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COMPOSES 4-PHENYLPIPERIDINE

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WO-A-96/24595

- **BUXTON P C ET AL: "Solid-state forms of paroxetine hydrochloride" INT. J. PHARM. (IJPHDE,03785173);88; VOL.42 (1-3); PP.135-43, BEECHAM PHARM.;BIOSCI. RES. CENT.; EPSOM SURREY; KT18 5XQ; UK (GB), XP000572028 cited in the application**

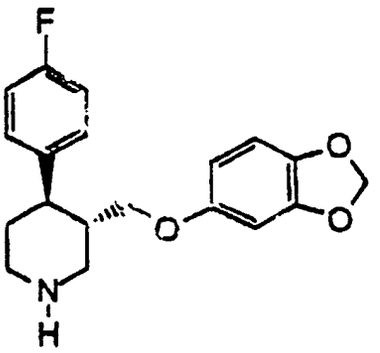
Remarks:
The file contains technical information submitted after the application was filed and not included in this specification

EP 0 994 872 B9

Description

[0001] The present invention relates to a group of tri-substituted, 4-phenylpiperidines, to a process for preparing such compounds, to a medicament comprising such compounds, and to the use of such compounds for the manufacture of a medicament.

[0002] The compound paroxetine, trans-4-(4'-fluorophenyl)-3-(3',4'-methylene dioxyphenoxymethyl)piperidine having the formula below:



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

[0003] Paroxetine has been used as a therapeutic agent in the form of a salt with pharmaceutically acceptable acids. The first clinical trials were conducted with the acetate salt.

[0004] A known useful salt of paroxetine is the hydrochloride. This salt is considered to be the active substance in several marketed pharmaceutical products, e.g. Paxil or Seroxat. A number of forms of paroxetine hydrochloride have been described:

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

[0005] The comparison of behaviour between anhydrous and hydrated form of paroxetine hydrochloride is described in the Intl. Journal of Pharmaceutics, 42, 135-143 (1988).

[0006] EP 223403 discloses paroxetine hydrochloride hemihydrate and pharmaceutical compositions based thereon.

[0007] Most of these known salts of paroxetine have unsuitable physico-chemical characteristics for ensuring safe and efficient handling during production thereof and formulation into final forms, since they are unstable (acetate, maleate) and possess undesirable hygroscopicity.

[0008] Furthermore their formation by crystallization from both aqueous or non-aqueous solvents is generally low-yielded and troublesome as they usually contain an undefined and unpredicted amount of bound solvent which is difficult to remove.

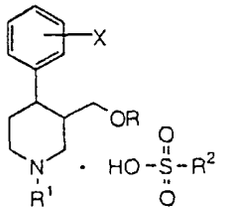
[0009] The crystalline paroxetine hydrochloride hemihydrate approaches these problems, but as stated in WO 95/16448, its limited photostability causes undesired colouration during classical wet tabletting procedure.

[0010] Moreover, crystalline paroxetine hydrochloride hemihydrate exhibits only limited solubility in water.

[0011] It has been generally suggested that where the aqueous solubility is low, for example less than 3 mg/ml, the dissolution rate at in vivo administration could be rate-limiting in the absorption process. The aqueous solubility of the paroxetine hemihydrate at room temperature exceeds this threshold by a relatively small margin.

[0012] An object of the present invention is to provide a compound with improved characteristics.

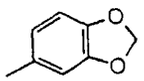
[0013] According to a first aspect, the present invention comprises a compound, and pharmaceutically acceptable salts, having the formula I:



- R represents an alkyl or alkynyl group having 1-4 carbon atoms, or a phenyl group optionally substituted by C_{1-4} alkyl, alkylthio, alkoxy, halogen, nitro, acylamino, methylsulfonyl or methylenedioxy, or represents tetrahydronaphthyl,
- R^1 represents hydrogen, trifluoro (C_{1-4}) alkyl, alkyl or alkynyl,
- X represents hydrogen, alkyl having 1-4 carbon atoms, alkoxy, trifluoroalkyl, hydroxy, halogen, methylthio or aralkoxy,
- R^2 represents:
  - a C1-C10 alkyl group,
  - a phenyl group optionally substituted by one or more of the following groups:
    - a C1-C10 alkyl group,
    - a halogen group,
    - a nitro group,
    - hydroxy group,
    - and/or an alkoxy group.

[0014] The inventors have found that these compounds exhibit good stability and very high solubility. This yields the advantage that high concentrations of the compound are obtainable in small volumes.

[0015] The R group is preferably the 3,4 methylenedioxyphenyl group of the formula:

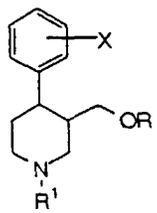


[0016] The X group is preferably a fluorine group attached to position 4 in the phenyl ring.

[0017] The R^2 group preferably represents a C1-C4 alkyl group, and most preferably represents a C1-C2 alkyl group in order to provide an optimum solubility.

[0018] The compounds can have a solubility at about 20°C of at least about 10 mg/ml water, preferably having a solubility in water of at least 100, for example 500 and most preferably of at least 1000 mg/ml water.

