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Substituted carbostyril derivatives as 5-HT1A receptor subtype agonists

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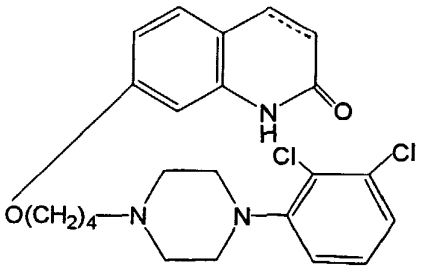
(54) Title: SUBSTITUTED CARBOSTYRIL DERIVATIVES AS 5-HT_{1A} RECEPTOR SUBTYPE AGONISTS



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(57) Abstract: The present invention relates to use of a compound for the production of a medicament for treating a patient suffering from a disorder of the central nervous system associated with 5-HT_{1A} receptor subtype, which the medicament comprising as an active ingredient a carbostyril derivative or a salt thereof represented by the formula (1), wherein the carbon-carbon bond between 3- and 4-positions in the carbostyril skeleton is a single or a double bond; and a pharmaceutically acceptable salt or solvate thereof.

DESCRIPTION

5-HT_{1A} RECEPTOR SUBTYPE AGONIST

BACKGROUND OF THE INVENTION

FIELD OF THE INVENTION

The present invention relates to a method of treating a patient suffering from a disorder of the central nervous system associated with the 5-HT_{1A} receptor subtype. The active ingredient comprises a carbostyril derivative or a salt or solvate thereof.

RELATED ART

U.S. Patent No. 5,006,528; European Patent No. 367,141 and Japanese Patent Kokai (Laid-open) 7-304,740 (1995) contain the same chemical structural formula as the carbostyril derivatives in the present invention, and their pharmacological properties are beneficial drug treatments for schizophrenia.

Carbostyril compounds, as well as those disclosed in Japanese Patent Kokai (Laid-open) 9-301,867 (1997) are useful for the treatment of anxiety.

The carbostyril derivatives disclosed in European Patent No. 226,441 have the genus of the carbostyril derivatives in the present invention, and they are useful for the treatment of hypoxia.

In addition to the above, the carbostyril derivatives disclosed in U.S. Patent No. 4,734,416; Canadian Patent No. 1,117,110; British Patent No. 2,017,701; German Patent Nos. 2,912,105 and

2,953,723; Japanese Patent Kokai(Laid-open)Nos. 54-130,587 (1979), 55-127,371 (1980) and 62-149,664 (1987) have the genus of the carbostyril derivatives in the present invention, and they have antihistaminic activities and central nervous controlling activities.

It is reported that aripiprazole (7-{4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy}-3,4-dihydrocarbostyril, also known as, OPC-14597, BMS-337,039 and OPS-31) binds with high affinity to dopamine D_2 receptors and with moderate affinity to dopamine D_3 and 5-HT_7 receptors (Masashi Sasa et al., CNS Drug Reviews, Vol. 3, No. 1, pp. 24-33).

Further, it is reported that aripiprazole possesses presynaptic dopaminergic autoreceptor agonistic activity, postsynaptic D_2 receptor antagonistic activity, and D_2 receptor partial agonistic activity (T. Kikuchi, K. Tottori, Y. Uwahodo, T. Hirose, T. Miwa, Y. Oshiro and S. Morita: J. Pharmacol. Exp. Ther., Vol. 274, pp. 329, (1995); T. Inoue, M. Domae, K. Yamada and T. Furukawa: J. Pharmacol. Exp. Ther., Vol. 277, pp. 137, (1996)).

However, it has not been reported that compounds in the present invention have agonistic activity at 5-HT_{1A} receptor subtype.

It has been reported that therapeutic interventions using 5-HT_{1A} receptor ligands may be useful drug treatments for alcohol abuse (Mark Kleven et al., European Journal of Pharmacology, Vol. 281,

(1995) pp. 219-228).

It is also reported that 5-HT_{1A} agonist drugs may be useful for the treatment and/or prophylaxis of disorders associated with neuronal degeneration resulting from ischemic events in mammals (U.S. Patent No. 5,162,375).

It is also reported that 5-HT_{1A} receptor hypersensitivity could be the biological basis for the increased frequency of migraine attack in stressful and anxious conditions (Massimo Leone et al., Neuro Report, Vol. 9, pp. 2605-2608(1998)).

