further salt having a high purity. The inventors have shown that such salts have a surprisingly high purity.

Similarly, the compounds of the present invention can react with a base, such as an inorganic and/or an organic base, to form (liberate) free bases of the corresponding compounds. As exemplified on paroxetine, the reaction proceeds according to the equation:



The free bases liberated from the compounds of the present invention have surprisingly higher purity than if prepared by known methods which is especially important in case of their use for production of pharmaceuticals.

Accordingly, the new compounds of the first aspect of the invention can also form hydrates and/or solvates by a contact with a corresponding reaction partner, i.e. with water and/or with a solvent. Examples of such further salts, hydrates and solvates, for example these of paroxetine, are the:

hydrochloride	oxalate	dihydrate
hydrobromide	succinate	trihydrate
hydroiodide	tartrate	hexahydrate
acetate	citrate	methanolate
propionate	embonate	ethanolate
maleate	hemihydrate	
fumarate	hydrate	

The inventors have shown that such salts have a surprisingly high purity.

Examples of bases which can be employed in the preparation of the free bases are: sodium hydroxide, potassium hydroxide, calcium hydroxide, ammonium hydroxide, sodium carbonate, methylamine, dimethylamine, triethylamine, pyridine and such like.

Since the compounds according to the present invention exhibit high solubility, they can be dosed, for example injected, in a high concentration, low volume solution, this method of dosing being particularly advantageous with certain patients, such as manic depressives and such like, i.e. patients who are unable or unwilling to swallow medicine.

The compounds of the present invention can be formulated into various types of pharmaceutical compositions for treatment of humans and animals. Pharmaceutical compositions according to the present invention comprise a compound of the invention alone or together with a pharmaceutically acceptable carrier or diluent. The preferred formulations are those for oral administration (tablets,

capsules) but formulations for parenteral or topical administration are also within the scope of the invention. The high water solubility of the compounds of the invention enables high dissolution rates in solid dosage forms based on the compounds of the invention to be obtained, during the in vitro release as well as good bioavailability after peroral application in vivo.

The tablets containing compounds of the present invention can be prepared both by tabletting procedure in which water is present (e.g. aqueous granulation) as well as by tabletting processing it which water is absent (direct compression, dry granulation) and may be coated by any suitable means of coating.

The present invention will now be further elucidated by way of the following examples and results.

EXPERIMENTAL

A seeding crystal of paroxetine methane sulfonate was made as follows:

2.7 g (8.2 mmol) of paroxetine was dissolved in
15 ml of hot ethanol.
1.0 g (10.4 mmol) of methanesulfonic acid in
15 ml of ethanol was added and the mixture was cooled to room temperature. When the mixture had reached room temperature the mixture was put in the freezer at −20° C. overnight. No crystal line compound was obtained. The mixture was evaporated to dryness leaving an oil. After 1 month at room temperature a waxy solid was obtained. Part of this solid was taken apart and the rest was dissolved in
10 ml of EtOAc. The waxy crystals were added and the mixture was put in the freezer at −20° C. overnight. A white crystalline product was precipitated. After filtration and drying in a vacuumoven
2.5 g (5.9 mmol) of paroxetine methane sulfonate was obtained.

Yield 72%

This seeding crystal was subsequently used in following examples 1 and 3.

EXAMPLES

Example 1

Paroxetine methane sulfonate from paroxetine

To a solution of 43.5 g (132 mmol) of paroxetine, prepared by the procedure disclosed in U.S. Pat. No. 4,007,196, 12.7 g (132 mmol) of methane sulfonic acid was added to 150 ml of boiling ethyl acetate. The mixture was left at room temperature for 2 hours. Subsequently the mixture was placed overnight at −20° C., with a seeding crystal. The obtained solid was filtered off and washed with
50 ml of ether. The obtained white solid was dried overnight in a vacuumoven.
47.1 g (111 mmol) of product

Yield 99.5%

Analytical characterization of the compound obtained is shown in Table 1. The purity of the compound obtained was 98% (HPLC).

Example 2

Paroxetine Benzene Sulfonate From Paroxetine

3.8 g (11.5 mmol) of paroxetine was dissolved in
10 ml of hot ethylacetate.
1.82 g (11.5 mmol) of anhydrous benzenesulfonic acid was added. The mixture was left at room temperature for 2 h. The mixture was evaporated to dryness and dissolved in dichloromethane, and evaporated again to dryness leaving an oil. This oil was solidified through high vacuum (0.1 mmHg) evaporation leaving
5.0 g (1.3 mmol) of an off white solid. To this solid was added
5 ml of acetone and the suspension was stirred for 5 minutes during which a white suspension was obtained. The solid was filtered off and dried under vacuum.
4.8 g (9.9 mmol) of product was obtained.

Yield 85%.

Analytical characterization of the compound obtained is shown in Table 1. The purity of the compound obtained was 99.4% (HPLC).

Example 3

Paroxetine p-toluene Sulfonate From Paroxetine

5.0 g (15 mmol) of paroxetine was dissolved in
25 ml of hot ethylacetate.
2.9 g (15 mmol) of p-toluenesulfonic acid was added. The mixture was left at room temperature for 2 h and subsequently put in the freezer, with a seeding crystal, for 14 h. The solid was filtered off and washed once with
10 ml of n-hexane. The obtained white solid was dried overnight in a vacuumoven.
4.8 g (10 mmol) of a white solid was obtained.

Yield 67%

Analytical characterization of the compound obtained is shown in Table 1. The purity of the compound obtained was 99.4% (HPLC).

Example 4

Paroxetine p-chlorobenzene Sulfonate From Paroxetine

1.1 g (3.3 mmol) of paroxetine was dissolved in
3 ml of hot ethylacetate.
0.76 g (3.3 mmol) of 90% p-chlorobenzenesulfonic acid was added. The mixture was left at room temperature for 1 h and washed with
5 ml of water. The organic layer was dried with Na_2SO_4, filtered and evaporated to dryness leaving
1.5 g (2.9 mmol) of an off white solid.

Yield 88%

Analytical characterization of the compound obtained is shown in Table 1. The purity of the compound obtained was 99.4% (HPLC).

Example 5

Paroxetine Maleate From Paroxetine Methane Sulfonate

1.0 g (2.4 mmol) of paroxetine methane sulfonate in
5 ml of hot water. To this solution was added
0.32 g (2.8 mmol) of maleic acid. The mixture was placed at 4° C. overnight after which a solid with a yellow oil was precipitated on the bottom of the flask. The solid/oil was filtered off and washed 3 times with
10 ml of ether and dried in a vacuumoven.
0.8 g (2.0 mmol) off white crystals were obtained

Yield 85%

The purity of the compound obtained was 99.5% (HPLC).

Example 6

Paroxetine Acetate From Paroxetine Methane Sulfonate

1.0 g (2.4 mmol) of paroxetine methane sulfonate in
5 ml of hot iso-propanol. To this solution was added
0.2 g (3.2 mmol) of acetic acid. The mixture was placed at 4° C. overnight after which a solid was precipitated. The solid was filtered off and washed 3 times with
10 ml of ether and dried in a vacuumoven.
0.5 g (1.3 mmol) off white crystals were obtained
Yield 54%

The purity of the compound obtained was 99.5% (HPLC).

Example 7

Paroxetine free base from paroxetine methane sulfonate

10.0 g (24.0 mmol) of paroxetine methane sulfonate in
150 ml of water and
200 ml of ethyl acetate. To this was added
12.4 g (31 mmol) of an aqueous 10 wt % NaOH solution and the suspension was stirred for 15 minutes. The layers were separated and the aqueous layer was extracted once with
50 ml of ethyl acetate. The combined organic layers are washed once with
100 ml of water and dried over Na_2SO_4. The Na_2SO_4 was filtered off and washed once with
50 ml of ethyl acetate. The ethyl acetate was evaporated off, leaving
7.5 g (22.8 mmol) of an oily product.
Yield 95%

The purity of the compound obtained was 99.5% (HPLC).

A number of the compounds obtained were analysed, the results being shown in tables 1–5 below:

TABLE 1

Characterization of salts of paroxetine with cortain organic acids $R\text{-}SO_3H$