[0019] According to a second aspect of the present invention, there is provided a process for preparing a compound as above, comprising the steps of mixing together a 4 phenylpiperidine compound, a salt and/or a base thereof having the formula II:



wherein:

- R represents an alkyl or alkynyl group having 1-4 carbon atoms, or a phenyl group optionally substituted by C_{1-4} alkyl, alkylthio, alkoxy, halogen, nitro, acylamino, methylsulfonyl or methylenedioxy, or represents tetrahydronaphthyl,
- R_1 represents hydrogen, trifluoro (C_{1-4}) alkyl, alkyl or alkynyl,
- X represents hydrogen, alkyl having 1-4 carbon atoms, alkoxy, trifluoroalkyl, hydroxy, halogen, methylthio or aralkoxy,

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

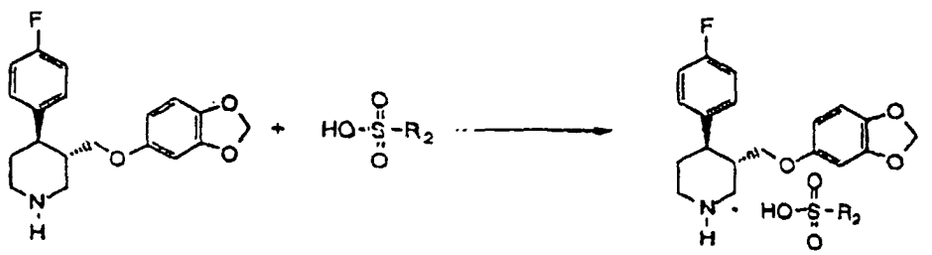
- a C1-C10 alkyl group,
- a phenyl group optionally substituted by one or more of the following groups:

- a C1-C10 alkyl group,
- a halogen group,
- a nitro group,
- a hydroxy group, and/or
- an alkoxy group,

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

[0020] The compounds of the invention can be prepared from the free base of the 4 phenylpiperidine, having the formula II, this preferably being paroxetine, by treatment with a sulfonic acid as defined above in a suitable solvent to form a solution of the desired acid addition salt, whereafter this is precipitated out of the solution.

[0021] The equation for paroxetine free base and sulfonic acids is as follows:

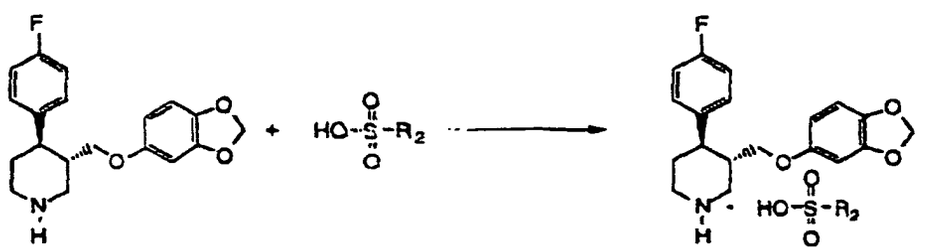


[0022] The forming of a solution may preferably proceed at temperatures from about 0°C to the boiling point of the solvent.

[0023] Optionally, the solution may be purified by treatment of activated charcoal, silica gel, kieselguhr or other suitable materials.

[0024] Alternatively, the solution of a salt of the invention can be formed by dissolution of a salt of 4 phenyl piperidine having the formula II with an organic sulfonic acid.

[0025] For example the compounds of the invention may be prepared from a paroxetine C1-C5 carboxylate, such as the acetate, by addition of corresponding organic sulfonic acid to the solution of the said carboxylate, as follows:

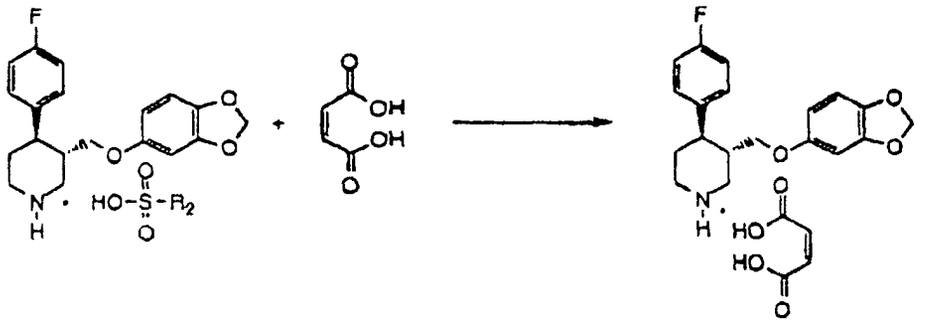


[0026] According to a third aspect of the present invention, there is provided a compound obtainable by this process.

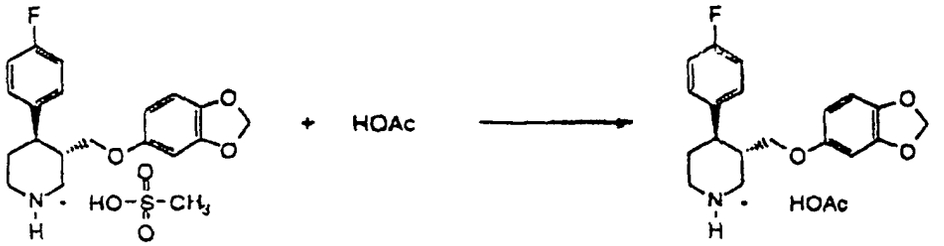
[0027] According to a fourth aspect of the present invention there is provided the above compound for use as a medicament and, according to a fifth aspect, a medicament comprising this compound, and to the use thereof for treating depressions, obsessive compulsive disorders, panic disorders, bulimia, anorexia, pain, obesity, senile demential, migraine, anorexia, social phobia, depressions arising from pre-menstrual tension.

[0028] According to another aspect of the present invention, there is provided the use of a compound according to any of the claims 1-8 and 11 for the manufacture of a medicament for treating depressions, obsessive compulsive disorders, panic disorders, bulimia, anorexia, pain, obesity, senile dementia, migraine, anorexia, social phobia, depressions arising from pre-menstrual tension.

