JUDGE GARDEPHE 09 CV 3987

IN THE UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF NEW YORK

SEPRACOR INC., Plaintiff, v. ALPHAPHARM PTY. LTD. and MYLAN INC., Defendants.	Civil Action No. _____

Plaintiff Sepracor Inc. ("Sepracor"), for its Complaint for Patent Infringement against Defendants Alphapharm Pty. Ltd. ("Alphapharm") and Mylan Inc. ("Mylan"), (collectively, "Defendants"), hereby alleges as follows:

PARTIES

1. Plaintiff Sepracor is a Delaware corporation having its principal place of business at 84 Waterford Drive, Marlborough, MA 01752.

2. Upon information and belief, Defendant Alphapharm is an Australian corporation having a place of business at Chase Building 2, 1 Wentworth Park Road, Glebe NSW 2037, Australia. Upon information and belief, Defendant Alphapharm derives substantial revenue from interstate and/or international commerce. Upon information and belief, Defendant Alphapharm has received FDA approval to sell drug products throughout the United States, including into this judicial district. Upon information and belief, Defendant Alphapharm conducts business in this judicial district. Upon information and belief, Defendant Alphapharm manufactures, sells and/or markets generic drugs for sale and use throughout the United States,

including in this judicial district. Upon information and belief, Defendant Alphapharm is a wholly owned subsidiary of Mylan Australia Pty., Ltd., which is a wholly owned subsidiary of Defendant Mylan. Upon information and belief, Defendant Alphapharm has previously consented to personal jurisdiction in this Court.

3. Upon information and belief, Defendant Mylan is a corporation organized under the laws of Pennsylvania having a place of business at 1500 Corporate Drive, Canonsburg, PA 15317. Upon information and belief, Defendant Mylan, itself and through Defendant Alphapharm, manufactures generic drugs for sale and use throughout the United States, including in this judicial district. Upon information and belief, Defendant Mylan has a place of business at 405 Lexington Ave, New York, NY 10174 and does business in this judicial district.

NATURE OF THE ACTION

4. This is a civil action for the infringement of United States Patent No. 6,864,257 ("the '257 patent"), United States Patent No. 6,319,926 ("the '926 patent"), United States Patent No. 6,444,673 ("the '673 patent") and United States Patent No. 7,381,724 ("the '724 patent"). This action arises under the patent laws of the United States, 35 U.S.C. §§ 100 *et seq.*

STATEMENT REGARDING PRIOR-FILED SUIT

5. This is not the first-filed action involving Sepracor and Defendants, the patents in suit, and the counts of patent infringement set forth below. Sepracor previously filed, on March 20, 2009, an identical action seeking to enjoin Alphapharm and Mylan (along with nine other groups of defendants) from infringing the '257, '926, '673, and '724 patents in the District of New Jersey, and that action has been assigned Civil Action No. 2:09-cv-01302 ("the New Jersey action"). Defendants Alphapharm and Mylan have previously consented to personal jurisdiction in the District of New Jersey and in the New Jersey action Mylan has now consented

to personal jurisdiction. Judicial economy would be promoted, and Plaintiff Sepracor's choice of forum respected, if the claims related to Sepracor's action for infringement of the '257, '926, '673, and '724 patents against Alphapharm and Mylan are addressed in the New Jersey action.

6. Sepracor filed this action as a protective measure in order to avoid waiving any rights under 21 U.S.C. and 35 U.S.C. Both before and after the New Jersey action was filed, Alphapharm and Mylan had refused to give consent to personal jurisdiction in New Jersey, but Mylan has now consented to personal jurisdiction in its Answer in the New Jersey action. Sepracor expects that personal jurisdiction will be maintained over Alphapharm (despite its denial) in the District of New Jersey and that the action will proceed in that forum against all defendants, in which case this second action would be unnecessary and voluntarily dismissed.

JURISDICTION AND VENUE

7. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331 and 1338(a). Venue is proper in this Court as to each Defendant pursuant to 28 U.S.C. §§ 1391(b), (c) and/or (d) and 1400(b).

8. This Court has personal jurisdiction over each of Defendants by virtue of the fact that, *inter alia*, each Defendant has committed, aided, abetted, contributed to and/or participated in the commission of a tortious act of patent infringement that has led to foreseeable harm and injury to Sepracor. This Court has personal jurisdiction over each of Defendants for the additional reasons set forth above and below and for other reasons that will be presented to the Court if such jurisdiction is challenged.

9. This Court has personal jurisdiction over Defendant Alphapharm.

10. This Court has personal jurisdiction over Defendant Mylan.

THE PATENTS

11. On March 8, 2005, the '257 patent, titled "Optically Active 5H-Pyrrolo[3,4-B] Pyrazine Derivative, Its Preparation and Pharmaceutical Compositions Containing It," was duly and legally issued to Sepracor as assignee. Since that time, Sepracor has been, and continues to be, the sole owner of the '257 patent and the sole owner of the right to sue and to recover for any infringement of that patent. A copy of the '257 patent is attached hereto as Exhibit A.

12. On September 3, 2002, the '673 patent, titled "Optically Active 5H-Pyrrolo[3,4-B] Pyrazine Derivative, Its Preparation and Pharmaceutical Compositions Containing It," was duly and legally issued to Sepracor as assignee. Since that time, Sepracor has been, and continues to be, the sole owner of the '673 patent and the sole owner of the right to sue and to recover for any infringement of that patent. A copy of the '673 patent is attached hereto as Exhibit B.

13. On November 20, 2001, the '926 patent, titled "Optically Active 5H-Pyrrolo[3,4-B] Pyrazine Derivative, Its Preparation and Pharmaceutical Compositions Containing It," was duly and legally issued to Sepracor as assignee. Since that time, Sepracor has been, and continues to be, the sole owner of the '926 patent and the sole owner of the right to sue and to recover for any infringement of that patent. A copy of the '926 patent is attached hereto as Exhibit C.

14. On June 3, 2008, the '724 patent, titled "Optically Active 5H-Pyrrolo[3,4-B] Pyrazine Derivative, Its Preparation and Pharmaceutical Compositions Containing Same," was duly and legally issued to Sepracor as assignee. Since that time, Sepracor has been, and continues to be, the sole owner of the '724 patent and the sole owner of the right to sue and to

recover for any infringement of that patent. A copy of the '724 patent is attached hereto as Exhibit D.

ACTS GIVING RISE TO THIS ACTION

INFRINGEMENT OF THE '257 PATENT

COUNT I – INFRINGEMENT OF THE '257 PATENT BY DEFENDANTS

15. Sepracor re-alleges paragraphs 1-14 as if fully set forth herein.

16. Upon information and belief, Defendants submitted ANDA No. 91-151 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(i)). ANDA No. 91-151 seeks the FDA approval necessary to engage in the commercial manufacture, use and sale of generic tablets containing 1 mg, 2 mg or 3 mg of the active ingredient eszopiclone prior to the expiration of the '257 patent. ANDA No. 91-151 specifically seeks FDA approval to market a proposed generic version of Sepracor's Lunesta® brand 1 mg, 2 mg and 3 mg eszopiclone tablets prior to the expiration of the '257 patent.

17. ANDA No. 91-151 alleges under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '257 patent are invalid. Sepracor received written notification of ANDA No. 91-151 and the § 505(j)(2)(A)(vii)(IV) allegations on March 10, 2009.

18. Defendants' submission to the FDA of ANDA No. 91-151, including the § 505(j)(2)(A)(vii)(IV) allegations, constitutes infringement of the '257 patent under 35 U.S.C. § 271(e)(2)(A).

19. Alphapharm and Mylan are jointly and severally liable for any infringement of the '257 patent. This is because, upon information and belief, Alphapharm and Mylan actively and knowingly caused to be submitted, assisted with, participated in, contributed

to and/or directed the submission of ANDA No. 91-151 and the § 505(j)(2)(A)(vii)(IV) allegations to the FDA.

20. Defendants' active and knowing participation in, contribution to, aiding, abetting and/or inducement of the submission to the FDA of ANDA No. 91-151 and the § 505(j)(2)(A)(vii)(IV) allegations constitutes infringement of the '257 patent under 35 U.S.C. § 271(e)(2)(A). Defendants' commercial manufacture, use, offer for sale, importation or sale of its proposed generic versions of Sepracor's Lunesta® brand products, or inducement of or contribution to such conduct, would further infringe the '257 patent under 35 U.S.C. § 271(a), (b) and/or (c).

21. Upon information and belief, Defendants were aware of the existence of the '257 patent and were aware that filing of the ANDA and certification with respect to the '257 patent constituted an act of infringement of that patent.

22. This case is an exceptional one and Sepracor is entitled to an award of its reasonable attorney fees under 35 U.S.C. § 285.