R = CH_3 (paroxetine methane sulfonate):
m.p.: 142°–144° C.
DSC curve (closed pan, 10° C./min): onset 145.8° C. 79.0 l/g
LR spectrum (KBr, in cm^{-1}): 531, 546, 777, 838, 931, 962, 1038, 1100, 1169, 1208, 1469, 1500, 1515, 1615, 2577, 2869, 2900, 3023.
1H-NMR (ppm): 1.99 (br d, H_{5eq}, 1H): 2.27 (ddd, H_{5ax}, 1H); 2.48–2.65 (m, H_3, 1H); 2.82–2.92 (m, H_4, CH_3, 4H); 2.95–3.20 (m, H_{2ax}, H_{6ax}, 2H); 3.47 (dd, H_7, 1H); 3.58–3.74 (m,H_{2eq}, H_{6eq}, $H_7$3H): 5.88 (x, H_7-2H); 6.10 (dd, $H_{6''}$ 1H); 6.33 (d, $H_{2''}$, 1H): 6.61 (d, $H_{5''}$, 1H); 7.09 (dd, $H_{3'}$, $H_{5'}$, 2H); 7.22 (dd $H_{2'}$, $H_{6'}$, 2H); 8.85 (br d, NH_{eq}, 1H); 9.11 (br d, NH_{ax}, 1H).
13C-NMR (ppm): 30.0 (s, C_5); 39.3 (s, C_3); 39.5 (s, C_4); 41.7 (s, SC); 44.6 (s, C_6); 46.8 (s, C_2); 67.4 (s, C_7); 97.8 (s, $C_{2''}$); 101.2 (s, $C_{7''}$); 105.4 (s, $C_{6''}$); 107.8 (s, $C_{5''}$); 115.8 (d, $C_{3''}$, C_5); 128.4 (s, $C_{6'}$, C_2); 137.1 (s, $C_{4''}$); 142.0 (s, C_1); 148.2 (s, C_3); 153.7 (s, $C_{1''}$); 161.9 (d, C_4,).
R= C_6H_5 (paroxetine benzene sulfonate):
m.p.: 55°–60° C.
IR spectrum (KBr, in $cm^{31\ 1}$): 530, 564, 614, 689, 728, 764, 828, 929, 993, 1007, 1029, 1121, 1179, 1229, 1443, 1471, 1486, 1514, 1600, 1628, 2557, 2842, 3029.
1H-NMR (ppm): 1.90 (br d, H_{5eg}, 1H); 2.10–2.28 (m, H_{5ax}, 1H); 2.38–2.52 (m, H_3, 1H); 2.82 (ddd, H_4, 1H); 3.02–3.18 (m, H_{2ax}, H_{6ax}, 2H); 3.37 (dd, H_7, 1H); 3.48 (d, H_7, 1H); 3.60–3.82 (m, H_{2eg}, H_{6eg}, 2H); 5.87 (s, $H_{7''}$, 2H); 6.06 (dd, $H_{6''}$, 1H); 6.29 (d, $H_{2''}$, 1H); 6.60 (d, $H_{5''}$, 1H); 6.90 (dd, H_3, H_5, 2H); 7.04 (dd, H_2, H_6, 2H); 7.40 (d, ArH, 3H); 7.94 (d, SArH, 2H); 8.81 (br d, NH_{eg}, 1H); 9.04 (br d, NH_{ax}, 1H).
13C-NMR (ppm): 29.9 (s, C_5); 39.2 (s, C_3); 41.5 (s, C_4); 44.8 (s, C_6); 47.0 (s, C_2); 67.3 (s, C_7); 97.9 (s, $C_{2''}$); 101.2 (s, $C_{7''}$); 105.5 (s, $C_{6''}$,) 107.8 (s, $C_{5''}$,); 115.7 (d, C_3, C_5,); 125.9 (s, C_b); 128.8 (s, C_d); 128.8 (s, C_6, C_2,); 130.6 (s, C_{ax}); 137.1 (s, $C_{4''}$); 141.9 (s, C_1); 144.1 (s, C_3); 148.2 (s, $C_{3''}$,); 153.7 (s, $C_{1''}$,); 161.8 (s, C_4,).
R = p-$CH_3C_6H_4$ (paroxetine p-toluene sulfonate):
m.p.: 148°–150° C.
DSC curve (closed pan, 10° C./min): onset 151.6° C., 71.6 l/g.
IR spectrum (KBr, in cm^{-1}): 529, 557, 673, 771, 800, 814, 921, 936, 1000, 1029, 1100, 1157, 1136, 1229, 1471, 1486, 1507, 1600, 2557, 2829, 3029.
1H-NMR (ppm): 1.89 (br d, H_{5eg}, 1H); 2.10–2.50 (m, H_{5ax}, H_3, CH_3, 5H); 2.82 (ddd, $H_4$1H); 2.97–3.18 (m, H_{2ax}, H_{6ax}, 2H); 3.36 (dd,$H_7$1H); 3.48 (dd, H_7, 1H); 3.52–3.77 (m, H_{2eg}, H_{6eg}, 2H); 5.87 (s, $H_{7''}$, 2H); 6.06 (dd, $H_{6''}$, 1H); 6.28 (d, $H_{2''}$, 1H); 6.59 (d, $H_{5''}$, 1H); 6.90 (dd, H_3, H_5, 2H); 7.05 (dd, H_2, H_6, 2H); 7.24 (d, CH, ArH, 2H); 7.83 (d, SArH, 2H); 8.91 (br d, NH_{eg}, 1H); 9.17 (br d, NH_{ax}, 1H).
13C-NMR (ppm): 21.3 (s, C_d); 29.9 (s, C_5); 39.2 (s, C_3); 41.5 (s, C_4); 44.7 (s, C_6); 46.9 (s, C_2); 67.3 (s, C_7); 97.8 (s, $C_{2''}$); 101.1 (s, $C_{7''}$); 105.5 (s, $C_{6''}$,); 107.8 (s, $C_{5''}$,); 115.6 (d, C_3, C_5,); 125.8 (s, C_b); 129.0 (s, C_6, C_2,); 129.1 (s, C_b); 137.2 (s, C_4-u); 140.8 (s, C_d); 141.5 (s, C_a); 141.9 (s, C_1); 148.2 (s, $C_{3''}$,); 153.8 (s, $C_{1''}$,); 161.8 (d, C_4,).
R = p-ClC_6H_4 (paroxetine p-chlorobenzene sulfonate):
m.p.: 75°–80° C.
LR spectrum (KBr, in cm^{-1}): 486, 557, 643, 736, 821, 1000, 1029, 1086, 1114, 1186, 1229, 1471, 1486, 1514, 1600, 1657, 2857, 3029.
1H-NMR (ppm): 1.91 (br d, H_{5eg}, 1H); 2.15 (ddd, H_{5ax}, 1H); 2.37–2.52 (m, H_3, 1H); 2.81 (ddd, H4, 1H); 2.93–3.21 (m, H_{2ax}, H_{6ax}, 2H); 3.37 (dd, H_7, 1H): 3.49 (d, H_7, 1H), 3.61–3.81 (m, H_{2eg}, H_{6eg}, 2H); 5.88 (s, $H_{7''}$, 2H); 6.05 (dd, $H_{6''}$, 1H); 6.27 (d, $H_{2''}$, 1H); 6.59 (d, $H_{5''}$, 1H); 6.91 (dd, H_3, H_5, 2H); 7.03 (dd, H_2, H_6, 2H); 7.39 (d, ClArH, 2H); 7.86 (d, SArH, 2H); 8.78 (br d, NH_{eg}, 1H); 9.02 (br d, NH_{ax}, 1H).
13C-NMR (ppm): 30.0 (s, C_5); 39.3 (s, C_3); 41.5 (s, C_4); 44.9 (s, C_6); 47.1 (s, C_2); 67.3 (s, C_7,); 97.9 (s, $C_{2''}$,); 101.2 (s, $C_{7''}$,); 105.5 (s, $C_{6''}$,); 107.9 (s, $C_{5''}$,); 115.8 (d, C_3, C_5,); 127.6 (s, C_b); 128.8 (s, C_6, C_2,); 132.0 (s, C_d); 137.0 (s, C_6); 137.2 (s, $C_{4''}$,); 141.8 (s, C_1,); 142.0 (s, C_6,); 148.2 (s, $C_{3''}$,); 153.6 (s, $C_{1''}$,); 161.8 (d, C_4,).

The compounds of the invention are crystalline, with defined melting points, DSC curves and IR spectra. It cannot be excluded that, under different conditions of their formation and under specific conditions, they could exist also in other crystalline or polymorph modifications which may differ from those as described herein. The compounds of the invention are also generally very stable and non-hygroscopic.

It should be understood that the present invention comprising acid addition salts with organic sulfonic acids are substantially free of the bound organic solvent. Preferably, the amount of bound organic solvent should be less than 2.0% (w/w) as calculated on the anhydrous basis. They nevertheless may contain crystallization water and also unbound water, that is to say water which is other than water of crystallization.

In the following tables 2 and 3, examples of results of hygroscopicity tests and stability tests (in comparison with known salts of paroxetine) are presented.

TABLE 2

Hygroscopicity of certain salts of paroxetine (40° C., 75% rel. hum).

water content (in %) at	t = 0	1 = 4 weeks
methane sulfonate	0.35	+0.04
p-toluene sulfonate	0.70	<0.02
hydrochloride	—	+2.5

TABLE 3

Solubility of paroxetine salts in water (in mg/ml)

	20° C.	50° C.
methane sulfonate	>1000	1300
p-toluene sulfonate	>1000	>1000
hydrochloride hemidhydrate	4.9	12.6
hydrochloride anhydrate	8.2	24.2

TABLE 4

Stability of paroxetine salts by HPLC (total amount of degradation in %).

	degradation 20° C.	80° C.
methane sulfonate	not observed	<0.2%, 3 months
p-toluene sulfonate	not observed	<0.2%, 3 months
maleate	0.2%, 12 months	>50%, 5 days

TABLE 5

Solubility of slats of paroxetine in nonaqueous solvents (in mg/ml)

		methane sulfonate	p-toluene sulfonate
Ethanol	20° C.	36	50
	78° C.	250	>500
2-Propanol	20° C.	7	14
	82° C.	330	>500
Acetone	20° C.	5	16
	56° C.	37	125
Ethyl acetate	20° C.	2	22
	77° C.	25	>500
n-Hexane	20° C.	<0.05	<0.05
	69° C.	0.05	<0.05

Examples of analytical data of the paroxetine salts and the free base prepared in Examples 5 to 7 are given in Table 6.

TABLE 6

Characterization of salts/free base of praoxetine

paroxetine maleate:

m.p.: 128–130° C.
1H-NMR (ppm); 1.65–2.00 (m, H_{5eq}, 2H); 2.00–2.50 (m, H_3, 1H); 2.55–3.15 (m, H_{2ax}, H_{6ax}, H_4, 3H); 3.15–3.75 (m, H_{2eq}, H_{6eq}, $H_{7\ 3H}$); 5.67 (s, H_7, 2H); 5.97 (s, H_a, 1H); 6.12 (dd, $H_{6'}$, 1H); 6.42 (d, $H_{2'}$, 1H) 6.67 (d, $H_{5'}$, 1H); 6.95–7.35 (m, $H_{2'}$, $H_{3'}$, $H_{5'}$, H_6, 4H).

paroxetine acetate:

m.p.; 123–125° C.
1H-NMR (ppm); 1.70–2.00 (m, H_{5eq}, H_{5ax}, 2H); 1.97 (s, H_a, 3H); 2.05–2.50 (m, H_3, 1H); 2.50–3.00 (m, H_4, H_{2ax}, H_{6ax}, 3H); 3.05–3.75 (m, H_{2eq}, H_{6eq}, H_7, 3H); 6.05 (s, $H_{7'}$, 2H); 6.28 (dd, $H_{6'}$, 1H); 6.58 (d, $H_{2'}$, 1H); 6.65 (d, $H_{5'}$, 1H); 7.10–7.50 (m, $H_{2'}$, $H_{3'}$, $H_{5'}$, $H_{6'}$, 4H).