[0029] According to another aspect of the present invention, there is provided the use of a compound of the invention as a reagent in further syntheses. More specifically, the compounds of the present invention can be used as a start reagent for forming further acid addition salts, for example for providing further paroxetine acid addition salts, by reacting with a suitable reagent, i.e. with a corresponding acid. For example, the formation of paroxetine maleate according to the present invention proceeds by the following equation:

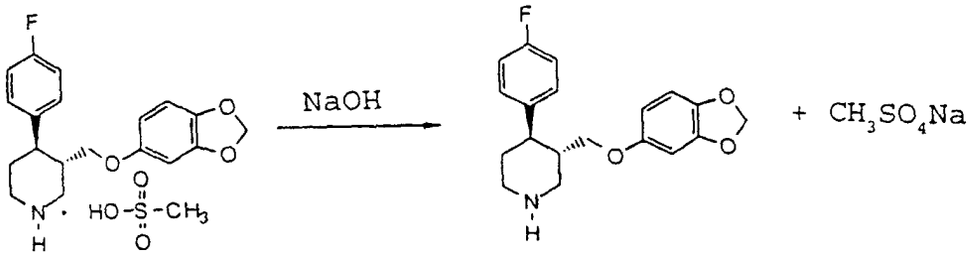


and the formation of paroxetine acetate proceeds as follows:



[0030] This is an advantageous route, since by using the substantially pure sulfonic acid salts according to the present invention as a start reagent, the preparation of a further salt, as above, results in this further salt having a high purity. The inventors have shown that such salts have a surprisingly high purity.

[0031] Similarly, the compounds of the present invention can react with a base, such as an inorganic and/or an organic base, to form (liberate) free bases of the corresponding compounds. As exemplified on paroxetine, the reaction proceeds according to the equation:



[0032] The free bases liberated from the compounds of the present invention have surprisingly higher purity than if prepared by known methods which is especially important in case of their use for production of pharmaceuticals.

[0033] Accordingly, the new compounds of the first aspect of the invention can also form hydrates and/or solvates by a contact with a corresponding reaction partner, i.e. with water and/or with a solvent. Examples of such further salts, hydrates and solvates, for example these of paroxetine, are the:

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

[0034] The inventors have shown that such salts have a surprisingly high purity.

[0035] Examples of bases which can be employed in the preparation of the free bases are: sodium hydroxide, potassium hydroxide, calcium hydroxide, ammonium hydroxide, sodium carbonate, methylamine, dimethylamine, triethylamine, pyridine and such like.

[0036] Since the compounds according to the present invention exhibit high solubility, they can be dosed, for example injected, in a high concentration, low volume solution, this method of dosing being particularly advantageous with certain patients, such as manic depressives and such like, i.e. patients who are unable or unwilling to swallow medicine.

[0037] The compounds of the present invention can be formulated into various types of pharmaceutical compositions for treatment of humans and animals. Pharmaceutical compositions according to the present invention comprise a compound of the invention alone or together with a pharmaceutically acceptable carrier or diluent. The preferred formulations are those for oral administration (tablets, capsules) but formulations for parenteral or topical administration are also within the scope of the invention. The high water solubility of the compounds of the invention enables high dissolution rates in solid dosage forms based on the compounds of the invention to be obtained, during the in vitro release as well as good bioavailability after peroral application in vivo.

[0038] The tablets containing compounds of the present invention can be prepared both by tabletting procedure in which water is present (e.g. aqueous granulation) as well as by tabletting processing it which water is absent (direct compression, dry granulation) and may be coated by any suitable means of coating.

[0039] The present invention will now be further elucidated by way of the following examples and results.

EXPERIMENTAL

[0040] A seeding crystal of paroxetine methane sulfonate was made as follows:

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

[0041] This seeding crystal was subsequently used in following examples 1 and 3.

Examples

Example 1

Paroxetine methane sulfonate from paroxetine

[0042] To a solution of 43.5 g (132 mmol) of paroxetine, prepared by the procedure disclosed in US 4007196,

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

[0043] Analytical characterization of the compound obtained is shown in Table 1. The purity of the compound obtained was 98% (HPLC) .

Example 2

Paroxetine benzene sulfonate from paroxetine

[0044]

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

[0045] Analytical characterization of the compound obtained is shown in Table 1. The purity of the compound obtained was 99.4% (HPLC) .

Example 3

Paroxetine p-toluene sulfonate from paroxetine

[0046]

5.0 g	(15 mmol) of paroxetine was dissolved in
25 ml	of hot ethylacetate.
2.9 g	(15 mmol) of p-toluenesulfonic acid was added. The mixture was left at room temperature for 2 h and subsequently put in the freezer, with a seeding crystal, for 14 h. The solid was filtered off and washed once with
10 ml	of n-hexane. The obtained white solid was dried overnight in a vacuumoven.
4.8 g	(10 mmol) of a white solid was obtained.
	Yield 67%

[0047] Analytical characterization of the compound obtained is shown in Table 1. The purity of the compound obtained was 99.4% (HPLC) .

Example 4

Paroxetine p-chlorobenzene sulfonate from paroxetine

[0048]

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

[0049] Analytical characterization of the compound obtained is shown in Table 1. The purity of the compound obtained was 99.4% (HPLC) .

Example 5

Paroxetine maleate from paroxetine methane sulfonate

[0050]

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

[0051] The purity of the compound obtained was 99.5% (HPLC).

Example 6

Paroxetine acetate from paroxetine methane sulfonate

[0052]

1.0 g	(2.4 mmol) of paroxetine methane sulfonate in
5 ml	of hot iso-propanol. To this solution was added
0.2 g	(3.2 mmol) of acetic acid. The mixture was placed at 4°C overnight after which a solid was precipitated. The solid was filtered off and washed 3 times with
10 ml	of ether and dried in a vacuumoven.
0.5 g	(1.3 mmol) off white crystals were obtained
	Yield 54%
	The purity of the compound obtained was 99.5% (HPLC).

Example 7

Paroxetine free base from paroxetine methane sulfonate

[0053]

10.0 g	(24.0 mmol) of paroxetine methane sulfonate in

(continued)

150 ml	of water and
200 ml	of ethyl acetate. To this was added
12.4 g	(31 mmol) of an aqueous 10 wt% NaOH solution and the suspension was stirred for 15 minutes. The layers were separated and the aqueous layer was extracted once with
50 ml	of ethyl acetate. The combined organic layers are washed once with
100 ml	of water and dried over Na_2SO_4. The Na_2SO_4 was filtered off and washed once with
50 ml	of ethyl acetate. The ethyl acetate was evaporated off, leaving
7.5 g	(22.8 mmol) of an oily product.
	Yield 95%
	The purity of the compound obtained was 99.5% (HPLC).

