Title: DERIVATIVE OF PAROXETINE

Abstract

Compounds of the formula (1) and alkali metal and amine and acid addition salts thereof are useful in the treatment of CNS disorders.
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DERIVATIVE OF PAROXETINE

The present invention relates to a novel compound, to processes for preparing it and to its use in treating medical disorders. In particular the present invention relates to a novel derivative of paroxetine.

Pharmaceutical products with antidepressant and anti-Parkinson properties are described in US-A-3912743 and US-A-4007196. An especially important compound among those disclosed is paroxetine, the \((-\)trans\) isomer of \(4-(4'-\text{fluorophenyl})-3-(3',4'-\text{methylenedioxyphenoxy}methyl)\)-piperidine. This compound is used in therapy as the hydrochloride salt for the treatment and prophylaxis of \textit{inter alia} depression, obsessive compulsive disorder (OCD) and panic.

This invention relates to a novel derivative of paroxetine.

According to the present invention there is provided a compound of formula (1)

![Chemical structure of the compound](image)

\[2-[(3S,4R)-\text{trans}-4-(4'-\text{fluorophenyl})-3-(3",4"-\text{methylendioxyphenoxy}methyl)piperidin-1-yl]butan-1,4-dioic acid]\]

The compound of this invention may exist in the free acid form as shown in formula (1) or as the corresponding zwitterion. Both forms are part of this invention.

The compound of formula (1) may also exist as salts for example with alkali metals or amines, or addition salts with strong acids.
Suitable salts include those with alkali metals, preferably sodium, potassium or lithium, or with a mineral acid, for example hydrochloric acid, or sulphonic acid. Amine salts may include salts with paroxetine itself. Also the compound of formula (1) may exist as a mono- or di-salt, or as a mixed salt.

A particularly important salt is the 1:1 (by mole) salt with paroxetine.

Compounds of structure (1) have a chiral centre on the piperidine nitrogen substituent as well as the two chiral centres on the piperidine ring, so may exist in two forms. These forms may be separated by crystallisation or chromatography, optionally in the form of a salt, for example a salt with an optically active base.

The individual isomers, and mixtures thereof, of the compounds of formula (1) and the above described salts are all within the scope of this invention.

The present invention also provides a method for the preparation of compounds of formula (1) by the addition reaction of paroxetine (as the free base) to maleic acid. The procedure may be carried out at elevated temperature in an appropriate solvent.

Among solvents suitable for the addition reaction are polar aprotic solvents, for example N,N-dimethylformamide, alcohols such as ethanol and isopropanol, and esters such as ethyl acetate, and hydrocarbons such as toluene.

The reaction of paroxetine with maleic acid tends to result in the recovery of the paroxetine salt of the compound of formula (1) rather than the free acid. Accordingly the free acid is suitably obtained by preparing the salt and treating the salt to recover the acid.

The paroxetine salt of compound (1) may conveniently be prepared by contacting paroxetine free base with maleic acid in a suitable solvent, for example toluene, ethyl acetate or 2-butanol, preferably at elevated temperature, for example above 60°C. The paroxetine salt of compound (1) may be isolated by crystallisation, and may be purified by a hot slurry, for example at reflux temperature in an appropriate solvent, for example an ester such as ethyl acetate, an alcohol such as propan-2-ol, or a ketone such as acetone.
The paroxetine salt of compound (1) may also be prepared from paroxetine maleate (1:1) salt by heating in an appropriate solvent, preferably butan-2-ol. Compound (1) may be isolated from its paroxetine salt by acidification with 1 equivalent of acid, for example hydrochloric acid. Hence compound (1) may be prepared by addition of 1 molar equivalent of hydrogen chloride in propan-2-ol to a suspension of the paroxetine salt of compound (1) in propan-2-ol with or without heating, and isolated as the free acid by crystallisation from the reaction medium by the addition of water and acetone. Alternatively, compound (1) free acid may be prepared from the isolated paroxetine salt by treatment with 1 equivalent of hydrochloric acid in acetone followed by crystallisation from the medium.