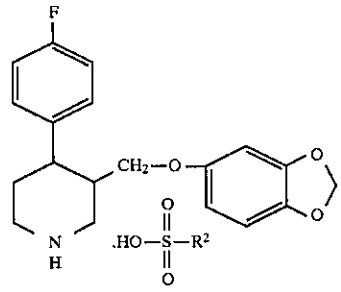
paroxetine:

1H-NMR (ppm): 1.60–2.00 (m, H_{3x}, H_{5eq}, 2H); 2.00–2.35 (m, H_3, 1H); 2.40–2.95 (m, H_4, H_{2ax}, 3H); 3.15–3.70 (m, H_{2eq}, H_{6eq}, H_7, 2H); 5.67 (s, H_7, 2H); 6.11 (dd, $H_{6'}$, 1H); 6.43 (d, $H_{2'}$, 1H); 6.62 (d, $H_{5'}$, 1H); 6.80–7.35 (m, $H_{2'}$, $H_{3'}$, $H_{5'}$, H_6, 4H).

It will be clear that the invention is not limited to the above description, but is rather determined by the following claims.

We claim:

1. A compound having the formula:



wherein R^2 represents C_1–C_{10} alkyl group or a substituted or unsubstituted phenyl group wherein the substituents are selected from the group consisting of C_1–C_{10} alkyl, halogen, nitro, hydroxy, alkoxy, and combinations thereof.

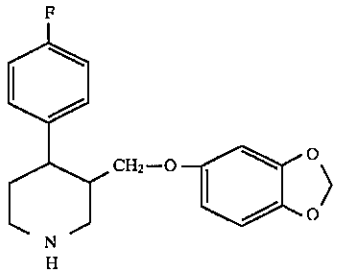
2. The compound according to claim 1, wherein the R^2 group represents a C_1–C_4 alkyl group.

3. The compound according to claim 1, wherein the R^2 group is a C_1–C_2 alkyl group.

4. The compound according to claim 1, having a solubility at about 20° C. of at least about 10 mg per ml water.

5. The compound according to claim 4, having a solubility in water of at least 1000 mg per ml at about 20° C.

6. A process, which comprises mixing together a compound, a salt, and/or a base thereof, having the formula:



with a sulfonic acid of the general formula R^2-SO_3H, wherein

R^2 represents C_1–C_{10} alkyl group or a substituted or unsubstituted phenyl group wherein the substituents are selected from the group consisting of C_1–C_{10} alkyl, halogen, nitro, hydroxy, alkoxy, and combinations thereof,

to produce a sulfonate salt compound according to claim 1.

7. The process according to claim 6, which further comprises mixing together said sulfonate salt compound with a reagent selected from the group consisting of hydrochloric acid, hydrobromic acid, hydriodic acid, acetic acid, propionic acid, maleic acid, fumaric acid, oxalic acid, succinic acid, tartaric acid, citric acid, embonic acid/pamoic acid, sulfuric acid, water, methanol, and ethanol, to form a salt or solvate of said reagent.

8. The process according to claim 7, wherein the salt of said reagent is produced and is recovered as a solid having a purity of at least 90 wt %.

9. The process according to claim 7, wherein said reagent is maleic acid; said mixing produces paroxetine maleate; and which further comprises recovering said paroxetine maleate in a purity of at least 98%.

10. The process according to claim 7, wherein said reagent is acetic acid; said mixing produces paroxetine acetate; and which further comprises recovering said paroxetine acetate in a purity of at least 98%.

11. A process according to claim 6, which further comprises mixing together said sulfonate salt compound with at least one of an organic or an inorganic base to form a free base thereof.

12. The process according to claim 11, wherein the base is selected from the group consisting essentially of: sodium hydroxide, potassium hydroxide, calcium hydroxide, ammonium hydroxide, sodium carbonate, methylamine, dimethylamine, triethylamine, and pyridine.

13. The process according to claim 11, further comprising isolating said free base in a purity of at least 95%.

14. The process according to claim 13, wherein said isolated free base has a purity of at least 98%.

15. The compound produced by the process according to claim 6.

16. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to claim 1 and at least one pharmaceutically acceptable carrier or diluent.

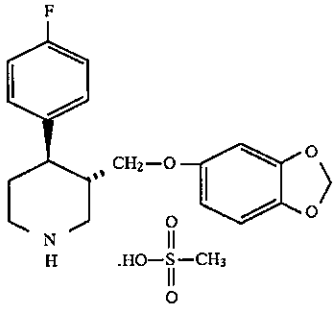
17. The pharmaceutical composition according to claim 16, wherein said composition is a solid dosage form.

18. A method for treating depression, obsessive/compulsive disorders, panic disorders, bulimia, anorexia, pain, obesity, senile dementia, migraine, or social phobias, which comprises administering to a patient in need thereof a therapeutically effective amount of the compound as claimed in claim 1.

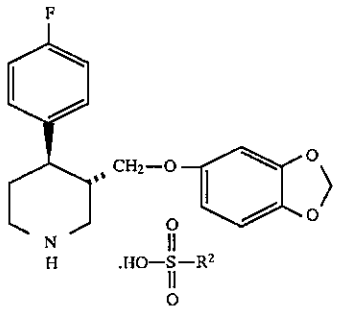
19. The method according to claim 18, wherein said patient is a human.

20. The method according to claim 18, wherein said method comprises administering an effective antidepressant amount of said compound to a patient suffering from depression.

21. A compound of the following formula:



22. A pharmaceutical composition comprising a therapeutically effective amount of a compound of the following formula:



wherein R^2 is methyl, ethyl, benzyl, p-chlorobenzyl, or tolyl; and

a pharmaceutically acceptable carrier or diluent.

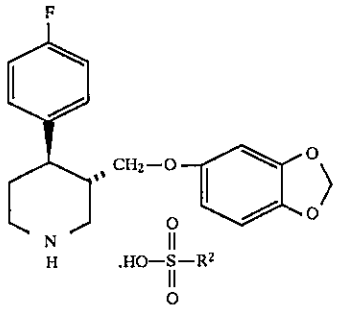
23. The pharmaceutical composition according to claim 22, wherein said composition is for oral administration.

24. The pharmaceutical composition according to claim 22, wherein R^2 is methyl.

25. The pharmaceutical composition according to claim 24, wherein said composition is a solid dosage form.

26. The pharmaceutical composition according to claim 25, wherein said composition is a tablet.

27. A method of treating depression, obsessive/compulsive disorders or panic disorders which comprises administering to a patient in need thereof an effective amount of a compound of the following formula:



wherein R^2 is methyl, ethyl, benzyl, p-chlorobenzyl, or tolyl.

28. The method according to claim 27, wherein R^2 is methyl.

29. The method according to claim 28, wherein an effective antidepressant amount is administered to said patient.

* * * * *

EXHIBIT B

US007598271B1

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

(10) **Patent No.: US 7,598,271 B1**
(45) **Date of Patent: Oct. 6, 2009**

(54) **CRYSTALLINE PAROXETINE METHANE SULFONATE**

(75) Inventors: **Franciscus Bernardus Gemma Benneker**, Nijmegen (NL); **Frans Van Dalen**, Nuenen (NL); **Jacobus Maria Lemmens**, Mook (NL); **Theodorus Hendricus Antonium Peters**, Arnhem (NL); **Frantisek Picha**, Brno (CZ)

(73) Assignee: **Noven Therapeutics, LLC**, Miami, FL (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 2072 days.

(21) Appl. No.: **09/200,743**

(22) Filed: **Nov. 30, 1998**

Related U.S. Application Data

(62) Division of application No. 08/872,023, filed on Jun. 10, 1997, now Pat. No. 5,874,447.

(51) **Int. Cl.**
A61K 31/445 (2006.01)
C07D 405/12 (2006.01)

(52) **U.S. Cl.** **514/321**; 514/317; 514/319; 546/197; 546/198; 546/205; 546/206; 546/236

(58) **Field of Classification Search** 514/317, 514/319, 321; 546/197, 198, 205, 206, 236
See application file for complete search history.

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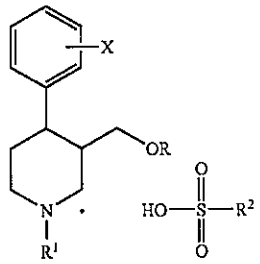
Primary Examiner—Celia Chang
(74) *Attorney, Agent, or Firm*—Foley & Lardner LLP

(57) **ABSTRACT**

The invention relates to a compound, and pharmaceutically acceptable salts, having the formula I:



wherein:

R represents an alkyl or alkynyl group having 1-4 carbon atoms, or a phenyl group optionally substituted by C_{1-4} alkyl, alkylthio, alkoxy, halogen, nitro, acylamino, methylsulfonyl or methylenedioxy, or represents tetrahydronaphthyl,

R^1 represents hydrogen, trifluoro (C_{1-4}) alkyl, alkyl or alkynyl,

X represents hydrogen, alkyl having 1-4 carbon atoms, alkoxy, trifluoroalkyl, hydroxy, halogen, methylthio or aralkoxy,

R^2 represents:

a C1-C10 alkyl group,

a phenyl group optionally substituted by one or more of the following groups:

a C1-C10 alkyl group,

a halogen group,

a nitro group,

hydroxy group,

and/or an alkoxy group.

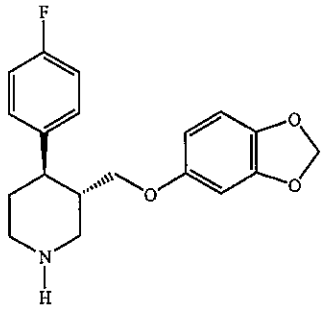
1 Claim, No Drawings

CRYSTALLINE PAROXETINE METHANE SULFONATE

This application is a divisional of prior application Ser. No. 08/872,023, filed Jun. 10, 1997 now U.S. Pat. No. 5,874,447, the entire contents of which are incorporated herein by reference.

The present invention relates to a group of tri-substituted, 4-phenylpiperidines, to a process for preparing such compounds, to a medicament comprising such compounds, and to the use of such compounds for the manufacture of a medicament.

The compound paroxetine, trans-4-(4'-fluorophenyl)-3-(3',4'-methylene dioxyphenoxymethyl)piperidine having the formula below:



is known and has been used in medicaments for treating, amongst other ailments, depression.

Paroxetine has been used as a therapeutic agent in the form of a salt with pharmaceutically acceptable acids. The first clinical trials were conducted with the acetate salt.

A known useful salt of paroxetine is the hydrochloride. This salt is considered to be the active substance in several marketed pharmaceutical products, e.g. Paxil or Seroxat. A number of forms of paroxetine hydrochloride have been described:

- the anhydrous form in several crystalline modifications (PCT Appl. WO 96/24595);
- the hydrated form—a hemihydrate (EP 223403) and in the solvated forms.