[0054] A number of the compounds obtained were analysed, the results being shown in tables 1-5 below:

Table 1
Characterization of salts of paroxetine with certain organic sulfonic acids $R\text{-}SO_3H$

R = CH_3 - (paroxetine methane sulfonate):
m.p.: 142°-144°C.
DSC curve (closed pan, 10°C/min): onset 145.8°C, 79.0 J/g.
IR spectrum (KBr, in cm^{-1}): 531, 546, 777, 838, 931, 962, 1038, 1100, 1169, 1208, 1469, 1500, 1515, 1615, 2577, 2869, 2900, 3023.
1H-NMR (ppm): 1.99 (br d, H_{5eq}, 1H); 2.27 (ddd, H_{5ax}, 1H); 2.48-2.65 (m, H_3, 1H); 2.82-2.92 (m, H_4 , CH_3, 4H); 2.95-3.20 (m, H_{2ax}, H_{6ax}, 2H); 3.47 (dd , H_7, 1H); 3.58-3.74 (m, H_{2eq}, H_{6eq}, H_7, 3H); 5.88 (s, $H_{7''}$, 2H); 6.10 (dd, $H_{6''}$, 1H); 6.33 (d, $H_{2''}$, 1H); 6.61 (d, $H_{5''}$, 1H); 7.09 (dd, $H_{3'}$, $H_{5'}$, 2H); 7.22 (dd , $H_{2'}$, $H_{6'}$, 2H); 8.85 (br d, NH_{eq}, 1H); 9.11 (br d, NH_{ax}, 1H).
13C-NMR (ppm): 30.0 (s, C_5); 39.3 (s, C_3); 39.5 (s, C_4); 41.7 (s, SC); 44.6 (s, C_6); 46.8 (s, C_2); 67.4 (s, C_7); 97.8 (s, $C_{2''}$); 101.2 (s, $C_{7''}$); 105.4 (s, $C_{6''}$); 107.8 (s, $C_{5''}$); 115.8 (d, $C_{3'}$, $C_{5'}$); 128.4 (s, $C_{6'}$, $C_{2'}$); 137.1 (s, $C_{4''}$); 142.0 (s, $C_{1'}$); 148.2 (s, $C_{3''}$); 153.7 (s, $C_{1''}$); 161.9 (d, $C_{4'}$).

R = C_6H_5- *(paroxetine benzene sulfonate):*
m.p.: 55°-60°C.
IR spectrum (KBr, in cm^{-1}): 530, 564, 614, 689, 728, 764, 828, 929, 993, 1007, 1029, 1121, 1179, 1229, 1443, 1471, 1486, 1514, 1600, 1628, 2557, 2842, 3029.
1H-NMR (ppm): 1.90 (br d, H_{5eq}, 1H); 2.10-2.28 (m , H_{5ax}, 1H); 2.38-2.52 (m, H_3, 1H); 2.82 (ddd, H_4, 1H); 3.02-3.18 (m, H_{2ax}, H_{6ax}, 2H); 3.37 (dd, H_7, 1H); 3.48 (d, H_7, 1H); 3.60-3.82 (m, H_{2eq}, H_{6eq}, 2H); 5.87 (s, $H_{7''}$, 2H); 6.06 (dd, $H_{6''}$, 1H); 6.29 (d, $H_{2''}$, 1H); 6.60 (d, $H_{5''}$, 1H); 6.90 (dd, $H_{3'}$, $H_{5'}$, 2H); 7.04 (dd, $H_{2'}$, $H_{6'}$, 2H); 7.40 (d, *ArH*, 3H); 7.94 (d, *SArH*, 2H); 8.81 (br d, NH_{eq}, 1H); 9.04 (br d, NH_{ax} 1H).
13C-NMR (ppm): 29.9 (s, C_5); 39.2 (s, C_3); 41.5 (s, C_4); 44.8 (s, C_6); 47.0 (s, C_2); 67.3 (s, C_7); 97.9 (s, $C_{2''}$); 101.2 (s, $C_{7''}$); 105.5 (s, $C_{6''}$) 107.8 (s, $C_{5''}$); 115.7 (d, $C_{3'}$, $C_{5'}$); 125.9 (s, C_b); 128.6 (s, C_d); 128.8 (s, $C_{6'}$, $C_{2'}$); 130.6 (s, $C_{c\pi}$); 137.1 (s, $C_{4''}$); 141.9 (s, $C_{1'}$); 144.1 (s, C_a); 148.2 (s, $C_{3''}$); 153.7 (s, $C_{1''}$); 161.8 (s, $C_{4'}$).

R = *p-$CH_3C_6H_4$ (paroxetine p-toluene sulfonate):*
m.p.: 148°-150°C.
DSC curve (closed pan, 10°C/min): onset 151.6°C, 71.6 J/g.
IR spectrum (KBr, in cm^{-1}): 529, 557, 671, 771, 800, 814, 921, 936, 1000, 1029, 1100, 1157, 1186, 1229, 1471, 1486, 1507, 1600, 2557, 2829, 3029.
1H-NMR (ppm): 1.89 (br d, H_{5eq}, 1H); 2.10-2.50 (m, H_{5ax}, H_3, CH_3, 5H); 2.82 (ddd, H_4, 1H); 2.97-3.18 (m, H_{2ax}, H_{6ax}, 2H); 3.36 (dd, H_7, 1H); 3.48 (dd, H_7, 1H); 3.52-3.77 (m, H_{2eq}, H_{6eq}, 2H); 5.87 (s, $H_{7''}$, 2H); 6.06 (dd, $H_{6''}$,1H); 6.28