It has recently been reported that (-)-(R)-2-[4-[[(3,4-dihydro-2H-1-benzopyran-2-yl)methyl]amino]-butyl]-1,2-benzisothiazol-3(2H)-one 1,1-dioxide monohydrochrolide (BAY-3702), a 5-HT_{1A} receptor agonist, has neuroprotective, anxiolytic- and antidepressant-like effects in animal models (Jean De Vry et al., European Journal of Pharmacology, Vol. 357, (1998), pp. 1-8).

It is also reported that 5-HT_{1A} receptor agonists appear to be broad spectrum antiemetic agents (Mary C. Wolff et al., European Journal of Pharmacology, Vol. 340, (1997), pp. 217-220; AB Alfieri et al., British Journal of Cancer, (1995), Vol. 72, pp. 1013-1015; Mary C. Wolff et al., Pharmacology Biochemistry and Behavior, 1995, Vol. 52, No. 3, pp. 571-575; James B. Lucot, European Journal of Pharmacology, 1997, Vol. 253, pp. 53-60).

Serotonin plays a role in several neurological and psychiatric disorders, including Alzheimer's disease, depression, nausea and vomiting, eating disorders, and migraine. (See Rasmussen et al., "Chapter 1. Recent Progress in Serotonin $5HT_{1A}$ Receptor Modulators", in Annual Reports in Medicinal Chemistry, Vol. 30, Section I, pp. 1-9, 1995, Academic Press, Inc.). WO 00/16777 discloses that a $5HT_{1A}$ receptor agonist, buspirone is efficacious in treating a variety of symptoms associated with ADHD, and that combined use of a D2 receptor agonist and 5-HT_{1A} agonist provides effective treatments for ADHD and Parkinson's disease.

$5HT_{1A}$ agonists are effective in the treatment of cognitive impairment in Alzheimer's disease, Parkinson's disease or senile dementia. US 5824680 discloses that a 5-HT_{1A} agonist, ipsapirone, is effective in treating Alzheimer's disease by improving memory. US 4687772 describes that a 5-HT_{1A} partial agonist, buspirone, is useful for improving short term memory in patients in need of treatment. WO 93/04681 discloses that use of 5-HT_{1A} partial agonists have been used for the treatment or prevention of cognitive disorders associated with Alzheimer's disease, Parkinson's disease or senile dementia.

$5HT_{1A}$ agonists are also effective in the treatment of depression. US 4771053 describes that a 5-HT_{1A} receptor partial agonist, gepirone, is useful in alleviation of certain primary depressive disorders,

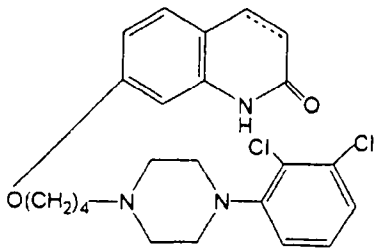
such as severe depression, endogenous depression, major depression with melancholia, and atypical depression. WO 01/52855 discloses that the combined use of the 5-HT_{1A} receptor partial agonist gepirone with an antidepressant can effectively treat depression.

The 5-HT_{1A} receptor partial agonist buspirone alleviates motor disorders such as neuroleptic induced parkinsonism and extrapyramidal symptoms. These observations are disclosed in US 4438119. Furthermore 5-HT_{1A} agonists reverse neuroleptic-induced catalepsy in rodents, which mimic movement impairments observed in Parkinson's disease (Mark J. Millan, Journal of Pharmacology and Experimental Therapeutics, 2000, Vol. 295, p853-861). Thus, aripiprazole can be used to manage psychosis in geriatric patients, Alzheimer's disease, Parkinson's disease or senile dementia, since it possesses potent, partial agonistic activities at D_2 and 5-HT_{1A} receptors. In addition, these patients might not experience extrapyramidal symptoms due to this property of aripiprazole.

SUMMARY OF THE INVENTION

The present invention provides method of treating a patient suffering from a disorder of the central nervous system associated with the 5-HT_{1A} receptor subtype.