The comparison of behaviour between anhydrous and hydrated form of paroxetine hydrochloride is described in the Intl. Journal of Pharmaceutics, 42, 135-143 (1988).

EP 223403 discloses paroxetine hydrochloride hemihydrate and pharmaceutical compositions based thereon.

Most of these known salts of paroxetine have unsuitable physico-chemical characteristics for ensuring safe and efficient handling during production thereof and formulation into final forms, since they are unstable (acetate, maleate) and possess undesirable hygroscopicity.

Furthermore their formation by crystallization from both aqueous or non-aqueous solvents is generally low-yielded and troublesome as they usually contain an undefined and unpredicted amount of bound solvent which is difficult to remove.

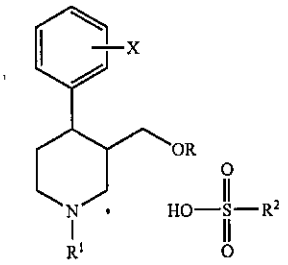
The crystalline paroxetine hydrochloride hemihydrate approaches these problems, but as stated in WO 95/16448, its limited photostability causes undesired colouration during classical wet tabletting procedure.

Moreover, crystalline paroxetine hydrochloride hemihydrate exhibits only limited solubility in water.

It has been generally suggested that where the aqueous solubility is low, for example less than 3 mg/ml, the dissolution rate at in vivo administration could be rate-limiting in the absorption process. The aqueous solubility of the paroxetine hemihydrate at room temperature exceeds this threshold by a relatively small margin.

An object of the present invention is to provide a compound with improved characteristics.

According to a first aspect, the present invention comprises a compound, and pharmaceutically acceptable salts, having the formula I:



R represents an alkyl or alkynyl group having 1-4 carbon atoms, or a phenyl group optionally substituted by C_{1-4} alkyl, alkylthio, alkoxy, halogen, nitro, acylamino, methylsulfonyl or methylenedioxy, or represents tetrahydronaphthyl,

R^1 represents hydrogen, trifluoro (C_{1-4}) alkyl, alkyl or alkynyl,

X represents hydrogen, alkyl having 1-4 carbon atoms, alkoxy, trifluoroalkyl, hydroxy, halogen, methylthio or aralkoxy,

R^2 represents:

a C1-C10 alkyl group,

a phenyl group optionally substituted by one or more of the following groups:

a C1-C10 alkyl group,

a halogen group,

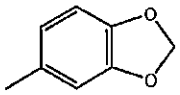
a nitro group,

hydroxy group,

and/or an alkoxy group.

The inventors have found that these compounds exhibit good stability and very high solubility. This yields the advantage that high concentrations of the compound are obtainable in small volumes.

The R group is preferably the 3,4 methylenedioxyphenyl group of the formula:

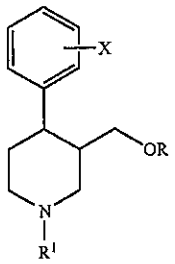


The X group is preferably a fluorine group attached to position 4 in the phenyl ring.

The R^2 group preferably represents a C1-C4 alkyl group, and most preferably represents a C1-C2 alkyl group in order to provide an optimum solubility.

The compounds can have a solubility at about 20° C. of at least about 10 mg/ml water, preferably having a solubility in water of at least 100, for example 500 and most preferably of at least 1000 mg/ml water.

According to a second aspect of the present invention, there is provided a process for preparing a compound as above, comprising the steps of mixing together a 4 phenylpiperidine compound, a salt and/or a base thereof having the formula II:



wherein:

R represents an alkyl or alkynyl group having 1-4 carbon atoms, or a phenyl group optionally substituted by C_{1-4} alkyl, alkylthio, alkoxy, halogen, nitro, acylamino, methylsulfonyl or methylenedioxy, or represents tetrahydronaphthyl,

R_1 represents hydrogen, trifluoro (C_{1-4}) alkyl, alkyl or alkynyl,

X represents hydrogen, alkyl having 1-4 carbon atoms, alkoxy, trifluoroalkyl, hydroxy, halogen, methylthio or aralkoxy,

with a sulfonic acid of the general formula R_2—SO_3H,

wherein R_2 represents:

a C1-C10 alkyl group,

a phenyl group optionally substituted by one or more of the following groups:

a C1-C10 alkyl group,

a halogen group,

a nitro group,

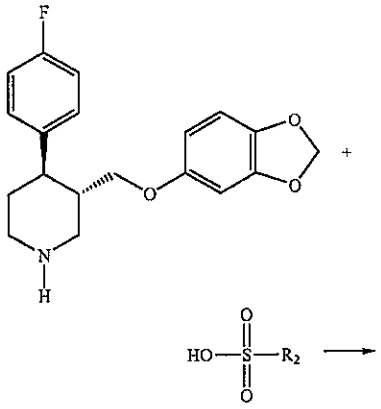
a hydroxy group, and/or

an alkoxy group,

to form a solution, followed by separating the compound formed from this solution.

The compounds of the invention can be prepared from the free base of the 4 phenylpiperidine, having the formula II, this preferably being paroxetine, by treatment with a sulfonic acid as defined above in a suitable solvent to form a solution of the desired acid addition salt, whereafter this is precipitated out of the solution.

The equation for paroxetine free base and sulfonic acids is as follows:



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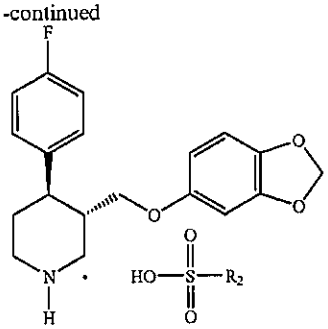
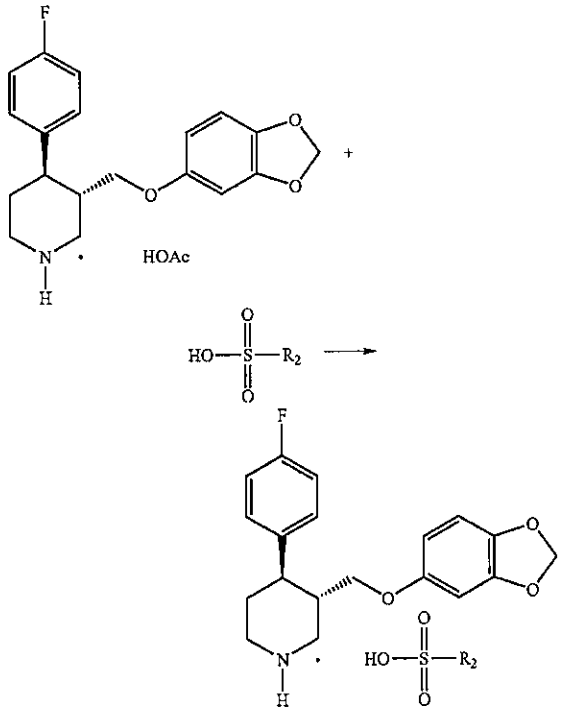


The forming of a solution may preferably proceed at temperatures from about 0° C. to the boiling point of the solvent.

Optionally, the solution may be purified by treatment of activated charcoal, silica gel, kieselguhr or other suitable materials.

Alternatively, the solution of a salt of the invention can be formed by dissolution of a salt of 4 phenyl piperidine having the formula II with an organic sulfonic acid.

For example the compounds of the invention may be prepared from a paroxetine C1-C5 carboxylate, such as the acetate, by addition of corresponding organic sulfonic acid to the solution of the said carboxylate, as follows:

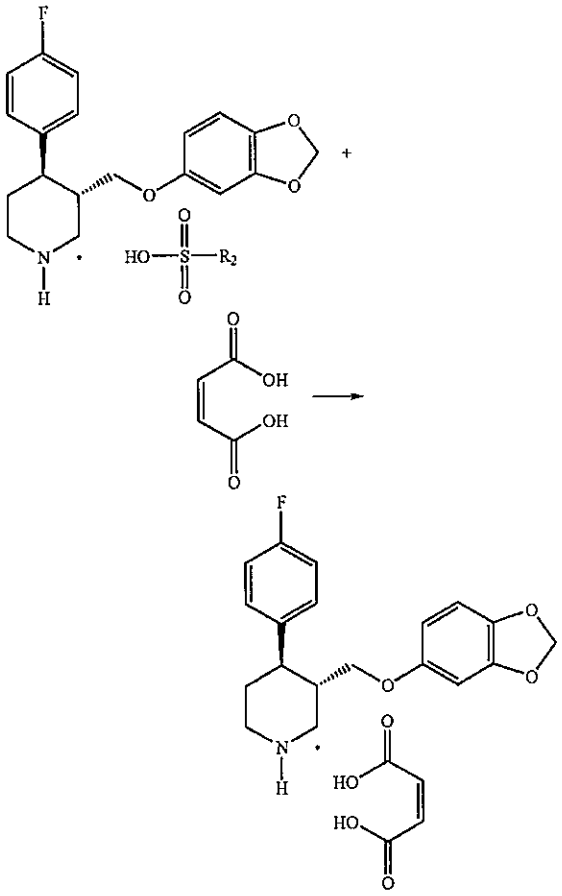


According to a third aspect of the present invention, there is provided a compound obtainable by this process.

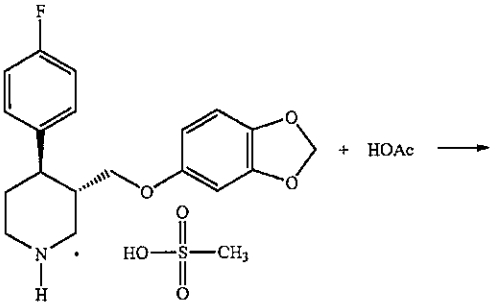
According to a fourth aspect of the present invention there is provided the above compound for use as a medicament and, according to a fifth aspect, a medicament comprising this compound, and to the use thereof for treating depressions, obsessive compulsive disorders, panic disorders, bulimia,

anorexia, pain, obesity, senile demential, migraine, anorexia, social phobia, depressions arising from pre-menstrual tension.