23. Sepracor will be irreparably harmed by Defendants' infringing activities unless those activities are enjoined by this Court. Sepracor does not have an adequate remedy at law.

INFRINGEMENT OF THE '673 PATENT

COUNT II – INFRINGEMENT OF THE '673 PATENT BY DEFENDANTS

24. Sepracor re-alleges paragraphs 1-23 as if fully set forth herein.

25. Upon information and belief, Defendants submitted ANDA No. 91-151 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(i)). ANDA No. 91-151 seeks the FDA approval necessary to engage in the commercial manufacture, use and sale of generic tablets containing 1 mg, 2 mg or 3 mg of the active ingredient

eszopiclone prior to the expiration of the '673 patent. ANDA No. 91-151 specifically seeks FDA approval to market a proposed generic version of Sepracor's Lunesta® brand 1 mg, 2 mg and 3 mg eszopiclone tablets prior to the expiration of the '673 patent.

26. ANDA No. 91-151 alleges under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '673 patent are invalid. Sepracor received written notification of ANDA No. 91-151 and the § 505(j)(2)(A)(vii)(IV) allegations on March 10, 2009.

27. Defendants' submission to the FDA of ANDA No. 91-151, including the § 505(j)(2)(A)(vii)(IV) allegations, constitutes infringement of the '673 patent under 35 U.S.C. § 271(e)(2)(A).

28. Alphapharm and Mylan are jointly and severally liable for any infringement of the '673 patent. This is because, upon information and belief, Alphapharm and Mylan actively and knowingly caused to be submitted, assisted with, participated in, contributed to and/or directed the submission of ANDA No. 91-151 and the § 505(j)(2)(A)(vii)(IV) allegations to the FDA.

29. Defendants' active and knowing participation in, contribution to, aiding, abetting and/or inducement of the submission of ANDA No. 91-151 and the § 505(j)(2)(A)(vii)(IV) allegations to the FDA constitutes infringement of the '673 patent under 35 U.S.C. § 271(e)(2)(A). Defendants' commercial manufacture, use, offer for sale, importation or sale of its proposed generic versions of Sepracor's Lunesta® brand products, or inducement of or contribution to such conduct, would further infringe the '673 patent under 35 U.S.C. § 271(a), (b) and/or (c).

30. Upon information and belief, Defendants were aware of the existence of the '673 patent and were aware that filing of the ANDA and certification with respect to the '673 patent constituted an act of infringement of that patent.

31. This case is an exceptional one and Sepracor is entitled to an award of its reasonable attorney fees under 35 U.S.C. § 285.

32. Sepracor will be irreparably harmed by Defendants' infringing activities unless those activities are enjoined by this Court. Sepracor does not have an adequate remedy at law.

INFRINGEMENT OF THE '926 PATENT

COUNT III– INFRINGEMENT OF THE '926 PATENT BY DEFENDANTS

33. Sepracor re-alleges paragraphs 1-32 as if fully set forth herein.

34. Upon information and belief, Defendants submitted ANDA No. 91-151 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(i)). ANDA No. 91-151 seeks the FDA approval necessary to engage in the commercial manufacture, use and sale of generic tablets containing 1 mg, 2 mg or 3 mg of the active ingredient eszopiclone prior to the expiration of the '926 patent. ANDA No. 91-151 specifically seeks FDA approval to market a proposed generic version of Sepracor's Lunesta® brand 1 mg, 2 mg and 3 mg eszopiclone tablets prior to the expiration of the '926 patent.

35. ANDA No. 91-151 alleges under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '926 patent are invalid. Sepracor received written notification of ANDA No. 91-151 and the § 505(j)(2)(A)(vii)(IV) allegations on March 10, 2009.

36. Defendants' submission to the FDA of ANDA No. 91-151, including the § 505(j)(2)(A)(vii)(IV) allegations, constitutes infringement of the '926 patent under 35 U.S.C. § 271(e)(2)(A).

37. Alphapharm and Mylan are jointly and severally liable for any infringement of the '926 patent. This is because, upon information and belief, Alphapharm and Mylan actively and knowingly caused to be submitted, assisted with, participated in, contributed to and/or directed the submission of ANDA No. 91-151 and its § 505(j)(2)(A)(vii)(IV) allegations to the FDA.

38. Defendants' active and knowing participation in, contribution to, aiding, abetting and/or inducement of the submission to the FDA of ANDA No. 91-151 and the § 505(j)(2)(A)(vii)(IV) allegations constitutes infringement of the '926 patent under 35 U.S.C. § 271(e)(2)(A). Defendants' commercial manufacture, use, offer for sale, importation or sale of its proposed generic versions of Sepracor's Lunesta® brand products, or inducement of or contribution to such conduct, would further infringe the '926 patent under 35 U.S.C. § 271(a), (b) and/or (c).

39. Upon information and belief, Defendants were aware of the existence of the '926 patent and were aware that filing of the ANDA and certification with respect to the '926 patent constituted an act of infringement of that patent.

40. This case is an exceptional one and Sepracor is entitled to an award of its reasonable attorney fees under 35 U.S.C. § 285.

41. Sepracor will be irreparably harmed by Defendants' infringing activities unless those activities are enjoined by this Court. Sepracor does not have an adequate remedy at law.

INFRINGEMENT OF THE '724 PATENT

COUNT IV – INFRINGEMENT OF THE '724 PATENT BY DEFENDANTS

42. Sepracor re-alleges paragraphs 1-41 as if fully set forth herein.

43. Upon information and belief, Defendants submitted ANDA No. 91-151 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(i)). ANDA No. 91-151 seeks the FDA approval necessary to engage in the commercial manufacture, use and sale of generic tablets containing 1 mg, 2 mg or 3 mg of the active ingredient eszopiclone prior to the expiration of the '724 patent. ANDA No. 91-151 specifically seeks FDA approval to market a proposed generic version of Sepracor's Lunesta® brand 1 mg, 2 mg and 3 mg eszopiclone tablets prior to the expiration of the '724 patent.

44. ANDA No. 91-151 alleges under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '724 patent are invalid. Sepracor received written notification of ANDA No. 91-151 and the § 505(j)(2)(A)(vii)(IV) allegations on March 10, 2009.

45. Defendants' submission to the FDA of ANDA No. 91-151, including the § 505(j)(2)(A)(vii)(IV) allegations, constitutes infringement of the '724 patent under 35 U.S.C. § 271(e)(2)(A).

46. Alphapharm and Mylan are jointly and severally liable for any infringement of the '724 patent. This is because, upon information and belief, Alphapharm and Mylan actively and knowingly caused to be submitted, assisted with, participated in, contributed to and/or directed the submission of ANDA No. 91-151 and the § 505(j)(2)(A)(vii)(IV) allegations to the FDA.

47. Defendants' active and knowing participation in, contribution to, aiding, abetting and/or inducement of the submission to the FDA of ANDA No. 91-151 and the

§ 505(j)(2)(A)(vii)(IV) allegations constitutes infringement of the '724 patent under 35 U.S.C. § 271(e)(2)(A). Defendants' commercial manufacture, use, offer for sale, importation or sale of its proposed generic versions of Sepracor's Lunesta® brand products, or inducement of or contribution to any such conduct, would further infringe the '724 patent under 35 U.S.C. § 271(a), (b) and/or (c).

48. Upon information and belief, Defendants were aware of the existence of the '724 patent and were aware that filing of the ANDA and certification with respect to the '724 patent constituted an act of infringement of that patent.

49. This case is an exceptional one and Sepracor is entitled to an award of its reasonable attorney fees under 35 U.S.C. § 285.

50. Sepracor will be irreparably harmed by Defendants' infringing activities unless those activities are enjoined by this Court. Sepracor does not have an adequate remedy at law.