Accordingly, in a first aspect there is provided use of a compound for the production of a medicament for treating a patient suffering from a disorder of the central nervous system associated with 5-HT_{1A} receptor subtype, selected from depression; cognitive impairment caused by Alzheimer's disease or Parkinson's disease; autism; Down's syndrome; attention deficit hyperactivity disorder (ADHD); Alzheimer's disease; Parkinson's disease; panic; obsessive compulsive disorder (OCD); sleep disorders; sexual dysfunction; alcohol abuse; drug addiction; emesis; motion sickness; obesity; and migraine, wherein said compound is a carbostyril compound of formula (1):



(1)

wherein the carbon-carbon bond between 3- and 4- positions in the carbostyril skeleton is a single or a double bond; and a pharmaceutically acceptable salt or solvate thereof.

In a second aspect, the invention provides a method for treating a patient suffering from a disorder of the central nervous system associated with 5-HT_{1A} receptor subtype selected from depression; cognitive impairment caused by Alzheimer's disease or Parkinson's disease; autism; Down's syndrome; attention deficit hyperactivity disorder (ADHD); Alzheimer's disease; Parkinson's disease; panic; obsessive compulsive disorder (OCD); sleep disorders; sexual

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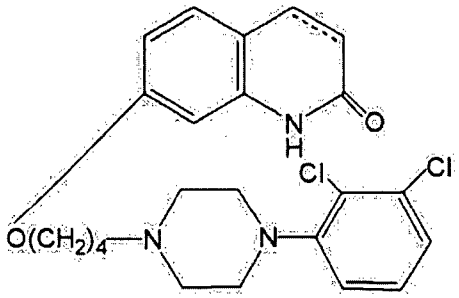
dysfunction; alcohol abuse; drug addiction; emesis; motion sickness; obesity; and migraine comprising administering to said patient a therapeutically effective amount of a carbostyril compound of formula (1):

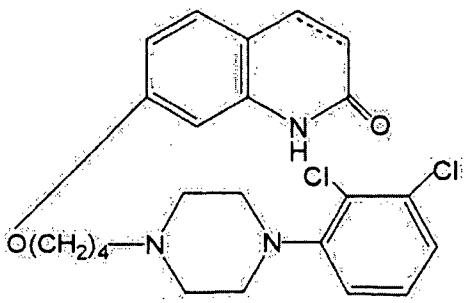


(1)

wherein the carbon-carbon bond between 3- and 4- positions in the carbostyril skeleton is a single or a double bond; and a pharmaceutically acceptable salt or solvate thereof.

DETAILED DESCRIPTION OF THE INVENTION

As the 5-HT_{1A} receptor subtype agonist compound for use in accordance with the present invention, carbostyril derivatives represented by the following formula (1) are used:



(1)

wherein the carbon-carbon bond between 3- and 4- positions in the carbostyril skeleton is a single or a double bond.

The compounds of the foregoing general formula (1) are known compounds, which are disclosed in publication such as U.S. Pat. No. 5,006,528 or which

can be readily prepared by the processes described in the above publication.

The carbostyril derivative represented by the formula (1) in the present invention can easily be converted into its acid-addition salt by reacting it with a pharmaceutically acceptable acid. Examples of such acid include inorganic acids, such as hydrochloric acid, sulfuric acid, phosphoric acid, hydrobromic acid and the like; organic acids, such as oxalic acid, maleic acid, fumaric acid, malic acid, tartaric acid, citric acid, benzoic acid and the like.

The solvent of solvates is a solvent conventionally used in recrystallization. Examples of solvates include hemihydrates, hydrates, and alcoholates, such as ethanolates, methanolates, isopropanolates and the like.

The desired compounds, prepared by the reactions mentioned above, can easily be isolated and purified by usual separation procedures such as solvent extraction, dilution, recrystallization, column chromatography, preparative thin layer chromatography and the like.

The potent, partial 5-HT_{1A} receptor agonist in the present invention is useful for various disorders of the central nervous system associated with the 5-HT_{1A} receptor subtype that induces bipolar disorders, such as bipolar I disorder with most recent hypomanic, manic, mixed, depressed or unspecified episode; bipolar

II disorder with recurrent major depressive episodes with hypomanic episodes, and cyclothymic disorder; depression, such as endogenous depression, major depression, melancholia, and treatment-resistant depression; panic disorder; obsessive compulsive disorder (OCD); sleep disorders; sexual dysfunction; alcohol abuse and drug addiction; cognitive impairment; neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease and the like, cognitive impairments caused by neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and related disorders; emesis; motion sickness; obesity; migraine; autism; Down's syndrome; and attention-deficit hyperactivity disorder (ADHD).