According to a sixth aspect of the present invention, there is provided the use of a compound of the invention as a reagent in further syntheses. More specifically, the compounds of the present invention can be used as a start reagent for forming further acid addition salts, for example for providing further paroxetine acid addition salts, by reacting with a suitable reagent, i.e. with a corresponding acid. For example, the formation of paroxetine maleate according to the present invention proceeds by the following equation:



and the formation of paroxetine acetate proceeds as follows:



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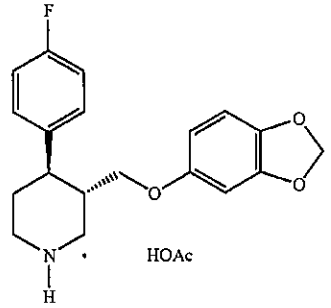
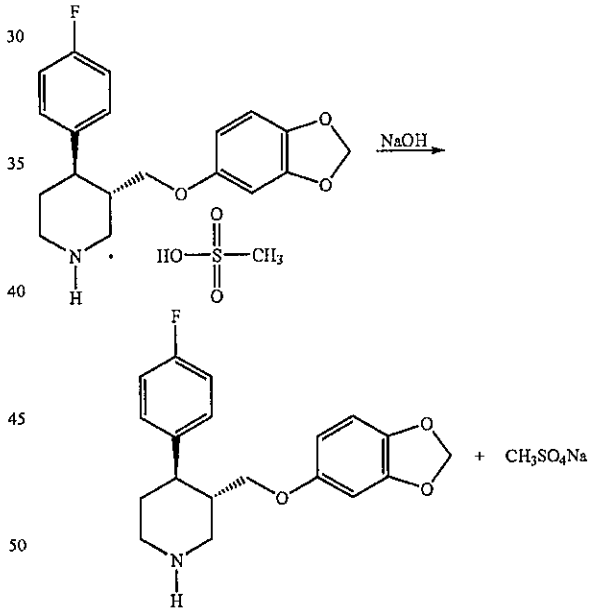


This is an advantageous route, since by using the substantially pure sulfonic acid salts according to the present invention as a start reagent, the preparation of a further salt, as above, results in this further salt having a high purity. The inventors have shown that such salts have a surprisingly high purity.

Similarly, the compounds of the present invention can react with a base, such as an inorganic and/or an organic base, to form (liberate) free bases of the corresponding compounds. As exemplified on paroxetine, the reaction proceeds according to the equation:



The free bases liberated from the compounds of the present invention have surprisingly higher purity than if prepared by known methods which is especially important in case of their use for production of pharmaceuticals.

Accordingly, the new compounds of the first aspect of the invention can also form hydrates and/or solvates by a contact with a corresponding reaction partner, i.e. with water and/or with a solvent. Examples of such further salts, hydrates and solvates, for example these of paroxetine, are the:

hydrochloride	oxalate	dihydrate
hydrobromide	succinate	trihydrate

-continued

hydroiodide	tartrate	hexahydrate
acetate	citrate	methanolate
propionate	embonate	ethanolate
maleate	hemihydrate	
fumarate	hydrate	

The inventors have shown that such salts have a surprisingly high purity.

Examples of bases which can be employed in the preparation of the free bases are: sodium hydroxide, potassium hydroxide, calcium hydroxide, ammonium hydroxide, sodium carbonate, methylamine, dimethylamine, triethylamine, pyridine and such like.

Since the compounds according to the present invention exhibit high solubility, they can be dosed, for example injected, in a high concentration, low volume solution, this method of dosing being particularly advantageous with certain patients, such as manic depressives and such like, i.e. patients who are unable or unwilling to swallow medicine.

The compounds of the present invention can be formulated into various types of pharmaceutical compositions for treatment of humans and animals. Pharmaceutical compositions according to the present invention comprise a compound of the invention alone or together with a pharmaceutically acceptable carrier or diluent. The preferred formulations are those for oral administration (tablets, capsules) but formulations for parenteral or topical administration are also within the scope of the invention. The high water solubility of the compounds of the invention enables high dissolution rates in solid dosage forms based on the compounds of the invention to be obtained, during the in vitro release as well as good bioavailability after peroral application in vivo.

The tablets containing compounds of the present invention can be prepared both by tabletting procedure in which water is present (e.g. aqueous granulation) as well as by tabletting processing it which water is absent (direct compression, dry granulation) and may be coated by any suitable means of coating.

The present invention will now be further elucidated by way of the following examples and results.

EXPERIMENTAL

A seeding crystal of paroxetine methane sulfonate was made as follows:

2.7 g	(8.2 mmol) of paroxetine was dissolved in
15 ml	of hot ethanol.
1.0 g	(10.4 mmol) of methanesulfonic acid in
15 ml	of ethanol was added and the mixture was cooled to room temperature. When the mixture had reached room temperature the mixture was put in the freezer at −20° C. overnight. No crystal line compound was obtained. The mixture was evaporated to dryness leaving an oil. After 1 month at room temperature a waxy solid was obtained. Part of this solid was taken apart and the rest was dissolved in
10 ml	of EtOAc. The waxy crystals were added and the mixture was put in the freezer at −20° C. overnight. A white crystalline product was precipitated. After filtration and drying in a vacuumoven
2.5 g	(5.9 mmol) of paroxetine methane sulfonate was obtained. Yield 72%

This seeding crystal was subsequently used in following examples 1 and 3.

Examples

Example 1

Paroxetine Methane Sulfonate from Paroxetine

To a solution of 43.5 g (132 mmol) of paroxetine, prepared by the procedure disclosed in U.S. Pat. No. 4,007,196,

12.7 g	(132 mmol) of methane sulfonic acid was added to
150 ml	of boiling ethyl acetate. The mixture was left at room temperature for 2 hours. Subsequently the mixture was placed overnight at −20° C., with a seeding crystal. The obtained solid was filtered off and washed with
50 ml	of ether. The obtained white solid was dried overnight in a vacuumoven.
47.1 g	(111 mmol) of product Yield 99.5%

Analytical characterization of the compound obtained is shown in Table 1. The purity of the compound obtained was 98% (HPLC).

Example 2

Paroxetine Benzene Sulfonate from Paroxetine

3.8 g	(11.5 mmol) of paroxetine was dissolved in
10 ml	of hot ethylacetate.
1.82 g	(11.5 mmol) of anhydrous benzenesulfonic acid was added. The mixture was left at room temperature for 2 h. The mixture was evaporated to dryness and dissolved in dichloromethane, and evaporated again to dryness leaving an oil. This oil was solidified through high vacuum (0.1 mmHg) evaporation leaving
5.0 g	(1.3 mmol) of an off white solid. To this solid was added
5 ml	of acetone and the suspension was stirred for 5 minutes during which a white suspension was obtained. The solid was filtered off and dried under vacuum.
4.8 g	(9.9 mmol) of product was obtained. Yield 85%

Analytical characterization of the compound obtained is shown in Table 1. The purity of the compound obtained was 99.4% (HPLC).

Example 3

Paroxetine p-Toluene Sulfonate from Paroxetine

5.0 g	(15 mmol) of paroxetine was dissolved in
25 ml	of hot ethylacetate.
2.9 g	(15 mmol) of p-toluenesulfonic acid was added. The mixture was left at room temperature for 2 h and subsequently put in the freezer, with a seeding crystal, for 14 h. The solid was filtered off and washed once with

-continued

10 ml	of n-hexane. The obtained white solid was dried overnight in a vacuumoven.
4.8 g	(10 mmol) of a white solid was obtained. Yield 67%

Analytical characterization of the compound obtained is shown in Table 1. The purity of the compound obtained was 99.4% (HPLC).

Example 4

Paroxetine p-Chlorobenzene Sulfonate from Paroxetine

1.1 g	(3.3 mmol) of paroxetine was dissolved in
3 ml	of hot ethylacetate.
0.76 g	(3.3 mmol) of 90% p-chlorobenzenesulfonic acid was added. The mixture was left at room temperature for 1 h and washed with
5 ml	of water. The organic layer was dried with Na_2SO_4, filtered and evaporated to dryness leaving
1.5 g	(2.9 mmol) of an off white solid. Yield 88%

Analytical characterization of the compound obtained is shown in Table 1. The purity of the compound obtained was 99.4% (HPLC).

Example 5

Paroxetine Maleate from Paroxetine Methane Sulfonate

1.0 g	(2.4 mmol) of paroxetine methane sulfonate in
5 ml	of hot water. To this solution was added
0.32 g	(2.8 mmol) of maleic acid. The mixture was placed at 4° C. overnight after which a solid with a yellow oil was precipitated on the bottom of the flask. The solid/oil was filtered off and washed 3 times with
10 ml	of ether and dried in a vacuumoven.
0.8 g	(2.0 mmol) off white crystals were obtained Yield 85%

The purity of the compound obtained was 99.5% (HPLC).

Example 6

Paroxetine Acetate from Paroxetine Methane Sulfonate

1.0 g	(2.4 mmol) of paroxetine methane sulfonate in
5 ml	of hot iso-propanol. To this solution was added
0.2 g	(3.2 mmol) of acetic acid. The mixture was placed at 4° C. overnight after which a solid was precipitated. The solid was filtered off and washed 3 times with

-continued

10 ml	of ether and dried in a vacuumoven.
0.5 g	(1.3 mmol) off white crystals were obtained Yield 54%

The purity of the compound obtained was 99.5% (HPLC).

Example 7

Paroxetine Free Base from Paroxetine Methane Sulfonate

10.0 g	(24.0 mmol) of paroxetine methane sulfonate in
150 ml	of water and
200 ml	of ethyl acetate. To this was added
12.4 g	(31 mmol) of an aqueous 10 wt % NaOH solution and the suspension was stirred for 15 minutes. The layers were separated and the aqueous layer was extracted once with
50 ml	of ethyl acetate. The combined organic layers are washed once with
100 ml	of water and dried over Na_2SO_4. The Na_2SO_4 was filtered off and washed once with
50 ml	of ethyl acetate. The ethyl acetate was evaporated off, leaving
7.5 g	(22.8 mmol) of an oily product. Yield 95%

The purity of the compound obtained was 99.5% (HPLC).

