

EXHIBIT A

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- (54) **OPTICALLY ACTIVE 5H-PYRROLO[3,4-B]PYRAZINE DERIVATIVE, ITS PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING IT**
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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 0 days.**
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Related U.S. Application Data

- (63) Continuation of application No. 09/124,651, filed on Jul. 29, 1998, 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.

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- (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 tranquilizers 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-piperaziny] 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 (LD₅₀) 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 LD₅₀ 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 approxi-

mately 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

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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 $[\alpha]_D^{20} = 83^\circ$ (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 $[\alpha]_D^{20} = 102^\circ$ (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 $[\alpha]_D^{20} = 135^\circ \pm 3^\circ$ (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 $[\alpha]_D^{20} = -21^\circ$ (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

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(3.13 g) of zopiclone, m.p. 206.9° C., the optical rotation of which is $[\alpha]_D^{20} = -133^\circ \pm 3^\circ$ (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 pharmaceutical composition according to claim 2, wherein the pharmaceutically acceptable carrier comprises a diluent.

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