PRAYER FOR RELIEF

WHEREFORE, Plaintiff Sepracor requests that:

A. A Judgment be entered declaring that Defendants Alphapharm and Mylan have infringed the '257, '673, '926, and '724 patents by submitting the aforesaid ANDA;

B. An Order be issued pursuant to 35 U.S.C. § 271(e)(4)(A) that the effective date of approval of Defendants' ANDA identified in this Complaint be a date that is not earlier than the expiration dates of the '257 patent, '673 patent, '926 patent and '724 patent, or any later expiration of exclusivity for the '257 patent, '673 patent, '926 patent or '724 patent to which Plaintiff is or becomes entitled;

C. An Order be issued that Defendants Alphapharm and Mylan, their officers, agents, servants and employees, and those persons in active concert or participation with any of them, are preliminarily and permanently enjoined from commercially manufacturing, using, offering for sale, importing or selling the proposed generic versions of Sepracor's Lunesta® brand products identified in this Complaint, and any other product that infringes or induces or contributes to the infringement of the '257, '673, '926 and '724 patents, prior to the expiration of the '257, '673, '926 and '724 patents, including any extensions to which Plaintiff is or becomes entitled;

D. Sepracor be awarded monetary relief if any Defendant commercially manufactures, uses, offers for sale, or sells a generic version of Sepracor's Lunesta® brand product, or any other product that infringes or induces or contributes to the infringement of the '257, '673, '926 or '724 patent, within the United States prior to the

expiration of those patents, including any extensions, and that any such monetary relief be awarded to Sepracor with prejudgment interest;

E. A Judgment be entered against each Defendant that this case is exceptional and that Sepracor is entitled to its reasonable attorney fees, costs and expenses that it incurs prosecuting this action as to that Defendant; and

F. Sepracor be awarded such other and further relief as this Court deems just and proper.

Dated: April 22, 2009

Respectfully submitted,

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LEGAL_US_E # 83303309.5

Exhibit A


US006864257B2

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

(10) **Patent No.: US 6,864,257 B2**
(45) **Date of Patent: Mar. 8, 2005**

(54) **OPTICALLY ACTIVE 5H-PYRROLO[3,4-B] PYRAZINE DERIVATIVE, ITS PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING IT**

(75) Inventors: **Claude Cotrel**, Paris (FR); **Gérard Roussel**, Soisy sur Seine (FR)

(73) Assignee: **Sepracor Inc.**, Marlborough, MA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 227 days.

(21) Appl. No.: **10/200,510**

(22) Filed: **Jul. 23, 2002**

(65) **Prior Publication Data**

US 2002/0193378 A1 Dec. 19, 2002

Related U.S. Application Data

(62) Division of application No. 09/722,438, filed on Nov. 28, 2000, now Pat. No. 6,444,673, which is a continuation of application No. 09/124,651, filed on Jul. 29, 1998, now Pat. No. 6,319,926, which is a continuation of application No. 08/493,946, filed on Jun. 23, 1995, now abandoned, which is a continuation of application No. 08/342,794, filed on Nov. 21, 1994, now abandoned, which is a continuation of application No. 08/232,313, filed on Apr. 25, 1994, now abandoned, which is a continuation of application No. 08/109,863, filed on Aug. 20, 1993, now abandoned, which is a continuation of application No. 08/034,199, filed on Mar. 19, 1993, now abandoned, which is a continuation of application No. 07/821,662, filed on Jan. 16, 1992, now abandoned.

(30) **Foreign Application Priority Data**

Jan. 17, 1991 (FR) 91 00490

(51) **Int. Cl.**[7] **C07D 487/04**; A61K 31/4985; A61P 25/20

(52) **U.S. Cl.** **514/249**

(58) **Field of Search** 514/249

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(List continued on next page.)

Primary Examiner—Mark L. Berch
(74) *Attorney, Agent, or Firm*—Heslin Rothenberg Farley & Mesiti P.C.

(57) **ABSTRACT**

Dextrorotatory isomer of 6-(5-chloro-2-pyridyl)-5-[(4-methyl-1-piperazinyl)carbonyloxy]-7-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazine, its preparation and pharmaceutical compositions containing it which are usable as tranquillisers and hypnotics.

7 Claims, No Drawings

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OPTICALLY ACTIVE 5H-PYRROLO[3,4-B] PYRAZINE DERIVATIVE, ITS PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING IT

This is a divisional of Application Ser. No. 09/722,438, filed Nov. 28, 2000, now U.S. Pat. No. 6,444,673 which is a continuation of Application Ser. No. 09/124,651, filed Jul. 29, 1998, now U.S. Pat. No. 6,319,926, which is a continuation of Application Ser. No. 08/493,946, filed Jun. 3, 1995 (abandoned), which is a continuation of Application Ser. No. 08/342,794, filed Nov. 21, 1994 (abandoned), which is a continuation of Application Ser. No. 08/232,313, filed Apr. 25, 1994 (abandoned), which is a continuation of Application Ser. No. 08/109,863, filed Aug. 20, 1993 (abandoned), which is a continuation of Application Ser. No. 08/034,199, filed Mar. 19, 1993 (abandoned), which is a continuation of Application Ser. No. 07/821,662, filed Jan. 16, 1992 (abandoned), the disclosures of which are incorporated herein by reference.

In French Patent FR 72/00,505, published under number 2,166,314, a description was given, in particular, of 6-(5-chloro-2-pyridyl)-5-[(4-methyl-1-piperazinyl) carbonyloxy]-7-oxo-6,7-dihydro-5H-pyrrolo[3,4-b] pyrazine, also known by the name of zopiclone, which is a noteworthy hypnotic product.

As a result of the presence of an asymmetric carbon atom at the 5-position of the 5H-pyrrolo[3,4-b]-pyrazine ring-system, zopiclone must be considered, in racemic form, to consist of a strictly equimolecular mixture of the laevorotatory and dextrorotatory forms.

It has now been found, and this forms the subject of the present invention, that the dextrorotatory isomer of zopiclone possesses properties which are not obvious in the light of those of racemic zopiclone.

The subject of the present invention is hence the dextrorotatory isomer of zopiclone, its preparation and pharmaceutical compositions containing it. In a racemic product, it is known that, often, one of the two enantiomers is active and that an enhancement of the toxicity may be linked to this activity, the other enantiomer being both markedly less active or inactive and less toxic. For such products, the gain in activity does not compensate for the drawbacks due to an enhanced toxicity.

In the case of zopiclone, it was found, surprisingly and unexpectedly, not only that the dextrorotatory isomer is approximately twice as active as the racemate while having a lower toxicity than that of the racemate, but that the laevorotatory isomer is both almost inactive and more toxic than the racemate.

For example, when administered orally to mice, zopiclone possesses a toxicity (LD_50) in the region of 850 mg/kg, whereas the dextrorotatory isomer has a toxicity in the region of 1.5 g/kg and the laevorotatory isomer possesses an LD_50 of between 300 and 900 mg/kg.

In animals, the dextrorotatory isomer of zopiclone displays hypnotic, sedative, anxiolytic, muscle-relaxant and anticonvulsant properties.

From the standpoint of the potency of action in the main tests demonstrating the tranquillising and hypnotic activity of zopiclone, such as the test of affinity for central benzodiazepine receptor sites-according to the technique of J. C. Blanchard and L. Julou, J. of Neurochemistry, 40, 601 (1983) based on the work of Squires and Braestrup, Nature, 266, 732–734 (1977), or the test of antagonist activity with respect to pentetrazol-induced convulsions according to the technique of Everett and Richards, J. Pharmacol., 81, 402 (1944), or in the writhing reflex test in mice according to the technique of Zbinden and Randall, Advances in Pharmacology 5, 213–291 (1967), the dextrorotatory isomer is approximately twice as active whereas the laevorotatory isomer is almost inactive.

According to the invention, the dextrorotatory isomer of zopiclone may be prepared from the corresponding racemate according to the usual methods, such as chiral-phase chromatography, resolution of an optically active salt, stereoselective enzymatic catalysis by means of an appropriate microorganism, or asymmetric synthesis.

More especially, the dextrorotatory isomer of zopiclone may be obtained by resolution of zopiclone by means of an optically active acid, working in an appropriate organic solvent.

As an optically active acid which is especially suitable, D(+)-O,O'-dibenzoyltartaric acid may be mentioned.

Generally, the reaction is performed in an organic solvent chosen from halogenated aliphatic hydrocarbons such as dichloromethane and nitriles such as acetonitrile, taken alone or mixed.

By working in this manner, the salt of the dextrorotatory isomer precipitates and the laevorotatory isomer is extracted from the mother liquors of crystallisation.

The dextrorotatory isomer of zopiclone is displaced from its salt by means of a base such as sodium hydroxide.

The dextrorotatory isomer of zopiclone is useful in humans for the treatment of states due to a dysfunction of the central nervous system.

The dextrorotatory isomer of zopiclone is, e.g., useful as a hypnosedative, tranquilliser, muscle relaxant and anticonvulsant.

However, the dextrorotatory isomer of zopiclone is more especially useful in man as a hypnotic.

Since it acts on the various parameters of sleep, the dextrorotatory isomer of zopiclone increases sleeptime and improves sleep quality, and decreases the number of episodes of waking at night and of early morning awakening.

The present invention relates to pharmaceutical compositions containing the dextrorotatory isomer of zopiclone or one of its pharmaceutically acceptable salts, in the pure state or in the presence of a diluent or a coating. These compositions may be employed orally, rectally or parenterally.