A number of the compounds obtained were analysed the results being shown in tables 1-5 below:

TABLE 1

Characterization of salts of paroxetine with certain organic sulfonic acids R—SO_3H

R = CH_3 - (paroxetine methane sulfonate):
m.p.: 142°-144° C.
DSC curve (closed pan, 10° C./min): onset 145.8° C., 79.0 J/g.
IR spectrum (KBr, in cm^{-1}): 531, 546, 777, 838, 931, 962, 1038, 1100, 1169, 1208, 1469, 1500, 1515, 1615, 2577, 2869, 2900, 3023.
1H-NMR (ppm): 1.99(br d, H_{5eq}, 1H); 2.27(ddd, H_{5ax}, 1H); 2.48-2.65(m, H_3, 1H); 2.82-2.92(m, H_4, CH_3, 4H); 2.95-3.20(m, H_{2ax}, H_{6ax}, 2H); 3.47(dd, H_7, 1H); 3.58-3.74(m, H_{2eq}, H_{6eq}, H_7, 3H); 5.88(s, $H_{7''}$, 2H); 6.10(dd, $H_{6''}$, 1H); 6.33(d, $H_{7'}$, 1H); 6.61(d, $H_{5''}$, 1H); 7.09(dd, $H_{3''}$, $H_{5''}$, 2H); 7.22(dd, $H_{2'}$, $H_{6'}$, 2H); 8.85(br d, NH_{eq}, 1H); 9.11(br d, NH_{ax}, 1H).
13C-NMR(ppm): 30.0(s, C_5); 39.3(s, C_3); 39.5(s, C_4); 41.7(s, SC); 44.6(s, C_6); 46.8(s, C_2); 67.4(s, C_7); 97.8(s, $C_{2''}$); 101.2(s, $C_{7''}$); 105.4(s, $C_{6''}$); 107.8(s, $C_{5''}$); 115.8(d, $C_{3'}$, $C_{5'}$); 128.4(s, $C_{6'}$, $C_{2'}$); 137.1(s, $C_{4''}$); 142.0(s, $C_{1'}$); 148.2(s, $C_{3''}$); 153.7(s, $C_{1''}$); 161.9(d, $C_{4''}$).
R = C_6H_5 - (paroxetine benzene sulfonate):
m.p.: 55°-60° C.
IR spectrum (KBr, in cm^{-1}): 530, 564, 614, 689, 728, 764, 828, 929, 993, 1007, 1029, 1121, 1179, 1229, 1443, 1471, 1486, 1514, 1600, 1628, 2557, 2842, 3029.
1H-NMR (ppm): 1.90(br d, H_{5eq}, 1H); 2.10-2.28(m, H_{5ax}, 1H); 2.38-2.52(m, H_3, 1H); 2.82(ddd, H_4, 1H); 3.02-3.18(m, H_{2ax}, H_{6ax}, 2H); 3.37(dd, H_7, 1H); 3.48(d, H_7, 1H); 3.60-3.82(m, H_{2eq}, H_{6eq}, 2H); 5.87(s, $H_{7''}$, 2H); 6.06(dd, $H_{6''}$, 1H); 6.29(d, $H_{2''}$, 1H); 6.60(d, $H_{5''}$, 1H); 6.90(dd, $H_{3'}$, $H_{5'}$, 2H); 7.04(dd, $H_{2'}$, $H_{6'}$, 2H); 7.40(d, ArH, 3H); 7.94(d, SArH, 2H); 8.81(br d, NH_{eq}, 1H); 9.04(br d, NH_{ax} 1H).
13C-NMR (ppm): 29.9(s, C_5); 39.2(s, C_3); 41.5(s, C_4); 4.48(s, C_6); 47.0(s, C_2); 67.3(s, C_7); 97.9(s, $C_{2''}$); 101.2(s, $C_{7''}$); 105.5(s, $C_{6''}$) 107.8(s, $C_{5''}$); 115.7(d, $C_{3'}$, $C_{5'}$); 125.9(s, C_b); 128.6(s, C_d); 128.8(s, $C_{6'}$, $C_{2'}$); 130.6(s, C_{em}); 137.1(s, $C_{4''}$); 141.9(s, $C_{1'}$); 144.1(s, C_a); 148.2(s, $C_{3''}$); 153.7(s, $C_{1''}$); 161.8(s, $C_{4'}$).
R = p-$CH_3C_6H_4$ (paroxetine p-toluene sulfonate):
m.p.: 148°-150°C.

TABLE 1-continued

Characterization of salts of paroxetine with certain organic sulfonic acids R—SO_3H

DSC curve (closed pan, 10° C./min): onset 151.6° C., 71.6 J/g.
IR spectrum (KBr, in cm^{-1}): 529, 557, 671, 771, 800, 814, 921, 936, 1000, 1029, 1100, 1157, 1186, 1229, 1471, 1486, 1507, 1600, 2557, 2829, 3029.
1H-NMR (ppm): 1.89(br d, H_{5eq}, 1H); 2.10-2.50(m, H_{5ax}, H_3, CH_3, 5H); 2.82(ddd, H_4, 1H); 2.97-3.18(m, H_{2ax}, H_{6ax}, 2H); 3.36(dd, H_7, 1H); 3.48(dd, H_7, 1H); 3.52-3.77(m, H_{2eq}, H_{6eq}, 2H); 5.87(s, $H_{7''}$, 2H); 6.06(dd, $H_{6''}$, 1H); 6.28(d, $H_{2''}$, 1H); 6.59(d, $H_{5''}$, 1H); 6.90(dd, $H_{3'}$, $H_{5'}$, 2H); 7.05(dd, $H_{2'}$, $H_{6'}$, 2H); 7.24(d, CH_3ArH, 2H); 7.83(d, SArH, 2H); 8.91(br d, NH_{eq}, 1H); 9.17(br d, NH_{ax}, 1H).
13C-NMR (ppm): 21.3(s, C_e); 29.9(s, C_5); 39.2(s, C_3); 41.5(s, C_4); 44.7(s, C_6); 46.9(s, C_2); 67.3(s, C_7); 97.8(s, $C_{2''}$); 101.1(s, $C_{7''}$); 105.5(s, $C_{6''}$); 107.8(s, $C_{5''}$); 115.6(d, $C_{3'}$, $C_{5'}$); 125.8(s, C_b); 129.0(s, $C_{6'}$, $C_{2'}$); 129.1(s, C_c); 137.2(s, $C_{4''}$); 140.8(s, C_d); 141.5(s, C_a); 141.9(s, $C_{1'}$); 148.2(s, $C_{3''}$); 153.8(s, $C_{1''}$); 161.8(d, C_4).
R = p-ClC_6H_4 (paroxetine p-chlorobenzene sulfonate);
m.p.; 75°-80° C.
IR spectrum (KBr, in cm^{-1}): 486, 557, 643, 736, 821, 1000, 1029, 1086, 1114, 1186, 1229, 1471, 1486, 1514, 1600, 1657, 2857, 3029.
1H-NMR (ppm): 1.91(br d, H_{5eq}, 1H); 2.15(ddd, H_{5ax}, 1H); 2.37-2.52(m, H_3, 1H); 2.81(ddd, H_4, 1H); 2.93-3.21(m, H_{2ax}, H_{6ax}, 2H); 3.37(dd, H_7, 1H); 3.49(d, H_7, 1H); 3.61-3.81(m, H_{2eq}, H_{6eq}, 2H); 5.88(s, $H_{7''}$, 2H); 6.05(dd, $H_{6''}$, 1H); 6.27(d, $H_{2''}$, 1H); 6.59(d, $H_{5''}$, 1H); 6.91(dd, $H_{3'}$, $H_{5'}$, 2H); 7.03(dd, $H_{2'}$, $H_{6'}$, 2H); 7.39(d, ClArH, 2H); 7.86(d, SArH, 2H); 8.78(br d, NH_{eq}, 1H); 9.02(br d, NH_{ax}, 1H).
13C-NMR (ppm): 30.0(s, C_5); 39.3(s, C_3); 41.5(s, C_4); 44.9(s, C_6); 47.1(s, C_2); 67.3(s, C_7); 97.9(s, $C_{2''}$); 101.2(s, $C_{7''}$); 105.5(s, $C_{6''}$); 107.9(s, $C_{5''}$); 115.8(d, $C_{3'}$, $C_{5'}$); 127.6(s, C_b); 128.8(s, $C_{6'}$, $C_{2'}$); 132.0(s, C_d); 137.0(s, C_c); 137.2(s, $C_{4''}$); 141.8(s, $C_{1'}$); 142.0(s, C_a); 148.2(s, $C_{3''}$); 153.6(s, $C_{1''}$); 161.8(d, C_4).

The compounds of the invention are crystalline, with defined melting points, DSC curves and IR spectra. It cannot be excluded that, under different conditions of their formation and under specific conditions, they could exist also in other crystalline or polymorph modifications which may differ from those as described herein. The compounds of the invention are also generally very stable and non-hygroscopic.

It should be understood that the present invention comprising acid addition salts with organic sulfonic acids are substantially free of the bound organic solvent. Preferably, the amount of bound organic solvent should be less than 2.0% (w/w) as calculated on the anhydrous basis. They nevertheless may contain crystallization water and also unbound water, that is to say water which is other than water of crystallization.

In the following tables 2 and 3, examples of results of hygroscopicity tests and stability tests (in comparison with known salts of paroxetine) are presented.

TABLE 2

Hygroscopicity of certain salts of paroxetine (40° C., 75% rel. hum).

water content (in %) at	t = 0	t = 4 weeks
methane sulfonate	0.35	+0.04
p-toluene sulfonate	0.70	<0.02
hydrochloride	—	+2.5

TABLE 3

Solubility of paroxetine salts in water (in mg/ml)

	20° C.	50° C.
methane sulfonate	>1000/10 min	1300
p-toluene sulfonate	>1000	>1000

TABLE 3-continued

Solubility of paroxetine salts in water (in mg/ml)

	20° C.	50° C.
hydrochloride hemihydrate	4.9	12.6
hydrochloride anhydrate	8.2	24.2

TABLE 4

Stability of paroxetine salts by HPLC (total amount of degradation in %).

	degradation	
	20° C.	80° C.
methane sulfonate	not observed	<0.2%, 3 months
p-toluene sulfonate	not observed	<0.2%, 3 months
maleate	0.2%, 12 months	>50%, 5 days

TABLE 5

Solubility of salts of paroxetine in nonaqueous solvents (in mg/ml)

		methane sulfonate	p-toluene sulfonate
Ethanol	20° C.	36	50
	78° C.	250	>500
2-Propanol	20° C.	7	14
	82° C.	330	>500
Acetone	20° C.	5	16
	56° C.	37	125
Ethyl acetate	20° C.	2	22
	77° C.	25	>500
n-Hexane	20° C.	<0.05	<0.05
	69° C.	0.05	<0.05

Examples of analytical data of the paroxetine salts and the free base prepared in Examples 5 to 7 are given in Table 6.