Table 1 (continued) Characterization of salts of paroxetine with certain organic sulfonic acids R-SO_3H
(d, $H_{2''}$, 1H); 6.59 (d, $H_{5''}$, 1H); 6.90 (dd, $H_{3'}$, $H_{5'}$, 2H); 7.05 (dd, $H_{2''}$, $H_{6'}$, 2H); 7.24 (d, CH_3ArH, 2H); 7.83 (d, $SArH$, 2H); 8.91 (br d, NH_{eq}, 1H); 9.17 (br d, NH_{ax}, 1H). 13C-NMR (ppm): 21.3 (s, C_e); 29.9 (s, C_5); 39.2 (s, C_3); 41.5 (s, C_4); 44.7 (s, C_6); 46.9 (s, C_2); 67.3 (s, C_7); 97.8 (s, $C_{2''}$); 101.1 (s, $C_{7''}$); 105.5 (s, $C_{6''}$); 107.8 (s, $C_{5''}$); 115.6 (d, $C_{3'}$, $C_{5'}$); 125.8 (s, C_b); 129.0 (s, $C_{6'}$, $C_{2'}$); 129.1 (s, C_c); 137.2 (s, $C_{4''}$); 140.8 (s, C_d); 141.5 (s, C_a); 141.9 (s, $C_{1'}$); 148.2 (s, $C_{3''}$); 153.8 (s, $C_{1''}$); 161.8 (d, $C_{4'}$).
R = *p-ClC_6H_4 (paroxetine p-chlorobenzene sulfonate)*; m.p.: 75°-80°C. IR spectrum (KBr, in cm^{-1}): 486, 557, 643, 736, 821, 1000, 1029, 1086, 1114, 1186,1229, 1471, 1486, 1514, 1600, 1657, 2857, 3029. 1H-NMR (ppm): 1.91 (br d, H_{5eq}, 1H); 2.15 (ddd, H_{5ax}, 1H); 2.37-2.52 (m, H_3, 1H); 2.81 (ddd, H_4, 1H); 2.93-3.21 (m, H_{2ax}, H_{6ax}, 2H); 3.37 (dd, H_7, 1H); 3.49 (d, H_7, 1H); 3.61-3.81 (m, H_{2eq}, H_{6eq}, 2H); 5.88 (s, $H_{7''}$, 2H); 6.05 (dd, $H_{6''}$, 1H); 6.27 (d, $H_{2''}$, 1H); 6.59 (d, $H_{5''}$, 1H); 6.91 (dd, $H_{3'}$, $H_{5'}$, 2H); 7.03 (dd, $H_{2'}$, $H_{6'}$, 2H); 7.39 (d, $ClArH$, 2H); 7.86 (d, $SArH$, 2H); 8.78 (br d, NH_{eq}, 1H); 9.02 (br d, NH_{ax}, 1H). 13C-NMR (ppm): 30.0 (s, C_5); 39.3 (s, C_3); 41.5 (s, C_4); 44.9 (s, C_6); 47.1 (s, C_2); 67.3 (s, C_7); 97.9 (s, $C_{2''}$); 101.2 (s, $C_{7''}$); 105.5 (s, $C_{6''}$); 107.9 (s, $C_{5''}$); 115.8 (d, $C_{3'}$, $C_{5'}$); 127.6 (s, C_b); 128.8 (s, $C_{6'}$, $C_{2'}$); 132.0 (s, C_d); 137.0 (s, C_c); 137.2 (s, $C_{4''}$); 141.8 (s, $C_{1'}$); 142.0 (s, C_a); 148.2 (s, $C_{3''}$); 153.6 (s, $C_{1''}$); 161.8 (d, $C_{4'}$).

[0055] The compounds of the invention are crystalline, with defined melting points, DSC curves and IR spectra. It cannot be excluded that, under different conditions of their formation and under specific conditions, they could exist also in other crystalline or polymorph modifications which may differ from those as described herein. The compounds of the invention are also generally very stable and non-hygroscopic.

[0056] It should be understood that the present invention comprising acid addition salts with organic sulfonic acids are substantially free of the bound organic solvent. Preferably, the amount of bound organic solvent should be less than 2.0% (w/w) as calculated on the anhydrous basis. They nevertheless may contain crystallization water and also unbound water, that is to say water which is other than water of crystallization.

[0057] In the following cables 2 and 3, examples of results of hygroscopicity tests and stability tests (in comparison with known salts of paroxetine) are presented.

Table 2

Hygroscopicity of certain salts of paroxetine (40°C, 75 % rel.hum).		
water content (in %) at	t = 0	t = 4 weeks
methane sulfonate	0.35	+ 0.04
p-toluene sulfonate	0.70	< 0.02
hydrochloride	-	+ 2.5

Table 3

Solubility of paroxetine salts in water (in mg/ml)		
	20°C	50°C
methane sulfonate	> 1000/10 min	1300
p-toluene sulfonate	> 1000	> 1000
hydrochloride hemihydrate	4.9	12.6
hydrochloride anhydrate	8.2	24.2

Table 4

Stability of paroxetine salts by HPLC (total amount of degradation in %).		
	degradation 20°C	80°C
methane sulfonate	not observed	< 0.2 %, 3 months
p-toluene sulfonate	not observed	< 0.2 %, 3 months
maleate	0.2 %, 12 months	> 50 %, 5 days

Table 5

Solubility of salts of paroxetine in nonaqueous solvents (in mg/ml)			
		methane sulfonate	p-toluene sulfonate
Ethanol	20°C	36	50
	78°C	250	> 500
2-Propanol	20°C	7	14
	82°C	330	> 500
Acetone	20°C	5	16
	56°C	37	125
Ethyl acetate	20°C	2	22
	77°C	25	> 500
n-Hexane	20°C	<0.05	<0.05
	69°C	0.05	<0.05

[0058] Examples of analytical data of the paroxetine salts and the free base prepared in Examples 5 to 7 are given in Table 6.

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

[0059] It will be clear that the invention is not limited to the above description, but is rather determined by the following claims.