As pharmaceutically acceptable salts, salts of inorganic acids (such as hydrochlorides, sulphates, nitrates, phosphates) or organic acids (such as the acetates, propionates, succinates, benzoates, fumarates, tartrates, theophyllineacetates, salicylates, phenolphthalinates, methylenebis (β-hydroxynaphthoates), or of substitution derivatives of these acids, may be mentioned.

As solid compositions for oral administration, tablets, pills, powders or granules may be used. In these compositions, the active product according to the invention is mixed with one or more inert diluents such as sucrose, lactose or starch. These compositions can also comprise substances other than diluents, e.g. a lubricant such as magnesium stearate.

As liquid compositions for oral administration, solutions, suspensions, syrups, elixirs and pharmaceutically acceptable emulsions, containing inert diluents such as water or liquid paraffin, may be used. These compositions can also comprise substances other than diluents, e.g. wetting, sweetening or flavouring products.

The compositions for parenteral administration can be suspensions, emulsions or aqueous or non-aqueous, sterile solutions. As a solvent or vehicle, propylene glycol, polyethylene glycol, vegetable oils, especially olive oil, and

injectable organic esters, e.g. ethyl oleate, may be employed. These compositions can contain adjuvants, especially wetting, emulsifying and dispersing agents. The sterilisation may be carried out in several ways, e.g. using a bacteriological filter, by incorporating sterilising agents in the composition, by irradiation or by heating. They may be prepared in the form of sterile compositions which can be dissolved at the time of use in sterile water or any other sterile injectable medium.

The compositions for rectal administration are suppositories which can contain, apart from the active product, excipients such as cocoa butter.

In human therapy, the doses depend on the effect sought and the treatment period; taken orally, they are generally between 2.5 and 15 mg per day for an adult.

The examples which follow, given without implied limitation, illustrate the present invention.

EXAMPLE 1

A solution of zopiclone (23.28 g; 0.06 mol) in dichloromethane (300 cc) is added to a solution of D(+)-O,O'-dibenzoyltartaric acid in the form of a monohydrate (22.56 g; 0.06 mol) in dichloromethane (300 cc). The reaction mixture is concentrated to dryness under reduced pressure. The crude salt obtained is recrystallised in acetonitrile (2000 cc) to give, in a 46% yield, a crystallised product (21.3 g), m.p. 160–165° C. (with decomposition), the optical rotation of which is $[\alpha]_D^{20}$=83° (c=0.5; acetone).

The product obtained is dissolved in dichloromethane (180 cc) under reflux. Acetonitrile (200 cc) is added and the mixture is left standing for 1 hour at a temperature of 5° C. The crystallised product obtained is recrystallised again under the same conditions. A crystallised salt (16.5 g), m.p. 160–165° C. (with decomposition), the optical rotation of which is $[\alpha]_D^{20}$=102° (c=0.5; acetone), is thereby obtained in a 36% yield.

The salt thereby obtained is dissolved in water (125 cc) in the presence of dichloromethane (125 cc). The mixture is alkalinised to pH 11 by slowly adding 2N aqueous sodium hydroxide solution. After settling has taken place, the aqueous phase is separated and extracted twice with dichloromethane. The combined organic phases are washed with water and then dried over magnesium sulphate. After filtration, evaporation of the solvent and recrystallisation of the product obtained in acetonitrile (80 cc), the dextrorotatory isomer (5.4 g) of zopiclone, m.p. 206.5° C., the optical rotation of which is $[\alpha]_D^{20}$=135°±3° (c=1.0; acetone), is obtained in a 23% yield.

The mother liquors of crystallisation of the salt of zopiclone with D(+)-O,O'-dibenzoyltartaric acid are concentrated to dryness under reduced pressure to give a salt (22.05 g) the optical rotation of which is $[\alpha]_D^{20}$=−21° (c=0.2; acetone).

The salt thereby obtained is dissolved in water (125 cc) in the presence of dichloromethane (125 cc). The mixture is alkalinised to pH 11 by slowly adding 2N aqueous sodium hydroxide solution. After settling has taken place, the aqueous phase is separated and extracted twice with dichloromethane. The combined organic phases are washed with water and then dried over magnesium sulphate. After filtration and evaporation of the solvent, the crystallised solid obtained (8.45 g) is recrystallised in acetonitrile (successively 100, 50 and 45 cc). The laevorotatory isomer (3.13 g) of zopiclone, m.p. 206.9° C., the optical rotation of which is $[\alpha]_D^{20}$=−133°±3° (c=1.0; acetone), is thereby obtained in a 13.9% yield.

EXAMPLE 2

Tablets containing 3 mg of active product and having the following composition are prepared according to the usual technique:

dextrorotatory isomer of zopiclone	0.003 g
starch	0.100 g
precipitated silica	0.035 g
magnesium stearate	0.005 g

What is claimed is:

1. A method of inducing an effect selected from the group consisting of a hypnotic effect, a sedative effect and a tranquilizing effect, in a human in need of said induction, comprising administering to the human an effective quantity of 6-(5-chloro-2-pyridyl)-5-[(4-methyl-1-piperazinyl) carbonyloxy]-7-oxo-6,7-dihydro-5H-pyrrolo[3,4-b] pyrazine, or a pharmaceutically acceptable salt thereof, in the form of its dextrorotatory isomer and essentially free of its levorotatory isomer.

2. The method according to claim 1, wherein said administering step comprises administering a pharmaceutical composition comprising an effective amount of said 6-(5-chloro-2-pyridyl)-5-[(4-methyl-1-piperazinyl)-carbonyloxy]-7-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazine, or a pharmaceutically acceptable salt thereof, in the form of its dextrorotatory isomer and essentially free of its levorotatory isomer, and a pharmaceutically acceptable carrier.

3. The method according to claim 1, wherein the pharmaceutically acceptable salt is a salt of a mineral acid, or a substituted derivative thereof, selected from the group consisting of hydrochlorides, sulfates, nitrates, and phosphates.

4. The method according to claim 1, wherein the pharmaceutically acceptable salt is a salt of an organic acid, or a substituted derivative thereof, selected from the group consisting of acetates, propionates, succinates, benzoates, fumarates, tartrates, theophyllineacetates, salicylates, and phenolphthalinates.

5. The method according to claim 1, wherein the effective quantity is from about 2.5 mg to about 15 mg per day.

6. The method according to claim 2,wherein the pharmaceutically acceptable carrier comprises a diluent.

7. The method according to claim 2 wherein the composition is administered orally, rectally or parenterally.

* * * * *

Exhibit B

US006444673B1

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

(10) **Patent No.: US 6,444,673 B1**
(45) **Date of Patent: Sep. 3, 2002**

(54) **OPTICALLY ACTIVE 5H-PYRROLO[3,4-B] PYRAZINE DERIVATIVE, ITS PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING IT**

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(73) Assignee: **Sepracor Inc.**, Marlborough, MA (US)

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

(21) Appl. No.: **09/722,438**

(22) Filed: **Nov. 28, 2000**

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(52) **U.S. Cl.** **514/249**; 540/350

(58) **Field of Search** 544/350; 514/249

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(57) **ABSTRACT**

Dextrorotatory isomer of 6-(5-chloro-2-pyridyl)-5-[(4-methyl-1-piperazinyl)carbonyloxy]-7-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazine, its preparation and pharmaceutical compositions containing it which are usable as tranquillizers and hypnotics.

8 Claims, No Drawings

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OPTICALLY ACTIVE 5H-PYRROLO[3,4-B] PYRAZINE DERIVATIVE, ITS PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING IT

This is a continuation of application Ser. No. 09/124,651, filed Jul. 29, 1998, which is a continuation of Ser. No. 08/493,946, filed Jun. 23, 1995 (abandoned), which is a continuation of Ser. No. 08/342,794, filed Nov. 21, 1994 (abandoned), which is a continuation of Ser. No. 08/232,313, filed Apr. 25, 1994 (abandoned), which is a continuation of Ser. No. 08/109,863, filed Aug. 20, 1993 (abandoned), which is a continuation of Ser. No. 08/034,199, filed Mar. 19, 1993 (abandoned), which is a continuation of Ser. No. 07/821,662, filed Jan. 16, 1992 (abandoned), the disclosure of which is incorporated herein by reference.

In French Patent FR 72/00,505, published under number 2,166,314, a description was given, in particular, of 6-(5-chloro-2-pyridyl)-5-[(4-methyl-1-piperazinyl) carbonyloxy]-7-oxo-6,7-dihydro-5H-pyrrolo[3,4-b] pyrazine, also known by the name of zopiclone, which is a noteworthy hypnotic product.

As a result of the presence of an asymmetric carbon atom at the 5-position of the 5H-pyrrolo(3,4-b)-pyrazine ring-system, zopiclone must be considered, in racemic form, to consist of a strictly equimolecular mixture of the laevorotatory and dextrorotatory forms.