TABLE 6

Characterization of salts/free base of paroxetine

paroxetine maleate:
m.p.: 128-130° C.
1H-NMR (ppm): 1.65-2.00(m, H_{5eq}, H_{ax}, 2H); 2.00-2.50(m, H_3, 1H); 2.55-3.15(m, H_{2ax}, H_{6ax}, H_4, 3H); 3.15-3.75(m, H_{2eq}, H_{6eq}, H_7, 3H); 5.67(s, $H_{7''}$, 2H); 5.97(s, H_a, 1H); 6.12(dd, $H_{6''}$, 1H); 6.42(d, $H_{2''}$, 1H); 6.67(d, $H_{5''}$, 1H); 6.95-7.35(m, $H_{2'}$, $H_{3'}$, $H_{5'}$, $H_{6'}$, 4H).
paroxetine acetate:
m.p.: 123-125° C.
1H-NMR (ppm): 1.70-2.00(m, H_{5eq}, H_{5ax}, 2H); 1.97(s, H_a, 3H); 2.05-2.50(m, H_3, 1H); 2.50-3.00(m, H_4, H_{2ax}, H_{6ax}, 3H); 3.05-3.75(m, H_{2eq}, H_{6eq}, H_7, 3H); 6.05(s, $H_{7''}$, 2H); 6.28(dd, $H_{6''}$, 1H); 6.58(d, $H_{2''}$, 1H); 6.65(d, $H_{5''}$, 1H); 7.10-7.50(m, $H_{2''}$, $H_{3'}$, $H_{5'}$, $H_{6'}$, 4H).
paroxetine;
1H-NMR (ppm): 1.60-2.00(m, H_{5ax}, H_{5eq}, 2H); 2.00-2.35(m, H_3, 1H); 2.40-2.95(m, H_4, H_{2ax}, H_{6ax}, 3H); 3.15-3.70(m, H_{2eq}, H_{6eq}, H_7, 2H); 5.67(s, $H_{7''}$, 2H); 6.11(dd, $H_{6''}$, 1H); 6.43(d, $H_{2''}$, 1H); 6.62(d, $H_{5''}$, 1H); 6.80-7.35(m, $H_{2'}$, $H_{3'}$, $H_{5'}$, $H_{6'}$, 4H).

It will be clear that the invention is not limited to the above description, but is rather determined by the following claims.

The invention claimed is:

1. Crystalline paroxetine methanesulfonate having the following IR peaks:

531, 546, 777, 838, 931, 962, 1038, 1100, 1169, 1208, 1469, 1500, 1515, 1615, 2577, 2869, 2900, 3023.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 7,598,271 B1
APPLICATION NO. : 09/200743
DATED : October 6, 2009
INVENTOR(S) : Benneker et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title Page:

The first or sole Notice should read --

Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 2073 days.

Signed and Sealed this
Seventeenth Day of May, 2011

David J. Kappos

David J. Kappos
Director of the United States Patent and Trademark Office

EXHIBIT C

US008658663B2

(12) **United States Patent**
Richards

(10) **Patent No.: US 8,658,663 B2**
(45) **Date of Patent: Feb. 25, 2014**

(54) **METHOD OF TREATING THERMOREGULATORY DISFUNCTION WITH PAROXETINE**

(75) Inventor: **Patricia Allison Tewes Richards**, Scarsdale, NY (US)

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 976 days.

(21) Appl. No.: **12/292,960**

(22) Filed: **Dec. 1, 2008**

(65) **Prior Publication Data**

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Related U.S. Application Data

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(51) **Int. Cl.**
A61K 31/435 (2006.01)

(52) **U.S. Cl.**
USPC **514/277**; 514/183; 514/463

(58) **Field of Classification Search**
USPC 514/222.2, 183, 277, 463
See application file for complete search history.

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(57) **ABSTRACT**

The present invention relates to a method for treating a patient suffering from a thermoregulatory dysfunction, especially hot flashes and flushes associated with hormonal changes due to naturally occurring menopause (whether male or female) or due to chemically or surgically induced menopause. The method is also applicable to treating the hot flashes, hot flushes, or night sweats associated with disease states that disrupt normal hormonal regulation of body temperature.

5 Claims, No Drawings

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METHOD OF TREATING THERMOREGULATORY DISFUNCTION WITH PAROXETINE

CROSS-REFERENCE TO RELATED APPLICATIONS

Not Applicable

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

Not Applicable

FIELD OF THE INVENTION

The present invention relates to a method for treating a patient suffering from a thermoregulatory dysfunction, especially hot flashes and flushes associated with hormonal changes due to naturally occurring menopause (whether male or female) or due to chemically or surgically induced menopause. The method is also applicable to treating the hot flashes, hot flushes, or night sweats associated with disease states that disrupt normal hormonal regulation of body temperature. The invention further relates to use of paroxetine or a salt thereof.

BACKGROUND OF THE INVENTION

Hot flashes or flushes are most typically seen in women who are in the process of going through menopause, but are also seen in women who have undergone surgical or chemically induced menopause. They are also seen (less frequently) in men who are undergoing the so-called "male menopause" or who have undergone hormonal ablative therapy. The hot flashes and flushes are connected with a disruption of the hormonal control of thermoregulatory function. In addition, disease states which disrupt the normal hormonal control over thermoregulatory function also result in such hot flashes and flushes.

In the past, the primary treatment for peri- and post-menopausal women having these thermoregulatory dysfunctions have been hormonal replacement therapy primarily because of the known substantial fluctuations in estrogen levels. However, many women, especially those having a history or at higher risk of breast cancer, are reluctant or will not accept hormone replacement therapy. More recently, serotonergic compounds (such as serotonin receptor reuptake inhibitors) and norepinepherine type compounds (particularly norepinepherine uptake inhibitors) have been investigated to some extent for the treatment of hot flashes and flushes in both men and women. Berendsen; *Hypothesis, The role of Serotonin in hot flushes*; Maturitas 36 (2000) 155-164 discusses the role of neurotransmitters, estrogens, and the drugs sertraline and venlafaxine.

US 2006-0100263 relates to combinations of bicifadine and another drug for hot flashes. Paroxetine is one of the "other" drugs mentioned as suitable for the combination therapy. US 2006-0020015 claims the use of combinations of norepinephcrine reuptake inhibitors in combination with serotonin reuptake inhibitors. The '015 application also mentions that selective serotonin reuptake inhibitors are being clinically evaluated in hot flashes and particularly mentions that fluoxetine is mentioned in this context in WO 9944601. US 2006-0020014 and US 2004-0130987 have similar disclosures. US 2004-1052710 mentions the use of serotonergic reuptake inhibitors in combination with norepinepherine

reuptake inhibitors for the treatment of vasomotor symptoms (the class to which hot flashes and flushes belong) with paroxetine being specifically mentioned as one possible serotonin reuptake inhibitor. US 2002-0042432 (now U.S. Pat. No. 6,369,051) claims the combinations of estrogenic substances with a selective serotonin reuptake inhibitor (SSRI) and paroxetine is specifically mentioned as one of the potential SSRIs for use in the claimed invention.

In addition, sertraline (another SSRI) was found to be effective to some degree in hot flashes as a standalone therapy in Trott, et al *An Open Tial of Sertraline for Menopausal Hot Flushes: Potential Involvement of Serotonin in Vasomotor Instability*; Del. Med. Jrl, September 1997, vol. 69, No. 9, 481-482 and in Roth et al; *SERTRALINE RELIEVES HOT FLASHES SECONDARY TO MEDICAL CASTRATION AS TREATMENT OF ADVANCED PROSTATE CANCER*; Psycho-Oncology 7: 129-132 (1998). U.S. Pat. No. 6,498,184 discusses the role of selective 5-HT_{2C} (a serotonin receptor subtype) agonists for the treatment of hot flushes. US 2004-0092519 relates to use of reboxetine (a selective noradrenaline reuptake inhibitor, i.e. NARI)) for treating hot flashes. Finally, Stearns et al; *A pilot trial assessing the efficacy of paroxetine hydrochloride (Paxil®) in controlling hot flashes in breast cancer survivors*; Annals of Oncology 11: 17-22, 2000 reports on studies of 10 mg and 20 mg per day dosings of paroxetine hydrochloride monotherapy in women for control of hot flushes.

While the above disclosures mention the use of SSRIs in combinations with other drugs for hot flushes, or paroxetine in particular in combination with other drugs, or even paroxetine as monotherapy for hot flushes, all of these references only mention dosings of paroxetine at 10 mg per day or greater, and generally in the range of 20-50 mg per day. The only exception is U.S. Pat. No. 6,369,051 which mentions a broad dosage range for the SSRI component of the SSRI/estrogenic substance combination, where the SSRI dose is given as 0.1-500 mg/day; preferably 1-200 mg/day, more preferably 20-50 mg/day. However this use is in combination with estrogens. Thus, it can be generally seen that antidepressant therapeutic dosing of the SSRI is typically indicated, or the range is so broad as to effectively not give any real teaching as to a particular dose.

It is generally recognized that at typical antidepressant therapeutic dosing of SSRIs (including paroxetine) there are significant side effects that the patient may not be willing to endure. Women with menopausal hot flashes may not be willing to take antidepressant doses of antidepressant drugs both due to side effects and reluctance to take a treatment for depression. In addition, patients who have multiple other drug treatments, especially cancer therapy treatments or cancer survivors generally do not want to have other medical issues to have to deal with. A simple side effect to most patients who are willing to endure the side effect in other contexts may be overwhelming to those having to deal with multiple drug treatments from other conditions. Thus, there remains a need to obtain relief from the thermoregulatory dysfunction of hot flushes and hot flashes as well as other vasomotor disruptions of thermal regulation while minimizing the side effects and risks associated with the therapeutic agents mentioned above.