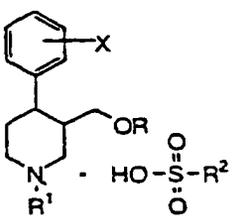
Reference

[0060]

- Psychopharmacology, 57, 151-153 (1978)]; ibid. 68, 229-233 (1980), European Journal of Pharmacology, 47, 351-358 (1978)]; in USP 4007196, the preparation of paroxetine maleate is reported.

Claims

1. A compound, and pharmaceutically acceptable salts, having the formula I:

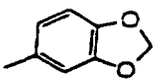


wherein:

- R represents a 3'4'-methylene-dioxyphenyl group,
- R^1 represents hydrogen, trifluoro (C_{1-4}) alkyl, alkyl or alkynyl,
- X represents hydrogen, alkyl having 1-4 carbon atoms, alkoxy, trifluoroalkyl, hydroxy, halogen, methylthio or aralkoxy,
- R^2 represents:
  - a C1-C10 alkyl group,
  - a phenyl group optionally substituted by one or more of the following groups:
    - a C1-C10 alkyl group,
    - a halogen group,
    - a nitro group,
    - hydroxy group,
    - and/or an alkoxy group,

wherein the alkyl or alkynyl groups for R^1, and the alkoxy groups for X and/or R^2 are such that the compound exhibits good stability and very high solubility.

2. Compound according to claim 1, wherein the R group is the 3,4-methylene-dioxyphenyl group of the formula:



and R^1 represents hydrogen.

3. Compound according to claim 1 or 2, wherein the X group is preferably a fluorine group attached to position 4 in the phenyl ring.

4. Compound according to claim 1-3, wherein the R^2 group represents a C1-C4 alkyl group.

5. Compound according to claims 1-4, wherein the R^2 group is a C1-C2 alkyl group.

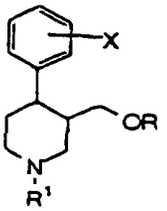
6. Compound according to any of the previous claims, having a solubility at about 20°C of at least about 10 mg per ml water.

7. Compound according to claim 6, having a solubility in water of at least 100, preferably at least 500 and most preferably of at least 1000 mg per ml.

8. Compound according to any of the preceding claims being selected from the group consisting essentially of:

- paroxetine methane sulfonate (formula I) wherein X is fluorine in the P-position, R is 3'4'-methylene-dioxyphenyl, R^1 is hydrogen and R^2 is methyl;
- paroxetine benzene sulfonate (formula I), wherein X is fluorine in the P-position, R is 3'4'-methylene-dioxyphenyl, R^1 is hydrogen, and R^2 is phenyl;
- paroxetine p-toluene sulfonate (formula I), wherein X is fluorine in the P-position, R is 3'4'-methylene-dioxyphenyl, R^1 is hydrogen and R^2 is methyl phenyl;
- paroxetine p-chlorobenzene sulfonate (formula I) wherein X is fluorine in the P-position, R is 3'4'-methylene-dioxyphenyl, R^1 is hydrogen and R^2 is chlorophenyl.

9. Process for preparing a compound according to any of the previous claims, comprising the steps of contacting together a compound, a salt and/or a base thereof, having the formula II:



wherein:

- R represents a 3'4'-methylene-dioxyphenyl group, - R^1 represents hydrogen, trifluoro (C_{1-4}) alkyl, alkyl or alkynyl,
- X represents hydrogen, alkyl having 1-4 carbon atoms, alkoxy, trifluoroalkyl, hydroxy, halogen, methylthio or aralkoxy, with a sulfonic acid of the general formula R^2-SO_3H, wherein R^2 represents:

  - a C1-C10 alkyl group,
  - a phenyl group optionally substituted by one or more of the following groups:

    - a C1-C10 alkyl group,
    - a halogen group,
    - a nitro group,
    - hydroxy group,
    - and/or an alkoxy group,

  to form a solution, whereafter the solid formed may be separated out.

10. Process for providing a compound according to any of the claims 1-8 in the form of a solvate, comprising the steps of contacting together a compound according to any of the claims 1-8 with a reagent selected from the group consisting essentially of:

water
methanol
ethanol.

11. Compound according to any of the claims 1-8 or a solvate thereof obtainable by the process according to claims 9 or 10.

12. Compound according to any of the claims 1-8 and 11, for use as a medicament.

13. Medicament comprising a compound according to any of the claims 1-8, 11, 12 and pharmaceutically acceptable carriers and/or diluents.

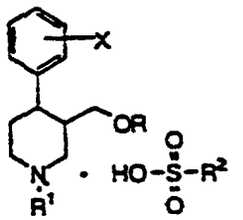
14. Medicament according to claim 13 in the form of a tablet, coated tablet or capsule.

15. Use of a compound according to any of the claims 1-8, 11, 12 for preparing a medicament.

16. Use of a compound according to any of the claims 1-8 and 11 for the manufacture of a medicament for treating depressions, obsessive compulsive disorders, panic disorders, bulimia, anorexia, pain, obesity, senile dementia, migraine, anorexia, social phobia, depressions arising from pre-menstrual tension.

Patentansprüche

1. Verbindung gemäß der Strukturformel I

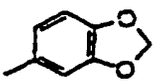


sowie deren pharmazeutisch annehmbaren Salze, wobei:

- R für eine 3'4'-Methylendioxyphenylgruppe steht,
- R^1 für Wasserstoff, Trifluoro-(C_{1-4})-alkyl, Alkyl oder Alkinyl steht,
- X für Wasserstoff, Alkyl mit 1-4 Kohlenstoffatomen, Alkoxy, Trifluoroalkyl, Hydroxy, Halogen, Methylthio oder Aralkoxy steht,
- R^2 für folgende steht:
  - eine C1-C10-Alkylgruppe,
  - eine Phenylgruppe gegebenenfalls substituiert durch mindestens eine der folgenden Gruppen:
    - eine C1-C10-Alkylgruppe,
    - eine Halogengruppe,
    - eine Nitrogruppe,
    - eine Hydroxygruppe,
    - und/oder eine Alkoxygruppe,

  wobei die für R^1 stehenden Alkyl- oder Alkinylgruppen und die für X und/oder R^2 stehenden Alkoxygruppen derart sind, daß die Verbindung eine gute Stabilität und eine sehr hohe Löslichkeit zeigt.