It has now been found, and this forms the subject of the present invention, that the dextrorotatory isomer of zopiclone possesses properties which are not obvious in the light of those of racemic zopiclone.

The subject of the present invention is hence the dextrorotatory isomer of zopiclone, its preparation and pharmaceutical compositions containing it. In a racemic product, it is known that, often, one of the two enantiomers is active and that an enhancement of the toxicity may be linked to this activity, the other enantiomer being both markedly less active or inactive and less toxic. For such products, the gain in activity does not compensate for the drawbacks due to an enhanced toxicity.

In the case of zopiclone, it was found, surprisingly and unexpectedly, not only that the dextrorotatory isomer is approximately twice as active as the racemate while having a lower toxicity than that of the racemate, but that the laevorotatory isomer is both almost inactive and more toxic than the racemate.

For example, when administered orally to mice, zopiclone possesses a toxicity (LD_50) in the region of 850 mg/kg, whereas the dextrorotatory isomer has a toxicity in the region of 1.5 g/kg and the laevorotatory isomer possesses an LD_50 of between 300 and 900 mg/kg.

In animals, the dextrorotatory isomer of zopiclone displays hypnotic, sedative, anxiolytic, muscle-relaxant and anticonvulsant properties.

From the standpoint of the potency of action in the main tests demonstrating the tranquillising and hypnotic activity of zopiclone, such as the test of affinity for central benzodiazepine receptor sites according to the technique of J. C. Blanchard and L. Julou, J. of Neurochemistry, 40, 601 (1983) based on the work of Squires and Braestrup, Nature, 266, 732–734 (1977), or the test of antagonist activity with respect to pentetrazol-induced convulsions according to the technique of Everett and Richards, J. Pharmacol., 81, 402 (1944), or in the writhing reflex test in mice according to the technique of Zbinden and Randall, Advances in Pharmacology 5, 213–291 (1967), the dextrorotatory isomer is approximately twice as active whereas the laevorotatory isomer is almost inactive.

According to the invention, the dextrorotatory isomer of zopiclone may be prepared from the corresponding racemate according to the usual methods, such as chiral-phase chromatography, resolution of an optically active salt, stereoselective enzymatic catalysis by means of an appropriate microorganism, or asymmetric synthesis.

More especially, the dextrorotatory isomer of zopiclone may be obtained by resolution of zopiclone by means of an optically active acid, working in an appropriate organic solvent.

As an optically active acid which is especially suitable, D(+)-O,O'-dibenzoyltartaric acid may be mentioned.

Generally, the reaction is performed in an organic solvent chosen from halogenated aliphatic hydrocarbons such as dichloromethane and nitriles such as acetonitrile, taken alone or mixed.

By working in this manner, the salt of the dextrorotatory isomer precipitates and the laevorotatory isomer is extracted from the mother liquors of crystallisation.

The dextrorotatory isomer of zopiclone is displaced from its salt by means of a base such as sodium hydroxide.

The dextrorotatory isomer of zopiclone is useful in humans for the treatment of states due to a dysfunction of the central nervous system.

The dextrorotatory isomer of zopiclone is, e.g., useful as a hypnosedative, tranquilliser, muscle relaxant and anticonvulsant.

However, the dextrorotatory isomer of zopiclone is more especially useful in man as a hypnotic.

Since it acts on the various parameters of sleep, the dextrorotatory isomer of zopiclone increases sleeptime and improves sleep quality, and decreases the number of episodes of waking at night and of early morning awakening.

The present invention relates to pharmaceutical compositions containing the dextrorotatory isomer of zopiclone or one of its pharmaceutically acceptable salts, in the pure state or in the presence of a diluent or a coating. These compositions may be employed orally, rectally or parenterally.

As pharmaceutically acceptable salts, salts of inorganic acids (such as hydrochlorides, sulphates, nitrates, phosphates) or organic acids (such as the acetates, propionates, succinates, benzoates, fumarates, tartrates, theophyllineacetates, salicylates, phenolphthalinates, methylenebis(β-hydroxynaphthoates), or of substitution derivatives of these acids, may be mentioned.

As solid compositions for oral administration, tablets, pills, powders or granules may be used. In these compositions, the active product according to the invention is mixed with one or more inert diluents such as sucrose, lactose or starch. These compositions can also comprise substances other than diluents, e.g. a lubricant such as magnesium stearate.

As liquid compositions for oral administration, solutions, suspensions, syrups, elixirs and pharmaceutically acceptable emulsions, containing inert diluents such as water or liquid paraffin, may be used. These compositions can also comprise substances other than diluents, e.g. wetting, sweetening or flavouring products.

The compositions for parenteral administration can be suspensions, emulsions or aqueous or non-aqueous, sterile solutions. As a solvent or vehicle, propylene glycol, polyethylene glycol, vegetable oils, especially olive oil, and injectable organic esters, e.g. ethyl oleate, may be employed. These compositions can contain adjuvants, especially wetting, emulsifying and dispersing agents. The sterilisation

may be carried out in several ways, e.g. using a bacteriological filter, by incorporating sterilising agents in the composition, by irradiation or by heating. They may be prepared. in the form of sterile compositions which can be dissolved at the time of use in sterile water or any other sterile injectable medium.

The compositions for rectal administration are suppositories which can contain, apart from the active product, excipients such as cocoa butter.

In human therapy, the doses depend on the effect sought and the treatment period; taken orally, they are generally between 2.5 and 15 mg per day for an adult.

The examples which follow, given without implied limitation, illustrate the present invention.

EXAMPLE 1

A solution of zopiclone (23.28 g; 0.06 mol) in dichloromethane (300 cc) is added to a solution of D(+)-O,O'-dibenzoyltartaric acid in the form of a monohydrate (22.56 g; 0.06 mol) in dichloromethane (300 cc). The reaction mixture is concentrated to dryness under reduced pressure. The crude salt obtained is recrystallised in acetonitrile (2000 cc) to give, in a 46% yield, a crystallised product (21.3 g), m.p. 160–165° C. (with decomposition), the optical rotation of which is $[\alpha]_D^{20}$=83°(c=0.5; acetone).

The product obtained is dissolved in dichloromethane (180 cc) under reflux. Acetonitrile (200 cc) is added and the mixture is left standing for 1 hour at a temperature of 5° C. The crystallised product obtained is recrystallised again under the same conditions. A crystallised salt (16.5 g), m.p. 160–165° C. (with decomposition), the optical rotation of which is $[\alpha]_D^{20}$=102° (c=0.5; acetone), is thereby obtained in a 36% yield.

The salt thereby obtained is dissolved in water (125 cc) in the presence of dichloromethane (125 cc). The mixture is alkalinised to pH 11 by slowly adding 2N aqueous sodium hydroxide solution. After settling has taken place, the aqueous phase is separated and extracted twice with dichloromethane. The combined organic phases are washed with water and then dried over magnesium sulphate. After filtration, evaporation of the solvent and recrystallisation of the product obtained in acetonitrile (80 cc), the dextrorotatory isomer (5.4 g) of zopiclone, m.p. 206.5° C., the optical rotation of which is $[\alpha]_D^{20}$=135°±3° (c=1.0; acetone), is obtained in a 23% yield.

The mother liquors of crystallisation of the salt of zopiclone with D(+)-O,O'-dibenzoyltartaric acid are concentrated to dryness under reduced pressure to give a salt (22.05 g) the optical rotation of which is $[\alpha]_D^{20}$=−21° (c=0.2; acetone).

The salt thereby obtained is dissolved in water (125 cc) in the presence of dichloromethane (125 cc). The mixture is alkalinised to pH 11 by slowly adding 2N aqueous sodium hydroxide solution. After settling has taken place, the aqueous phase is separated and extracted twice with dichloromethane. The combined organic phases are washed with water and then dried over magnesium sulphate. After filtration and evaporation of the solvent, the crystallised solid obtained (8.45 g) is recrystallised in acetonitrile (successively 100, 50 and 45 cc). The laevorotatory isomer

(3.13 g) of zopiclone, m.p. 206.9° C., the optical rotation of which is $[\alpha]_D^{20}$=−133°±3° (c=1.0; acetone), is thereby obtained in a 13.9% yield.

EXAMPLE 2

Tablets containing 3 mg of active product and having the following composition are prepared according to the usual technique:

dextrorotatory isomer of zopiclone	0.003 g
starch	0.100 g
precipitated silica	0.035 g
magnesium stearate	0.005 g

What is claimed is:

1. 6-(5-chloro-2-pyridyl)-5-[(4-methyl-1-piperazinyl) carbonyloxy]-7-oxo-6,7-dihydro-5H-pyrrolo[3,4-b] pyrazine, or a pharmaceutically acceptable salt thereof, in the form of its dextrorotatory isomer and essentially free of its levorotatory isomer.