Paroxetine is a well characterized molecule in the pharmaceutical and patent literature. Chemical processes for its manufacture are detailed in U.S. Pat. No. 4,861,893; U.S. Pat. No. 6,172,233; U.S. Pat. No. 6,326,496; U.S. Pat. No. 6,433,179; U.S. Pat. No. 6,541,637 U.S. Pat. No. 6,686,473; U.S. Pat. No. 6,716,985; U.S. Pat. No. 6,881,845; U.S. Pat. No. 6,900,327; and U.S. Pat. No. 6,956,121 to name a few. It is known to exist in various solvate and polymorphic forms

include various hydrates, anhydrous forms, isopropanolates, ethanolates, etc, amorphous as well as multiple crystalline forms such as are disclosed in for example, U.S. Pat. No. 4,721,723; U.S. Pat. No. 5,039,803; U.S. Pat. No. 5,672,612; U.S. Pat. No. 5,872,132; U.S. Pat. No. 5,900,423; U.S. Pat. No. 6,080,759; U.S. Pat. No. 6,133,277; U.S. Pat. No. 6,436,956; U.S. Pat. No. 6,440,459; and U.S. Pat. No. 6,638,948, among others. Various pharmaceutical dosage forms are known from the foregoing patents as well as from U.S. Pat. No. 5,955,475; U.S. Pat. No. 6,113,944; U.S. Pat. No. 6,645,523; U.S. Pat. No. 6,660,298; and U.S. Pat. No. 6,699,882 and others for example. Some paroxetine derivatives are disclosed in U.S. Pat. No. 6,063,927. U.S. Pat. No. 6,440,459 and US 2004/0143120 disclose paroxetine maleate and making paroxetine hydrochloride from the maleate. US 2002/0193406; US 2002/0035130; and US 2001/0023253 disclose particularly the mesylate salt, but also many others. US 2002/0090394 discloses controlled release compositions of paroxetine. Paroxetine has also been indicated for a wide range of treatments ranging from its use as an antidepressant (U.S. Pat. No. 4,007,196) to neurologic and mental disorders, (U.S. Pat. No. 5,470,846) to CNS disorders (U.S. Pat. No. 5,985,322) to treatments for nicotine withdrawal, premenstrual symptoms, post-traumatic stress disorder, heroin addiction, etc. Each of the foregoing patent disclosures is incorporated herein (in its entirety) by reference.

OBJECT OF THE INVENTION

It is therefore an object of the invention to provide to a patient suffering from a thermoregulatory dysfunction a dosage form of paroxetine suitable for administration of from 0.1 mg/day to less than an antidepressant effective dosage of paroxetine per day.

Another object of the invention is to provide to a patient suffering from a thermoregulatory dysfunction a dosage form of paroxetine suitable for administration of from 0.1 mg/day to less than 10 mg/day.

Still another object of the invention is to provide to a patient suffering from a thermoregulatory dysfunction a treatment thereof with paroxetine that substantially avoids most and/or substantially reduces the side effects typically obtained from an antidepressant effective amount of paroxetine.

Still further objects of the invention will be apparent to those of ordinary skill.

SUMMARY OF THE INVENTION

The foregoing objects are achieved by providing a method of treating a thermoregulatory dysfunction treatment using paroxetine as free base or a pharmaceutically acceptable salt thereof, in an anhydrate, a hydrate, or solvate form, in any non-crystalline or any crystalline polymorphic form of any of the foregoing in a dosage of from about 0.1 mg/day up to less than an antidepressant therapeutically effective amount of paroxetine.

BRIEF DESCRIPTION OF THE DRAWING

Not Applicable

DETAILED DESCRIPTION OF THE INVENTION

The present invention is a method of treating a thermoregulatory dysfunction treatment using paroxetine as free base or a pharmaceutically acceptable salt thereof, in an anhydrate, a hydrate, or solvate form, in any non-crystalline or any crystalline polymorphic form of any of the foregoing in a dosage of from about 0.1 mg/day up to less than an antidepressant therapeutically effective amount of paroxetine. The invention is also a dosage form of paroxetine in a dose which is less than that effective for its use as an antidepressant.

For the present invention, paroxetine may be in the form of the free base or any pharmaceutically acceptable salt thereof. Pharmaceutically acceptable salts include, but are not limited to, hydrohalides (such as hydrochloride, hydrobromide, hydroiodide), sulfates (such as sulfate, bisulfate), phosphates (such as mono, di, or tri basic phosphate), oxalate, mesylate, tosylate, pamoate, citrate, carbonate, bicarbonate, maleate, malate, fumarate, as well as many others set forth in the patent references indicated in paragraph 0010 above. Preferably, the paroxetine is present as the free base, the hydrochloride salt, or the mesylate salt or mixtures thereof. Most preferably the paroxetine is present as the hydrochloride salt or the mesylate salt. Paroxetine for use in the present invention may be in the anhydrate, hemihydrate, monohydrate, or higher hydrate forms. Paroxetine for use in the present invention may also be either amorphous or crystalline, the choice being made by the formulator depending upon the formulation and dissolution characteristics desired. Crystalline forms have better stability, but amorphous forms have faster dissolution profiles.

The dosage is about 0.1 mg/day up to less than an antidepressant effective amount of paroxetine (based on the free base, anhydrate); preferably up to about 9.5 mg/day. Preferably the paroxetine can be administered to achieve the invention in amounts of at least 0.5 mg/day, more preferably at least 1 mg/day, still more preferably at least 2 mg/day, even more preferably at least 4 mg/day, up to preferably not more than about 9 mg/day, more preferably not more than about 8.5 mg/day, still more preferably not more than 8 mg/day. Other non-limiting dosages that are specifically suitable for the present invention include 2 mg/day, 2.5 mg/day, 3 mg/day, 3.5 mg/day, 4 mg/day, 4.5 mg/day, 5 mg/day, 5.5 mg/day, 6 mg/day, 6.5 mg/day, 7 mg/day, 7.5 mg/day, 8 mg/day, and 8.5 mg/day.

The present invention is applicable to the treatment of thermoregulatory dysfunction and in particular to such conditions (without limitation) as hot flushes, hot flashes, night sweats, etc. whether or not related to menopause (female or male), perimenopause, hormone ablative therapy (including, but not limited to, anti-estrogenic therapy and antiandrogenic therapy), treatments with other chemical agent or therapeutic agents that are antiestrogenic or antiandrogenic or interfere with thermoregulatory function, surgical procedures (such as, without limitation castration, hysterectomy, ooectomy, etc), and disease states interfering with normal thermoregulatory functioning. Most preferably, the present invention is directed to the treatment of perimenopausal and postmenopausal hot flashes, hot flushes and night sweats in women, whether due to aging, therapeutically induced menopause, or surgically induced menopause. The invention is also preferably directed to hot flashes or hot flushes or night sweats in men whether such symptoms are due to aging, chemical castration, hormonal ablative therapy, or surgical castration.

EXAMPLES

The following non-limiting Examples are presented only to exemplify various embodiments of the invention and do not limit it in any fashion.

Example 1

Females having hot flashes associated with menopause are administered paroxetine (based on free base non-solvate, anhydrate) as follows:

Form of Paroxetine	Dosage
Hydrochloride	1.0
Hydrochloride	2.0
Hydrochloride	3.0
Hydrochloride	4.0
Hydrochloride	5.0
Hydrochloride	6.0
Hydrochloride	7.0
Hydrochloride	8.0
Hydrochloride	9.0
Hydrochloride	9.5
Mesylate	1.0
Mesylate	2.0
Mesylate	3.0
Mesylate	4.0
Mesylate	5.0
Mesylate	6.0
Mesylate	7.0
Mesylate	8.0
Mesylate	9.0
Mesylate	9.5

After a few days to weeks, the symptoms ameliorate.

Example 2

Females having hot flashes associated with menopause are administered paroxetine (based on free base non-solvate, anhydrate) as follows:

Form of Paroxetine HCl	Dosage
Anhydrous	1.0
Anhydrous	2.0
Anhydrous	3.0
Anhydrous	4.0
Anhydrous	5.0
Anhydrous	6.0
Anhydrous	7.0
Anhydrous	8.0
Anhydrous	9.0
Anhydrous	9.5

-continued

Form of Paroxetine HCl	Dosage
Hemihydrate	1.0
Hemihydrate	2.0
Hemihydrate	3.0
Hemihydrate	4.0
Hemihydrate	5.0
Hemihydrate	6.0
Hemihydrate	7.0
Hemihydrate	8.0
Hemihydrate	9.0
Hemihydrate	9.5
Monohydrate	1.0
Monohydrate	2.0
Monohydrate	3.0
Monohydrate	4.0
Monohydrate	5.0
Monohydrate	6.0
Monohydrate	7.0
Monohydrate	8.0
Monohydrate	9.0
Monohydrate	9.5

After a few days to weeks, the symptoms ameliorate.

The invention claimed is:

1. A method for treating a patient suffering from a thermoregulatory dysfunction associated with menopause comprising administering paroxetine mesylate to said patient in an amount, based on the paroxetine moiety, of 7.5 mg/day.

2. The method of claim 1, wherein said thermoregulatory dysfunction is a condition selected from the group consisting of hot flashes, hot flushes, night sweats and combinations thereof.

3. The method of claim 1, wherein the paroxetine mesylate is in a crystalline form.

4. The method of claim 1, wherein the paroxetine mesylate is in an amorphous form.

5. A method for treating a patient suffering from a thermoregulatory dysfunction associated with menopause comprising administering paroxetine to said patient, wherein said paroxetine is in the form of a pharmaceutically acceptable mesylate salt, in amorphous or crystalline form, and mixtures thereof, wherein said paroxetine mesylate is administered in an amount, based on the paroxetine moiety, of 7.5 mg/day.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 8,658,663 B2
APPLICATION NO. : 12/292960
DATED : February 25, 2014
INVENTOR(S) : Patricia Allison Tewes Richards

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

ON THE TITLE PAGE, ITEM (54) AND IN THE SPECIFICATION, COLUMN 1, LINES 1-3,

Please delete "METHOD OF TREATING THERMOREGULATORY DISFUNCTION WITH PAROXETINE" and replace with -- METHOD OF TREATING THERMOREGULATORY DYSFUNCTION WITH PAROXETINE --.

Signed and Sealed this
Seventh Day of October, 2014

Michelle K. Lee

Michelle K. Lee
Deputy Director of the United States Patent and Trademark Office