2. Verbindung gemäß Anspruch 1, wobei die R-Gruppe die 3,4-Methylendioxyphenylgruppe der Strukturformel



ist und R^1 für Wasserstoff steht.

3. Verbindung gemäß Anspruch 1 oder 2, wobei die X-Gruppe bevorzugt eine Fluor-Gruppe in 4-Position des Phenylrings ist.

4. Verbindung gemäß Anspruch 1-3, wobei die R^2-Gruppe eine C1-C4-Alkylgruppe ist.

5. Verbindung gemäß Ansprüchen 1-4, wobei die R^2-Gruppe eine C1-C2-Alkylgruppe ist.

6. Verbindung gemäß einem der vorstehenden Ansprüche, mit einer Löslichkeit bei ca. 20 °C von mindestens ca. 10 mg pro ml Wasser.

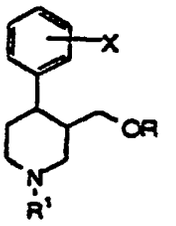
7. Verbindung gemäß Anspruch 6, mit einer Löslichkeit in Wasser von mindestens 100 vorzugsweise mindestens 500 und meist bevorzugt mindestens 1000 mg pro ml.

8. Verbindung gemäß einem der vorstehenden Ansprüche, ausgewählt aus der Gruppe, die im wesentlichen besteht aus:

- Paroxetinmethansulfonat (Strukturformel I), wobei X Fluor in p-Position ist, R 3'4'-Methylendioxyphenyl ist, R^1 Wasserstoff ist und R^2 Methyl ist;

- Paroxetinbenzolsulfonat (Strukturformel I), wobei X Fluor in der p-Position ist, R 3'4'-Methylendioxyphenyl ist, R^1 Wasserstoff ist und R^2 Phenyl ist;
- Paroxetin-p-toluolsulfonat (Strukturformel I), wobei X Fluor in der p-Position ist, R 3'4'-Methylendioxyphenyl ist, R^1 Wasserstoff ist und R^2 Methylphenyl ist;
- Paroxetin-p-chlorbenzolsulfonat (Strukturformel I), wobei X Fluor in der p-Position ist, R 3'4'-Methylendioxyphenyl ist, R^1 Wasserstoff ist und R^2 Chlorphenyl ist.

9. Verfahren zur Herstellung einer Verbindung gemäß einem der vorstehenden Ansprüche, umfassend das Inkontaktbringen einer Verbindung mit der Strukturformel II



oder eines Salzes und/oder einer Base davon, wobei

- R für eine 3'4'-Methylendioxyphenylgruppe steht,
- R^1 für Wasserstoff, Trifluoro-(C_{1-4})-alkyl, Alkyl oder Alkinyl steht,
- X für Wasserstoff, Alkyl mit 1-4 Kohlenstoffatomen, Alkoxy, Trifluoroalkyl, Hydroxy, Halogen, Methylthio oder Aralkoxy steht,

mit einer Sulfonsäure der allgemeinen Formel R^2-SO_3H, wobei R^2 folgende Bedeutung hat:

- eine C1-C10-Alkylgruppe,
- eine Phenylgruppe, gegebenenfalls substituiert durch mindestens eine der folgenden Gruppen:
  - eine C1-C10-Alkylgruppe,
  - eine Halogengruppe,
  - eine Nitrogruppe,
  - eine Hydroxygruppe,
  - und/oder eine Alkoxygruppe,

um eine Lösung zu bilden, wonach der gebildete Feststoff abgetrennt werden kann.

10. Verfahren zur Herstellung einer Verbindung gemäß einem der Ansprüche 1-8 in Form eines Solvats, umfassend die Schritte des Inkontaktbringens einer Verbindung gemäß einem der Ansprüche 1-8 mit einem Reagenz ausgewählt aus der Gruppe bestehend aus: Wasser, Methanol, Ethanol.

11. Verbindung gemäß einem der Ansprüche 1-8 oder ein Solvat davon, herstellbar durch das Verfahren gemäß Anspruch 9 oder 10.

12. Verbindung gemäß einem der Ansprüche 1-8 und 11 zur Verwendung als Arzneimittel.

13. Arzneimittel umfassend eine Verbindung gemäß einem der Ansprüche 1-8, 11, 12 und pharmazeutisch annehmbare Trägerstoffe und/oder Füllstoffe.

14. Arzneimittel gemäß Anspruch 13 in Form einer Tablette, einer beschichteten Tablette oder einer Kapsel.

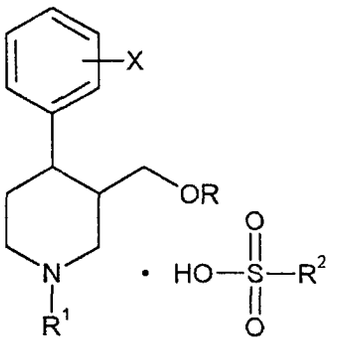
15. Verwendung einer Verbindung gemäß einem der Ansprüche 1-8, 11, 12 zur Herstellung eines Arzneimittels.

16. Verwendung einer Verbindung gemäß einem der Ansprüche 1-8 und 11 für die Herstellung eines Arzneimittels zur Behandlung von Depressionen, Zwangsneurosen, Panikerkrankungen, Bulimie, Anorexie, Schmerz, Fettsucht,

Altersdemenz, Migräne, Anorexie, sozialer Phobien sowie Depressionen basierend auf dem prä-menstruellen Syndrom.