2. A pharmaceutical composition comprising an effective amount of the dextrorotatory isomer, essentially free of the levorotatory isomer of 6-(5-chloro-2-pyridyl)-5-[(4-methyl-1-piperazinyl)-carbonyloxy]-7-oxo-6,7-dihydro-5H-pyrrolo [3,4-b]pyrazine, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

3. The compound according to claim 1, wherein the pharmaceutically acceptable salt is a salt of a mineral acid, or a substituted derivative thereof, selected from the group consisting of hydrochlorides, sulfates, nitrates, and phosphates.

4. The compound according to claim 1, wherein the pharmaceutically acceptable salt is a salt of an organic acid, or a substituted derivative thereof, selected from the group consisting of acetates, propionates, succinates, benzoates, fumarates, tartrates, theophyllineacetates, salicylates, and phenolphthalinates.

5. The pharmaceutical composition according to claim 2, wherein the pharmaceutically acceptable salt is a salt of a mineral acid, or a substituted derivative thereof, selected from the group consisting of hydrochlorides, sulfates, nitrates, and phosphates.

6. The pharmaceutical composition according to claim 2, wherein the pharmaceutically acceptable salt is a salt of an organic acid, or a substituted derivative thereof, selected from the group consisting of acetates, propionates, succinates, benzoates, fumarates, tartrates, theophyllineacetates, salicylates, and phenolphthalinates.

7. The pharmaceutical composition according to claim 2, wherein the therapeutically effective amount of 6-(5-chloro-2-pyridyl)-5-[(4-methyl-1-piperazinyl)-carbonyloxy]-7-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazine, or a pharmaceutically acceptable salt thereof, is from about 2.5 mg to about 15 mg.

8. The pharmaceutically composition according to claim 2, wherein the pharmaceutically acceptable carrier comprises a diluent.

* * * * *

Exhibit C

US006319926B1

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

(10) **Patent No.: US 6,319,926 B1**
(45) **Date of Patent: *Nov. 20, 2001**

(54) **OPTICALLY ACTIVE 5H-PYRROLO[3, 4-B] PYRAZINE DERIVATIVE, ITS PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING IT**

(75) Inventors: **Claude Cotrel**, Paris; **Gérard Roussel**, Soisy sur Seine, both of (FR)

(73) Assignee: **Sepracor Inc.**, Marlborough, MA (US)

(*) Notice: This patent issued on a continued prosecution application filed under 37 CFR 1.53(d), and is subject to the twenty year patent term provisions of 35 U.S.C. 154(a)(2).

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

(21) Appl. No.: **09/124,651**

(22) Filed: **Jul. 29, 1998**

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(63) Continuation of application No. 08/493,946, filed on Jun. 23, 1995, now abandoned, which is a continuation of application No. 08/342,794, filed on Nov. 21, 1994, now abandoned, which is a continuation of application No. 08/232,313, filed on Apr. 25, 1994, now abandoned, which is a continuation of application No. 08/109,863, filed on Aug. 20, 1993, now abandoned, which is a continuation of application No. 08/034,199, filed on Mar. 19, 1993, now abandoned, which is a continuation of application No. 07/821,662, filed on Jan. 16, 1992, now abandoned.

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(52) **U.S. Cl.** **514/249**; 544/350

(58) **Field of Search** 514/249

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(57) **ABSTRACT**

Dextrorotatory isomer of 6-(5-chloro-2-pyridyl)-5[(4-methyl-1-piperazinyl)carbonyloxy]-7-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazine, its preparation and pharmaceutical compositions containing it which are usable as tranquillizers and hypnotics.

1 Claim, No Drawings

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OPTICALLY ACTIVE 5H-PYRROLO[3, 4-B] PYRAZINE DERIVATIVE, ITS PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING IT

This is a continuation of application Ser. No. 08/493,946, filed Jun. 23, 1995, now abandoned, which is a continuation application of Ser. No.: 08/342,794, filed Nov. 21, 1994, now abandoned, which is a continuation application of Ser. No.: 08/232,313, filed Apr. 25, 1994, now abandoned, which is a continuation application of Ser. No.: 08/109,863, filed Aug. 20, 1993, now abandoned, which is a continuation application of Ser. No.: 08/034,199, filed Mar. 19, 1993, now abandoned, which is a continuation application of Ser. No.: 07/821,662, filed Jan. 16, 1992, now abandoned, which are incorporated herein by reference.

In French Patent FR 72/00,505, published under number 2,166,314, a description was given, in particular, of 6-(5-chloro-2-pyridyl)-5-[(4-methyl-1-piperazinyl) carbonyloxy]-7-oxo-6,7-dihydro-5 H-pyrrolo [3,4-b] pyrazine, also known by the name of zopiclone, which is a noteworthy hypnotic product.

As a result of the presence of an asymmetric carbon atom at the 5-position of the 5 H-pyrrolo[3,4-b]-pyrazine ring-system, zopiclone must be considered, in racemic form, to consist of a strictly equimolecular mixture of the laevorotatory and dextrorotatory forms.

It has now been found, and this forms the subject of the present invention, that the dextrorotatory isomer of zopiclone possesses properties which are not obvious in the light of those of racemic zopiclone.

The subject of the present invention is hence the dextrorotatory isomer of zopiclone, its preparation and pharmaceutical compositions containing it. In a racemic product, it is known that, often, one of the two enantiomers is active and that an enhancement of the toxicity may be linked to this activity, the other enantiomer being both markedly less active or inactive and less toxic. For such products, the gain in activity does not compensate for the drawbacks due to an enhanced toxicity.

In the case of zopiclone, it was found, surprisingly and unexpectedly, not only that the dextrorotatory isomer is approximately twice as active as the racemate while having a lower toxicity than that of the racemate, but that the laevorotatory isomer is both almost inactive and more toxic than the racemate.

For example, when administered orally to mice, zopiclone possesses a toxicity ($LD_5 1$) in the region of 850 mg/kg, whereas the dextrorotatory isomer has a toxicity in the region of 1.5 g/kg and the laevorotatory isomer possesses an $LD_5 1$ of between 300 and 900 mg/kg.

In animals, the dextrorotatory isomer of zopiclone displays hypnotic, sedative, anxiolytic, muscle-relaxant and anticonvulsant properties.

From the standpoint of the potency of action in the main tests demonstrating the tranquillising and hypnotic activity of zopiclone, such as the test of affinity for central benzodiazepine receptor sites according to the technique of J. C. Blanchard and L. Julou, J. of Neurochemistry, 40, 601 (1983) based on the work of Squires and Braestrup, Nature, 266, 732–734 (1977), or the test of antagonist activity with respect to pentetrazol-induced convulsions according to the technique of Everett and Richards, J. Pharmacol., 81, 402 (1944), or in the writhing reflex test in mice according to the technique of Zbinden and Randall, Advances in Pharmacology 5, 213–291 (1967), the dextrorotatory isomer is approximately twice as active whereas the laevorotatory isomer is almost inactive.

According to the invention, the dextrorotatory isomer of zopiclone may be prepared from the corresponding racemate according to the usual methods, such as chiral-phase chromatography, resolution of an optically active salt, stereoselective enzymatic catalysis by means of an appropriate microorganism, or asymmetric synthesis.

More especially, the dextrorotatory isomer of zopiclone may be obtained by resolution of zopiclone by means of an optically active acid, working in an appropriate organic solvent.

As an optically active acid which is especially suitable, D(+)-O,O'-dibenzoyltartaric acid may be mentioned.

Generally, the reaction is performed in an organic solvent chosen from halognenated aliphatic hydrocarbons such as dichloromethane and nitrites such as acetonitrile, taken alone or mixed.

By working in this manner, the salt of the dextrorotatory isomer precipitates and the laevorotatory isomer is extracted from the mother liquors of crystallisation.

The dextrorotatory isomer of zopiclone is displaced from its salt by means of a base such as sodium hydroxide.

The dextrorotatory isomer of zopiclone is useful in humans for the treatment of states due to a dysfunction of the central nervous system.

The dextrorotatory isomer of zopiclone is, e.g., useful as a hypnosedative, tranquilliser, muscle relaxant and anticonvulsant.

However, the dextrorotatory isomer of zopiclone is more especially useful in man as a hypnotic.

Since it acts on the various parameters of sleep, the dextrorotatory isomer of zopiclone increases sleeptime and improves sleep quality, and decreases the number of episodes of waking at night and of early morning awakening.

The present invention relates to pharmaceutical compositions containing the dextrorotatory isomer of zopiclone or one of its pharmaceutically acceptable salts, in the pure state or in the presence of a diluent or a coating. These compositions may be employed orally, rectally or parenterally.