Alternatively, neutralisation of the paroxetine salt of compound (1) with 1 molar equivalent of an acid such as hydrochloric acid followed by evaporation or lyophilisation, produces a solid mixture of the salt of paroxetine with the acid, for example paroxetine hydrochloride, and compound (1), and this two component pharmaceutical salt is also included within the scope of this invention.

Other salts of compound (1), for example mono sodium or mono lithium salts may be prepared by reaction of compound (1) with 1 equivalent of base, for example sodium or lithium hydroxide respectively.

Another class of salts of compound (1) may be formed by reaction with 2 equivalents of strong base, such as for example the disodium or dipotassium salt.

Paroxetine free base may be prepared according to the procedures generally outlined in US Patent No 4,007,196 and EP-B-0 223403. Maleic acid is commercially available.

Compound (1) and its salts of this invention are anticipated to be useful to treat and prevent the following disorders:

- Alcoholism
- Depression
- Panic Disorder
- Obesity
- Migraine
- Anorexia
- Pre-Menstrual Syndrome (PMS)
- Trichotillomania
- Anxiety
- Obsessive Compulsive Disorder
- Chronic Pain
- Senile Dementia
- Bulimia
- Social Phobia
- Adolescent Depression
- Dysthymia
Substance Abuse

These disorders are hereinafter referred to as "the Disorders".

Accordingly, the present invention further provides a method for treating and/or preventing any one or more of the Disorders by administering an effective and/or prophylactic amount of a compound of the invention to a sufferer in need thereof.

The present invention further provides a pharmaceutical composition for use in the treatment and/or prevention of any one or more of the Disorders which comprises an admixture of a compound of the invention with a pharmaceutically acceptable carrier.

The present invention also provides the use of a compound of the invention for treating and/or preventing any one or more of the Disorders.

The present invention also provides the use of a compound of the invention in the manufacture of a medicament for treating and/or preventing any one or more of the Disorders.

Most suitably the present invention is applied to the treatment of depression, OCD and panic.

Compositions containing a compound of this invention may be formulated for administration by any route, and examples are oral, sub-lingual, rectal, topical, parenteral, intravenous or intramuscular administration. Preparations may, if desired, be designed to give slow release of the paroxetine derivative or salt.

The medicaments may, for example, be in the form of tablets, capsules, sachets, vials, powders, granules, lozenges, reconstitutable powders, or liquid preparations, for example solutions or suspensions, or suppositories.

The composition is usually presented as a unit dose composition containing from 1 to 200mg of active ingredient calculated on a free base basis, more usually from 5 to 100mg, for example 10 to 50mg such as 10, 12.5, 15, 20, 25, 30 or 40mg by a human patient. Most preferably unit doses contain 20mg of active ingredient calculated on a free base basis. Such a composition is normally taken from 1 to 6 times daily, for example 2, 3 or 4 times daily so that the total amount of active agent administered is within the range 5 to 400mg
of active ingredient calculated on a free base basis. Most preferably the unit dose is taken once a day.

Preferred unit dosage forms include tablets or capsules.

The compositions of this invention may be formulated by conventional methods of admixture such as blending, filling and compressing.

Suitable carriers for use in this invention include a diluent, a binder, a disintegrant, a colouring agent, a flavouring agent and/or preservative. These agents may be utilised in conventional manner, for example in a manner similar to that already used for marketed anti-depressant agents.

Specific examples of pharmaceutical compositions include those described EP-B-0223403, and US 4,007,196 in which the products of the present invention may be used as the active ingredients.

The following Examples illustrate the invention.