Compounds of the present invention may be suitably prepared into pharmaceutically acceptable formulations (see U.S. Patent No. 5,006,528, European Patent No. 367,141 and Japanese Kokai (Laid-open) 7-304,740 (1995), and Japanese Patent Application No. 2000-194976 incorporated by reference herein).

The dosage of these pharmaceutical preparations of the invention may be selected appropriately depending on the method of administration, the

patient's age, sex and other factors, severity of the disease and other factors. Generally, however, the daily dose of the active ingredient compound is preferably within the range of about 0.0001 to about 50 mg per kilogram of body weight. It is desirable that the active ingredient compound be contained in each unit dosage form in an amount of about 0.001 to about 1,000 mg, particularly 0.01 to 100 mg, more particularly 0.1 to 50 mg, yet more particularly 1 mg to 20 mg.

Pharmacological tests

1. MATERIALS AND METHODS

1.1 Test Compound

7-{4-[4-(2,3-Dichlorophenyl)-1-piperazinyl]-butoxy}-3,4-dihydrocarbostyril (aripiprazole) was used as test compound.

1.2 Reference Compounds

Serotonin (5-HT) and WAY-100635 (N-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-N-(2-pyridimyl)-cyclohexanecarboxamide, a 5-HT_{1A} receptor antagonist, manufactured by RBI (Natick, MA) were used as reference compounds.

1.3 Vehicle

Dimethyl sulfoxide (DMSO) manufactured by Sigma Chemical Co. (St. Louis, MO) was used as vehicle.

1.4 Preparation of Test and Reference Compounds

Test compound was dissolved in 100% dimethyl

sulfoxide (DMSO) to yield 100 µM stock solutions (final concentration of DMSO in all tubes containing test compound was 1%, v/v). All other reference compounds were prepared by the same method using double-distilled water rather than DMSO.

1.5 Experimental Procedure for the [^{35}S]GTP$_\gamma$S Binding Assay

Test and reference compounds were studied in triplicate at 10 different concentrations (0.01, 0.1, 1, 5, 10, 50, 100, 1000, 10000 and 50000 nM) for their effects upon basal [^{35}S]GTP$_\gamma$S binding to h5-HT$_{1A}$ CHO cell membranes. Reactions were performed in 5 ml glass test tubes containing 8 µl of test/reference drug mixed with 792 µl of buffer (25 mM Tris HCl, 50 mM NaCl, 5 mM $MgCl_2$, 0.1 mM EGTA, pH = 7.4) containing GDP (1 µM), [^{35}S]GTP$_\gamma$S (0.1 nM) and h5-HT$_{1A}$ CHO cell membranes (10 µg protein/reaction; NEN Life Science Products, Boston, MA; catalog # CRM035, lot # 501-60024, GenBank # X13556). Reactions proceeded for 60 min at room temperature and were terminated by rapid filtration through Whatman GF/B filter paper, using a Brandel harvester and 4x3 ml ice-cold buffer washes. ^{35}S radioactivity bound to the filter paper was measured using liquid scintillation counting (1272 Clinigamma, LKB/Wallach).

1.6 Experimental Procedure to Determine the Binding Affinity of Test compound (aripiprazole) at the h5-HT$_{1A}$ Receptor

Test compound was studied in triplicate at 10 different concentrations (0.01, 0.1, 1, 10, 50, 100, 500, 1000, 5000 and 10000 nM) to determine its displacement of [^{3}H]8-OH-DPAT (1 nM; NEN Life Sciences; catalog # NET 929, lot # 3406035, Specific Activity = 124.9 Ci/mmol) binding to h5-HT_{1A} receptors in CHO cell membranes (15 - 20 µg protein; NEN Life Science Products, catalog # CRM035, lot # 501-60024). Membranes (396 µl) were incubated in 5 ml glass tubes containing [^{3}H]8-OH-DPAT (396 µl), test compound or vehicle (8 µl) and buffer A (50 mM Tris.HCl, 10 mM $MgSO_4$, 0.5 mM EDTA, 0.1% (w/v) ascorbic acid, pH = 7.4). All assays proceeded for 60 min at room temperature and were terminated by rapid filtration through Whatman GF/B filter paper (presoaked in buffer B; 50 mM Tris.HCl, pH = 7.4), using a Brandel harvester and 4×1 ml ice-cold washes with buffer B. Non-specific binding was determined in the presence of 10 µM (+)8-OH-DPAT.