As pharmaceutically acceptable salts, salts of inorganic acids (such as hydrochlorides, sulphates, nitrates, phosphates) or organic acids (such as the acetates, propionates, succinates, benzoates, fumarates, tartrates, theophyllineacetates, salicylates, phenolphthalinates, methylenebis (β-hydroxynaphthoates), or of substitution derivatives of these acids, may be mentioned.

As solid composition s for oral administration, tablets, pills, powders or granules may be used. In these compositions, the active product according to the invention is mixed with one or more inert diluents such as sucrose, lactose or starch. These compositions can also comprise substances other than diluents, e.g. a lubricant such as magnesium stearate.

As liquid compositions for oral administration, solutions, suspensions, syrups, elixirs and pharmaceutically acceptable emulsions, containing inert diluents such as water or liquid paraffin, may be used. These compositions can also comprise substances other than diluents, e.g. wetting, sweetening or flavouring products.

The compositions for parenteral administration can be suspensions, emulsions or aqueous or non-aqueous, sterile solutions. As a solvent or vehicle, propylene glycol, polyethylene glycol, vegetable oils, especially olive oil, and injectable organic esters, e.g. ethyl oleate, may be employed. These compositions can contain adjuvants, especially wetting, emulsifying and dispersing agents. The sterilisation may be carried out in several ways, e.g. using a bacteriological filter, by incorporating sterilising agents in the

composition, by irradiation or by heating. They may be prepared in the form of sterile compositions which can be dissolved at the time of use in sterile water or any other sterile injectable medium.

The compositions for rectal administration are suppositories which can contain, apart from the active product, excipients such as cocoa butter.

In human therapy, the doses depend on the effect sought and the treatment period; taken orally, they are generally between 2.5 and 15 mg per day for an adult.

The examples which follow, given without implied limitation, illustrate the present invention.

EXAMPLE 1

A solution of zopiclone (23.28 g; 0.06 mol) in dichloromethane (300 cc) is added to a solution of D(+)-O,O'-dibenzoyltartaric acid in the form of a monohydrate (22.56 g; 0.06 mol) in dichloromethane (300 cc). The reaction mixture is concentrated to dryness under reduced pressure. The crude salt obtained is recrystallised in acetonitrile (2000 cc) to give, in a 46 % yield, a crystallised product (21.3 g), m.p. 160–165° C. (with decomposition), the optical rotation of which is $[\alpha]_D^{20}$=83° C. (c =0.5; acetone).

The product obtained is dissolved in dichloromethane (180 cc) under reflux. Acetonitrile (200 cc) is added and the mixture is left standing for 1 hour at a temperature of 5° C. The crystallised product obtained is recrystallised again under the same conditions. A crystallised salt (16.5 g), m.p. 160–165° C. (with decomposition), the optical rotation of which is $[\alpha]_D^{20}$=102° (c=0.5; acetone), is thereby obtained in a 36 % yield.

The salt thereby obtained is dissolved in water (125 cc) in the presence of dichloromethane (125 cc). The mixture is alkalinised to pH 11 by slowly adding 2 N aqueous sodium hydroxide solution. After settling has taken place, the aqueous phase is separated and extracted twice with dichloromethane. The combined organic phases are washed with water and then dried over magnesium sulphate. After filtration, evaporation of the solvent and recrystallisation of the product obtained in acetonitrile (80 cc), the dextrorotatory isomer (5.4 g) of zopicione, m.p. 206.5° C., the optical rotation of which is $[\alpha]_D^{20}$=135°±3° (c=1.0; acetone), is obtained in a 23% yield.

The mother liquors of crystallisation of the salt of zopiclone with D(+)-O,O'-dibenzoyltartaric acid are concentrated to dryness under reduced pressure to give a salt (22.05 g) the optical rotation of which is $[\alpha]_D^{20}$=–21 ° (c=0.2; acetone).

The salt thereby obtained is dissolved in water (125 cc) in the presence of dichloromethane (125 cc). The mixture is alkalinised to pH 11 by slowly adding 2 N aqueous sodium hydroxide solution. After settling has taken place, the aqueous phase is separated and extracted twice with dichloromethane. The combined organic phases are washed with water and then dried over magnesium sulphate. After filtration and evaporation of the solvent, the crystallised solid obtained (8.45 g) is recrystallised in acetonitrile (successively 100, 50 and 45 cc). The laevorotatory isomer (3.13 g) of zopiclone, m.p. 206.9° C., the optical rotation of which is $[\alpha]_D^{20}$=–133°±3° (c=1.0; acetone), is thereby obtained in a 13.9% yield.

EXAMPLE 2

Tablets containing 3 mg of active product and having the following composition are prepared according to the usual technique:

dextrorotatory isomer of zopiclone . . . 0.003 g

starch . . . 0.100 g

precipitated silica . . . 0.035 g

magnesium stearate . . . 0.005 g

What is claimed is:

1. A method for improving sleep quality or time comprising the step of administering an effective quantity of 6-(5-chloro-2-pyridyl)-5-[(4-methyl-1-piperazinyl) carbonyloxy]-7-oxo-6,7-dihydro-5H-pyrrolo[3,4-b] pyrazine, or a pharmaceutically acceptable salt thereof, in the form of its dextrorotatory isomer and essentially free of its levorotatory isomer, to a human.

* * * * *

Exhibit D


US007381724B2

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

(10) **Patent No.: US 7,381,724 B2**
(45) **Date of Patent: *Jun. 3, 2008**

(54) **OPTICALLY ACTIVE 5H-PYRROLO[3,4-B]PYRAZINE DERIVATIVE, ITS PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING SAME**

(75) Inventors: **Claude Cotrel**, Paris (FR); **Gerard Roussel**, Soisy sur Seine (FR)

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This patent is subject to a terminal disclaimer.

(21) Appl. No.: **11/416,570**

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

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(57) **ABSTRACT**

Dextrorotatory isomer of 6-(5-chloro-2-pyridyl)-5-[(4-methyl-1-piperazinyl)carbonyloxy]-7-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazine, its preparation and pharmaceutical compositions containing it which are usable as tranquillisers and hypnotics.

5 Claims, No Drawings

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OPTICALLY ACTIVE 5H-PYRROLO[3,4-B]PYRAZINE DERIVATIVE, ITS PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING SAME

CROSS RERERENCE TO RELATED APPLICATIONS

This application is a continuation of application Ser. No. 10/951,844, filed Sep. 28, 2004, now U.S. Pat. No. 7,125,874, which is a continuation of application Ser. No. 10/200,510, filed Jul. 23, 2002, now U.S. Pat. No. 6,864,257, which is a divisional of application Ser. No. 09/722,438, filed Nov. 28, 2000, now U.S. Pat. No. 6,444,673, which is a continuation of application Ser. No. 09/124,651, filed Jul. 29, 1998, now U.S. Pat. No. 6,319,926, which is a continuation of application Ser. No. 08/493,946, filed Jun. 23, 1995 (abandoned), which is a continuation of application Ser. No. 08/342,794, filed Nov. 21, 1994 (abandoned), which is a continuation of application Ser. No. 08/232,313, filed Apr. 25, 1994 (abandoned), which is a continuation of application Ser. No. 08/109,863, filed Aug. 20, 1993 (abandoned), which is a continuation of application Ser. No. 08/034,199, filed Mar. 19, 1993 (abandoned), which is a continuation of application Ser. No. 07/821,662, filed Jan. 16, 1992 (abandoned). U.S. Ser. No. 07/821,662 claimed the priority of French application 91 00490, filed Jan. 17, 1991. The entire contents of each of the prior applications are incorporated herein by reference.

In French Patent FR 72/00,505, published under number 2,166,314, a description was given, in particular, of 6-(5-chloro-2-pyridyl)-5-[(4-methyl-1-piperazinyl)carbonyloxy]-7-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazine, also known by the name of zopiclone, which is a noteworthy hypnotic product.

As a result of the presence of an asymmetric carbon atom at the 5-position of the 5H-pyrrolo[3,4-b]-pyrazine ring-system, zopiclone must be considered, in racemic form, to consist of a strictly equimolecular mixture of the laevorotatory and dextrorotatory forms.

It has now been found, and this forms the subject of the present invention, that the dextrorotatory isomer of zopiclone possesses properties which are not obvious in the light of those of racemic zopiclone.

The subject of the present invention is hence the dextrorotatory isomer of zopiclone, its preparation and pharmaceutical compositions containing it. In a racemic product, it is known that, often, one of the two enantiomers is active and that an enhancement of the toxicity may be linked to this activity, the other enantiomer being both markedly less active or inactive and less toxic. For such products, the gain in activity does not compensate for the drawbacks due to an enhanced toxicity.