**Example 1**

A mixture of paroxetine base and maleic acid (0.5 mole equivalents) in ethyl acetate (5 volumes) was stirred and heated to reflux to give a clear solution, then cooled to room temperature. The crystalline solid which formed was collected by filtration, washed with ethyl acetate and dried under vacuum to give 1-N-(3S,4R)-trans-(4'-fluorophenyl)-3-[3',4'-methylenedioxyethyl[phenoxyethyl] piperidinyl butandioic acid as the paroxetine salt.

**Example 2**

N-phenyloxy carbonyl paroxetine (5.0 kg), potassium hydroxide flake (4.5 kg) and toluene (75.0 litres) were heated to reflux under a nitrogen atmosphere. After stirring for 4 hours at reflux the contents of the reactor were allowed to cool to room temperature. Water (50 litres) was added and the mixture stirred for 30 minutes and then allowed to settle. The lower aqueous layer was drained from the reactor and the toluene layer heated to reflux and dried in a Dean and Stark apparatus. Toluene (10 litres) was added and approximately 10 litres of the solvent was removed by distillation. The remaining solution was cooled to
approximately 90-95°C and solid maleic acid (1.04 kg) was added with vigorous stirring. The temperature was held at 40°C for two hours to allow for the bulk of the crystallisation to occur, then the product was filtered and dried to give 1-N-(3S,4R)-trans-(4'-fluorophenyl)-3-[3',4'-methylenedioxyethylphenoxymethyl] piperidinyl butandioic acid (3.7 kg, approximately 30% pure).

A portion of this solid (340 g) was suspended in ethyl acetate (1.5 litres) and heated at reflux for 1 hour. The suspension was cooled slightly and the solid collected by filtration. The solid was washed with ethyl acetate and dried under vacuum to give 50.56g of pure 1-N-(3S,4R)-trans-(4'-fluorophenyl)-3-[3',4'-methylenedioxyethylphenoxymethyl] piperidinyl butandioic acid as the 1:1 paroxetine salt, as a white crystalline solid.

Characterisation:

IR (υmax cm⁻¹) 1608, 1512, 1376, 1298, 1234, 1181, 1143, 1106, 1033, 930, 831, 780, 721, 542.

MS (positive ion electrospray) 330 (M+H)⁺ (100%), 446 (M+H)⁺ (15%)
(negative ion electrospray) 889 (2M-H)⁺ (100%).

Melting point 185-191°C.

Example 3.
Preparation of 1-N-(3S,4R)-trans-(4-fluorophenyl)-3-[3,4-methylenedioxyethylmethylxoxymethyl] piperidinyl butandioic acid paroxetine salt.

Maleic acid (0.176 g) was added to a solution of paroxetine free base (0.5 g) in toluene at 90-95°C with rapid stirring. The reaction mixture was stirred at this temperature for 1 hour then cooled to 40-50°C and the crystalline product that formed isolated by filtration. The solid was re-suspended in hot ethyl acetate and stirred for 1 hour. The hot suspension was filtered to give the title compound as a white solid.

Example 4
Preparation of 1-N-(3S,4R)-trans-(4-fluorophenyl)-3-[3,4-methylenedioxyethylmethylxoxymethyl] piperidinyl butandioic acid.
A suspension of 1-N-(3S,4R)-trans-(4-fluorophenyl)-3-[3,4-methylenedioxy)methoxy)methyl] piperidinyl butandioic acid paroxetine salt (5.06 g) in propan-2-ol (50 ml) was treated with a solution of hydrogen chloride in propan-2-ol (6N, 1.3 ml). The reaction mixture was briefly heated to reflux to form a clear solution, then cooled to room temperature, diluted with acetone (5 ml) and then water (150 ml). The resulting cloudy solution was stirred and scratched to induce crystallisation. Filtration and drying gave the title compound as a white crystalline solid (1.43 g).

Characterisation:

MS (positive ion electrospray) 330 (M+H)+(90%), 446 (M+H)+(100%).
(negative ion electrospray) 444 (M-H)+(60%), 889 (2M-H)+(100%).