1.7 Parameters Determined

Serotonin (5-HT) is a full 5-HT_{1A} receptor agonist which stimulates increases in basal [^{35}S]$GTP_\gamma S$ binding to h5-HT_{1A} receptors in recombinant CHO cell membranes. Test compound was studied at 10 concentrations to determine their effects upon basal [^{35}S]$GTP_\gamma S$ binding relative to that produced by 10 µM 5-HT. The relative potency (EC_{50}, 95% confidence interval) and intrinsic agonist activity (% of E_{max} for 10 µM 5-HT) was calculated for each compound by computerized non-linear

regression analysis of complete concentration-effect data. The binding affinity of test compound at the h5-HT_{1A} receptor was determined by its ability to prevent [^{3}H]8-OH-DPAT binding to CHO cell membranes that express this receptor. Non-linear regression analysis of the competition binding data was used to calculate an inhibition constant (IC_{50}, 95% confidence interval), which is the concentration of test compound that occupies half of the h5-HT_{1A} sites specifically bound by [^{3}H]8-OH-DPAT. The affinity of h5-HT_{1A} receptors for test compound (Ki, 95% confidence interval) was calculated by the equation, $Ki = (IC_{50})/(1+([[^3H]8\text{-}OH\text{-}DPAT]/Kd)$, where the Kd for [^{3}H]8-OH-DPAT at h5-HT_{1A} = 0.69 nM (NEN Life Sciences). All estimates of drug binding affinity, potency and intrinsic efficacy at the h5-HT_{1A} receptor were calculated using GraphPad Prism version 3.00 for Windows (GraphPad Software, San Diego, CA).

2. RESULTS

Test compound and 5-HT produced concentration-dependent increases above basal [^{35}S]$GTP_\gamma S$ binding. 1% DMSO tested alone had no effect upon basal or drug-induced [^{35}S]$GTP_\gamma S$ binding.

Test compound (EC_{50} = 2.12 nM), 5-HT (EC_{50} = 3.67 nM), potently stimulated basal [^{35}S]$GTP_\gamma S$ binding. Potency and intrinsic agonist efficacy estimates were derived by non-linear regression analysis with correla-

tion coefficients (r^2)>0.98 in each case (Table 1). Test compound exerted partial agonist efficacies in the 65 - 70% range. WAY-100635 produced no significant change (unpaired Student's t-test) in basal [^{35}S]GTP$_\gamma$S binding at all concentrations tested (Table 1). WAY-100635 did, however, completely inhibit the effects of 5-HT and test compound upon [^{35}S]GTP$_\gamma$S binding to h5-HT$_{1A}$ receptors in CHO cell membranes (Table 2). Tables 1 and 2 are shown below.

Test compound demonstrated high affinity binding to h5-HT$_{1A}$ receptors in CHO cell membranes (IC_{50} = 4.03 nM, 95% confidence interval = 2.67 to 6.08 nM; Ki = 1.65 nM, 95% confidence interval = 1.09 to 2.48 nM).

Table 1 Potency (EC_{50}) and Intrinsic Agonist Efficacy (E_{max}) of Test compound and Reference Drugs in a h5-HT$_{1A}$ [^{35}S]GTP$_\gamma$S CHO-cell Membrane Binding Assay.

Drug	EC_{50}, nM (95% Confidence Interval)	E_{max} (% ± SEM)	Goodness of Fit (r^2)
Test Compound	2.12 (0.87 to 5.16)	68.13 ± 3.16	0.986
5-HT	3.67 (1.56 to 8.63)	98.35 ± 4.47	0.986
WAY-100635	-	-	-

Table 2 Inhibitory Potency (IC_{50}) of WAY-100635 versus 1 μM Concentration of 5-HT and Test compound in a h5-HT_{1A} [^{35}S]$GTP_{\gamma}S$ CHO-cell Membrane Binding Assay.