In the case of zopiclone, it was found, surprisingly and unexpectedly, not only that the dextrorotatory isomer is approximately twice as active as the racemate while having a lower toxicity than that of the racemate, but that the laevorotatory isomer is both almost inactive and more toxic than the racemate.

For example, when administered orally to mice, zopiclone possesses a toxicity (LD_50) in the region of 850 mg/kg, whereas the dextrorotatory isomer has a toxicity in the region of 1.5 g/kg and the laevorotatory isomer possesses an LD_50 of between 300 and 900 mg/kg.

In animals, the dextrorotatory isomer of zopiclone displays hypnotic, sedative, anxiolytic, muscle-relaxant and anticonvulsant properties.

From the standpoint of the potency of action in the main tests demonstrating the tranquillising and hypnotic activity of zopiclone, such as the test of affinity for central benzodiazepine receptor sites according to the technique of J. C. Blanchard and L. Julou, J. of Neurochemistry, 40, 601 (1983) based on the work of Squires and Braestrup, Nature, 266, 732-734 (1977), or the test of antagonist activity with respect to pentetrazol-induced convulsions according to the technique of Everett and Richards, J. Pharmacol., 81, 402 (1944), or in the writhing reflex test in mice according to the technique of Zbinden and Randall, Advances in Pharmacology 5, 213-291 (1967), the dextrorotatory isomer is approximately twice as active whereas the laevorotatory isomer is almost inactive.

According to the invention, the dextrorotatory isomer of zopiclone may be prepared from the corresponding racemate according to the usual methods, such as chiral-phase chromatography, resolution of an optically active salt, stereoselective enzymatic catalysis by means of an appropriate microorganism, or asymmetric synthesis.

More especially, the dextrorotatory isomer of zopiclone may be obtained by resolution of zopiclone by means of an optically active acid, working in an appropriate organic solvent.

As an optically active acid which is especially suitable, D(+)-O,O'-dibenzoyltartaric acid may be mentioned.

Generally, the reaction is performed in an organic solvent chosen from halogenated aliphatic hydrocarbons such as dichloromethane and nitrites such as acetonitrile, taken alone or mixed.

By working in this manner, the salt of the dextrorotatory isomer precipitates and the laevorotatory isomer is extracted from the mother liquors of crystallisation.

The dextrorotatory isomer of zopiclone is displaced from its salt by means of a base such as sodium hydroxide.

The dextrorotatory isomer of zopiclone is useful in humans for the treatment of states due to a dysfunction of the central nervous system.

The dextrorotatory isomer of zopiclone is, e.g., useful as a hypnosedative, tranquilliser, muscle relaxant and anticonvulsant.

However, the dextrorotatory isomer of zopiclone is more especially useful in man as a hypnotic.

Since it acts on the various parameters of sleep, the dextrorotatory isomer of zopiclone increases sleeptime and improves sleep quality, and decreases the number of episodes of waking at night and of early morning awakening.

The present invention relates to pharmaceutical compositions containing the dextrorotatory isomer of zopiclone or one of its pharmaceutically acceptable salts, in the pure state or in the presence of a diluent or a coating. These compositions may be employed orally, rectally or parenterally.

As pharmaceutically acceptable salts, salts of inorganic acids (such as hydrochlorides, sulphates, nitrates, phosphates) or organic acids (such as the acetates, propionates, succinates, benzoates, fumarates, tartrates, theophyllineacetates, salicylates, phenolphthalinates, methylenebis (β-hydroxynaphthoates), or of substitution derivatives of these acids, may be mentioned.

As solid compositions for oral administration, tablets, pills, powders or granules may be used. In these compositions, the active product according to the invention is mixed with one or more inert diluents such as sucrose, lactose or

starch. These compositions can also comprise substances other than diluents, e.g. a lubricant such as magnesium stearate.

As liquid compositions for oral administration, solutions, suspensions, syrups, elixirs and pharmaceutically acceptable emulsions, containing inert diluents such as water or liquid paraffin, may be used. These compositions can also comprise substances other than diluents, e.g. wetting, sweetening or flavouring products.

The compositions for parenteral administration can be suspensions, emulsions or aqueous or non-aqueous, sterile solutions. As a solvent or vehicle, propylene glycol, polyethylene glycol, vegetable oils, especially olive oil, and injectable organic esters, e.g. ethyl oleate, may be employed. These compositions can contain adjuvants, especially wetting, emulsifying and dispersing agents. The sterilisation may be carried out in several ways, e.g. using a bacteriological filter, by incorporating sterilising agents in the composition, by irradiation or by heating. They may be prepared in the form of sterile compositions which can be dissolved at the time of use in sterile water or any other sterile injectable medium.

The compositions for rectal administration are suppositories which can contain, apart from the active product, excipients such as cocoa butter.

In human therapy, the doses depend on the effect sought and the treatment period; taken orally, they are generally between 2.5 and 15 mg per day for an adult.

The examples which follow, given without implied limitation, illustrate the present invention.

EXAMPLE 1

A solution of zopiclone (23.28 g; 0.06 mol) in dichloromethane (300 cc) is added to a solution of D(+)-O,O'-dibenzoyltartaric acid in the form of a monohydrate (22.56 g; 0.06 mol) in dichloromethane (300 cc). The reaction mixture is concentrated to dryness under reduced pressure. The crude salt obtained is recrystallised in acetonitrile (2000 cc) to give, in a 46% yield, a crystallised product (21.3 g), m.p. 160-165° C. (with decomposition), the optical rotation of which is $[\alpha]_D^{20}$=83° (c=0.5; acetone).

The product obtained is dissolved in dichloromethane (180 cc) under reflux. Acetonitrile (200 cc) is added and the mixture is left standing for 1 hour at a temperature of 5° C. The crystallised product obtained is recrystallised again under the same conditions. A crystallised salt (16.5 g), m.p. 160-165° C. (with decomposition), the optical rotation of which is $[\alpha]_D^{20}$=102° (c=0.5; acetone), is thereby obtained in a 36% yield.

The salt thereby obtained is dissolved in water (125 cc) in the presence of dichloromethane (125 cc). The mixture is alkalinised to pH 11 by slowly adding 2N aqueous sodium hydroxide solution. After settling has taken place, the aqueous phase is separated and extracted twice with dichloromethane. The combined organic phases are washed with water and then dried over magnesium sulphate. After filtration, evaporation of the solvent and recrystallisation of the product obtained in acetonitrile (80 cc), the dextrorotatory isomer (5.4 g) of zopiclone, m.p. 206.5° C., the optical rotation of which is $[\alpha]_D^{20}$=135°±3° (c=1.0; acetone), is obtained in a 23% yield.

The mother liquors of crystallisation of the salt of zopiclone with D(+)-O,O'-dibenzoyltartaric acid are concentrated to dryness under reduced pressure to give a salt (22.05 g) the optical rotation of which is $[\alpha]_D^{20}$=−21° (c=0.2; acetone).

The salt thereby obtained is dissolved in water (125 cc) in the presence of dichloromethane (125 cc). The mixture is alkalinised to pH 11 by slowly adding 2N aqueous sodium hydroxide solution. After settling has taken place, the aqueous phase is separated and extracted twice with dichloromethane. The combined organic phases are washed with water and then dried over magnesium sulphate. After filtration and evaporation of the solvent, the crystallised solid obtained (8.45 g) is recrystallised in acetonitrile (successively 100, 50 and 45 cc). The laevorotatory isomer (3.13 g) of zopiclone, m.p. 206.9° C., the optical rotation of which is $[\alpha]_D^{20}$=−133°±3° (c=1.0; acetone), is thereby obtained in a 13.9% yield.

EXAMPLE 2

Tablets containing 3 mg of active product and having the following composition are prepared according to the usual technique:

dextrorotatory isomer of zopiclone	0.003 g
starch	0.100 g
precipitated silica	0.035 g
magnesium stearate	0.005 g

The invention claimed is:

1. A mixture of isomers of 6-(5-chloro-2-pyridyl)-5-[(4-methyl-1-piperazinyl)carbonyl-oxy]-7-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazine, wherein the mixture has an optical rotation $[\alpha]_D^{20}$ of 135°±3° when measured at 1.0 g/100 mL in acetone.

2. A pharmaceutical composition comprising the mixture of claim 1 and one or more pharmaceutically acceptable diluents, coatings, lubricants, wetting products, sweetening products, flavouring products, solvents, vehicles or adjuvants.

3. The pharmaceutical composition of claim 2 that is in the form of a tablet, pill, powder or granule.

4. The pharmaceutical composition of claim 2 that is in the form of a tablet.

5. A method of inducing an effect selected from the group consisting of a hypnotic effect, a sedative effect and a tranquilizing effect, comprising administering to a human in need thereof an effective amount of the mixture of claim 1.

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