Revendications

1. Composé, et ses sels acceptables en pharmacie, de formule I :

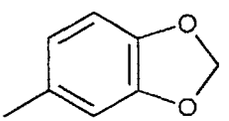


dans laquelle

- R représente un groupe 3',4'-méthylène-dioxyphényle,
- R^1 représente l'hydrogène ou un radical trifluoro(alkyle en C_1 à C_4), alkyle ou alcynyle,
- X représente l'hydrogène, un groupe alkyle ayant de 1 à 4 atomes de carbone, alcoxy, trifluoroalkyle, hydroxy, un halogène, un groupe méthylthio ou aralcoxy,
- R^2 représente :
  - un groupe alkyle en C_1 à C_{10},
  - un groupe phényle éventuellement substitué par un ou plusieurs des groupes suivants :
    - un groupe alkyle en C_1 à C_{10},
    - un groupe halogéno,
    - un groupe nitro,
    - un groupe hydroxy,
    - et/ou un groupe alcoxy,

où les groupes alkyle et alcynyle pour R^1, et les groupes alcoxy pour X et/ou R^2, sont tels que le composé présente une bonne stabilité et une très forte solubilité.

2. Composé selon la revendication 1, dans lequel le groupe R est le groupe 3,4-méthylène-dioxyphényle de formule :



et R^1 représente l'hydrogène.

3. Composé selon la revendication 1 ou 2, dans lequel le groupe X est de préférence un groupe fluor rattaché en position 4 du cycle phényle.

4. Composé selon les revendications 1 à 3, dans lequel le groupe R^2 représente un groupe alkyle en C_1 - C_4.

5. Composé selon les revendications 1 à 4, dans lequel le groupe R^2 est un groupe alkyle en C_1 - C_2.

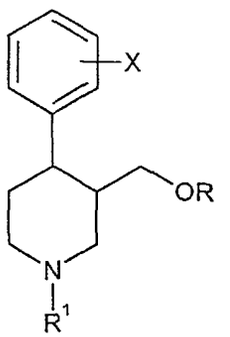
6. Composé selon l'une quelconque des revendications précédentes, ayant une solubilité à environ 20°C d'au moins environ 10 mg par ml d'eau.

7. Composé selon la revendication 6, ayant une solubilité dans l'eau d'au moins 100, de préférence d'au moins 500 et tout spécialement d'au moins 1000 mg par ml.

8. Composé selon l'une quelconque des revendications précédentes, choisi dans l'ensemble constitué essentiellement de :

- méthanesulfonate de paroxétine (formule I) où X est le fluor en position P, R est le radical 3',4'-méthylène-dioxyphényle, R^1 est l'hydrogène et R^2 est le radical méthyle ;
- benzènesulfonate de paroxétine (formule I) où X est le fluor en position P, R est le radical 3',4'-méthylène-dioxyphényle, R^1 est l'hydrogène et R^2 est le radical phényle ;
- p-toluènesulfonate de paroxétine (formule I), où X est le fluor en position P, R est le radical 3',4'-méthylène-dioxyphényle, R^1 est l'hydrogène et R^2 est le radical méthylphényle ;
- p-chlorobenzènesulfonate de paroxétine (formule I), où X est le fluor en position P, R est le radical 3',4'-méthylène-dioxyphényle, R^1 est l'hydrogène et R^2 est le radical chlorophényle.

9. Procédé pour préparer un composé selon l'une quelconque des revendications précédentes, comprenant les étapes consistant mettre en contact ensemble un composé, un sel et/ou une base de celui-ci, de formule II :



dans laquelle :

- R représente un groupe 3',4'-méthylène-dioxyphényle,
- R^1 représente l'hydrogène ou un radical trifluoro(alkyle en C_1 à C_4), alkyle ou alcynyle,
- X représente l'hydrogène, un groupe alkyle ayant de 1 à 4 atomes de carbone, alcoxy, trifluoroalkyle, hydroxy, un halogène, un groupe méthylthio ou aralcoxy, avec un acide sulfonique de formule générale R^2-SO_3H, dans laquelle R^2 représente :

  - un groupe alkyle en C_1 à C_{10},
  - un groupe phényle éventuellement substitué par un ou plusieurs des groupes suivants :

    - un groupe alkyle en C_1 à C_{10},
    - un groupe halogéno,
    - un groupe nitro,
    - un groupe hydroxy,
    - et/ou un groupe alcoxy,

pour former une solution, après quoi le solide formé peut être séparé.

10. Procédé pour obtenir un composé selon l'une quelconque des revendications 1 à 8 sous la forme d'un produit de solvatation, comprenant les étapes consistant à mettre en contact ensemble un composé selon l'une quelconque des revendications 1 à 8 avec un réactif choisi dans l'ensemble constitué essentiellement par :

l'eau,
le méthanol, et
l'éthanol.

11. Composé selon l'une quelconque des revendications 1 à 8, ou un produit de solvatation de celui-ci, pouvant être obtenu par le procédé selon la revendication 9 ou 10.

12. Composé selon l'une quelconque des revendications 1 à 8 et 11, à utiliser en tant que médicament.

13. Médicament comprenant un composé selon l'une quelconque des revendications 1 à 8, 11 et 12, et des véhicules et/ou diluants acceptables en pharmacie.

14. Médicament selon la revendication 13, sous la forme d'un comprimé, d'un comprimé enrobé ou d'une capsule.

15. Utilisation d'un composé selon l'une quelconque des revendications 1 à 8, 11 et 12, pour la préparation d'un médicament.

16. Utilisation d'un composé selon l'une quelconque des revendications 1 à 8 et 11 pour la fabrication d'un médicament destiné à traiter des dépressions, des troubles obsessionnels impulsifs, des troubles de panique, une boulimie, une anorexie, une douleur, une obésité, une démence sénile, une migraine, une anorexie, une phobie sociale, des dépressions provenant d'un syndrome prémenstruel.