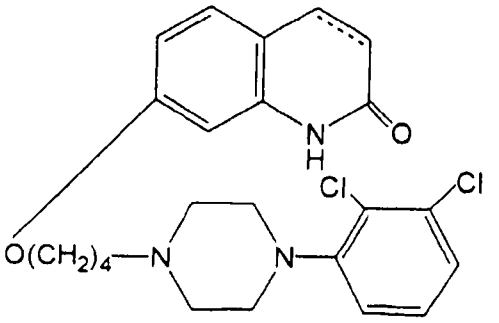
Drug Combination	WAY-100635 Inhibition Potency, IC_{50}, nM (95% Confidence Interval)	Goodness of Fit (r^2)
5-HT + WAY-100635	217.1 (127.4 to 369.7)	0.988
Test compound + WAY-100635	392.2 (224.1 to 686.2)	0.989

The reference to any prior art in this specification is not, and should not be taken as, an acknowledgment or any form of suggestion that that prior art forms part of the common general knowledge in Australia.

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. Use of a carbostyril compound of formula (1):



(1)

wherein the carbon-carbon bond between 3- and 4- positions in the carbostyril skeleton is a single or a double bond; and a pharmaceutically acceptable salt or solvate thereof, for the production of a medicament effective in the treatment of disorders of the central nervous system associated with 5-HT_{1A} receptor subtype, selected from depression; cognitive impairment caused by Alzheimer's disease or Parkinson's disease; autism; Down's syndrome; attention deficit hyperactivity disorder (ADHD); Alzheimer's disease; Parkinson's disease; panic; obsessive compulsive disorder (OCD); sleep disorders; sexual dysfunction; alcohol abuse; drug addiction; emesis; motion sickness; obesity; and migraine.

2. The use of Claim 1 wherein the disorder is depression.

3. The use of Claim 2 wherein the depression is selected from endogenous depression, major depression, melancholia or treatment-resistant depression.

4. The use of Claim 1 wherein the disorder is autism,

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Down's syndrome, or attention deficit hyperactivity disorder (ADHD).

5. The use of Claim 1 wherein the disorder is Alzheimer's disease or Parkinson's disease.

6. The use of Claim 1 wherein the disorder is panic, obsessive compulsive disorder (OCD), sleep disorders, sexual dysfunction, alcohol and drug addiction, emesis, motion sickness, obesity or migraine.

7. The use according to any one of claims 1-6 wherein the carbostyril compound is 7-{4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy}-3,4-dihydrocarbostyril.

8. A method for treating a patient suffering from a disorder of the central nervous system associated with 5-HT_{1A} receptor subtype selected from depression; cognitive impairment caused by Alzheimer's disease or Parkinson's disease; autism; Down's syndrome; attention deficit hyperactivity disorder (ADHD); Alzheimer's disease; Parkinson's disease; panic; obsessive compulsive disorder (OCD); sleep disorders; sexual dysfunction; alcohol abuse; drug addiction; emesis; motion sickness; obesity and migraine, comprising administering to said patient a therapeutically effective amount of a carbostyril compound of formula (1):

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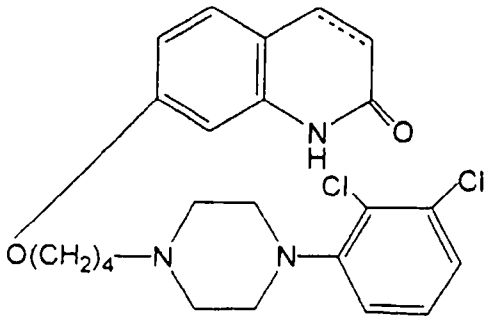

(1)

wherein the carbon-carbon bond between 3- and 4- positions in the carbostyril skeleton is a single or a double bond; and a pharmaceutically acceptable salt or solvate thereof.

9. The method of Claim 8 wherein the disorder is depression.

10. The method of Claim 9 wherein the depression is selected from endogenous depression, major depression, melancholia or treatment-resistant depression.

11. The method of Claim 8 wherein the disorder is autism, Down's syndrome, or attention deficit hyperactivity disorder (ADHD).

12. The method of Claim 8 wherein the disorder is Alzheimer's disease or Parkinson's disease.

13. The method of Claim 8 wherein the disorder is panic, obsessive compulsive disorder (OCD), sleep disorders, sexual dysfunction, alcohol and drug addiction, emesis, motion sickness, obesity or migraine.

14. The method according to any one of claims 8-13 wherein

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the carbostyril compound is 7-{4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy}-3,4-dihydrocarbostyril.

15. A use of carbostyril compound, or a pharmaceutically acceptable salt or solvate thereof substantially as hereinbefore described and/or exemplified.

16. A method for treating a disorder of the central nervous system associated with 5-HT_{1A} substantially as hereinbefore described and/or exemplified.