Example 5

A stirred suspension of 1-N-(3S,4R)-trans-(4-fluorophenyl)-3-[3,4-methylenedioxy)methoxy)methyl] piperidinyl butandioic acid 1:1 paroxetine salt (2.60 g) in acetone (50 ml) was treated with a solution of aqueous hydrochloric acid (0.5 ml, 5 molar) and the mixture was stirred vigorously at room temperature. Water (15 ml) was added to give a cloudy solution which was seeded with 1-N-(3S,4R)-trans-(4-fluorophenyl)-3-[3,4-methylenedioxy)methoxy)methyl] piperidinyl butandioic acid. Further stirring and scratching induced crystallisation of 1-N-(3S,4R)-trans-(4-fluorophenyl)-3-[3,4-methylenedioxy)methoxy)methyl] piperidinyl butandioic acid as a white crystalline solid (0.62 g).
CLAIMS

1. A compound of formula (1)

2. A compound of claim 1 in the form of an alkali metal salt, an amine salt or an acid addition salt.

3. A compound of claim 1 in the form of the paroxetine salt thereof.

4. A compound of claim 1 in the form of the hydrochloride salt thereof.

5. A solid blend of a compound according to any preceding claim and paroxetine hydrochloride.

6. A process for preparing a compound according to any preceding claim, which comprises reacting paroxetine in solution with maleic acid.

7. A process for preparing a blend of claim 5 which comprises treating a compound of claim 3 with hydrochloric acid.

8. A method of treating the Disorders which comprises administering to a patient in need thereof an effective amount of a compound according to any one of claims 1 to 5 or prepared using the process of claim 6 or 7.

9. A pharmaceutical composition for use in the treatment and/or prevention of any one or more of the Disorders which comprises a compound according to any one of claims 1 to
5 or prepared using the process of claim 6 or 7, together with a pharmaceutically acceptable carrier.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D405/12 A61P25/00 A61K31/205 A61K31/19

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

B. FIELDS SEARCHED

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

IPC 7 C07D A61P A61K

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

Electronic database consulted during the international search (name of data base and where practical, search terms used):

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>EP 0 188 081 A (FERROSAN AS) 23 July 1986 (1986-07-23) claim 1</td>
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Further documents are listed in the continuation of box C. Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance.

"E" earlier document but published on or after the international filing date.

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another invention, or similar special reason (as specified).

"O" document relating to an oral disclosure, use, exhibition or other means.

"P" document published prior to the international filing date but later than the priority date.

Date of the actual completion of the international search: 31 January 2000

Date of mailing of the international search report: 16/02/2000

Name and mailing address of the ISA:

European Patent Office, P. B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel: (+31-70) 340-2040, Tx: 31 051 epo nl, Fax: (+31-70) 340-3016

Authorized officer: Bader, K.

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| P, X     | WO 98 56787 A (SYNTCHON B V)  
17 December 1998 (1998-12-17)  
see the claims  
page 7, line 10 - 1 line 15  
page 17, line 10; table 6 | 1,6-9 |
| P, X     | WO 99 52901 A (MAN JOHN; JACEWICZ VICTOR  
WITOLD (GB); JONES ALAN DAVID (GB); SMIT)  
21 October 1999 (1999-10-21)  
page 7, line 25 - page 14, line 9 | 1,6-9 |
| P, X     | WO 99 40084 A (CROWE DAVID; KEEFFE DEIRDRE  
O (GB); SMITHKLINE BEECHAM PLC (GB); U)  
12 August 1999 (1999-08-12)  
page 4, line 15 - 1 line 26 | 1,6-9 |
## INTERNATIONAL SEARCH REPORT

**Box I** Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

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

1. **X** Claims Nos.;
   - because they relate to subject matter not required to be searched by this Authority, namely:
     - **Remark:** Although claim(s) 8 is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

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

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

**Box II** Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

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

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

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

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

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

**Remark on Protest**

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

Form PCT/ISA/210 (continuation of first sheet (1)) (July 1998)
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