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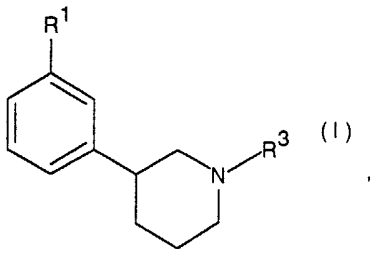
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(54) Virsraksts: **AIZVIETOTI (S)-3-FENILPIPERIDĪNA ATVASINĀJUMI, TO IEGŪŠANA UN IZMANTOŠANA PAR DOFAMĪNA AUTORECEPTORU ANTAGONISTIEM**

(57) Kopsavilkums: Izgudrojums apraksta savienojumu, kas ir (S)-enantiomērs ar formulu I



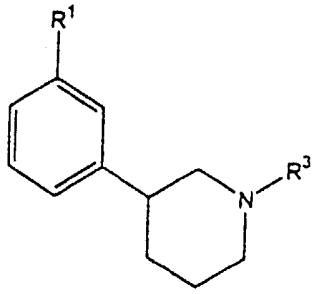
(I)

kur
R^1 ir CN, OSO_2CH_3, OSO_3CF_3, CHO, $CONH_2$, $S(O)_{0-2}CH_3$, $S(O)_{0-2}CF_3$, SO_2NH_2 vai $NHSO_2CF_3$; un R^3 ir ūdeņraža atoms, CF_3, CH_2CF_3, C_{1-8}alkilgrupa, C_{3-8}cikloalkilgrupa, C_{4-9}ciklo-alkilmetilgrupa, C_{2-8}alkenilgrupa, C_{2-8}alkinilgrupa, 3,3,3-trifluorpropilgrupa, 4,4,4-trifluorbutilgrupa vai CH_2SCH_3; vai tā farmaceitiski pieņemamu sāli. Savienojumiem piemīt selektīvas farmakoloģiskās īpašības attiecībā uz dofamīnreceptoru, un tie ir izmantojami centrālās nervu sistēmas traucējumu, kas ietver depresijas simptomus, geriartriskus traucējumus (mentālo un kustības funkciju), šizofrēniju, narkolepsiju, minimālu smadzeņu disfunkciju, aptaukošanos, seksuālos traucējumus, ārstēšanā un personu, kas pārmērīgi lieto medikamentus, rehabilitācijā.

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IZGUDROJUMA FORMULA

1. Savienojums, kas ir (S)-enantiomērs ar formulu I



(I),

kur R^1 ir CN, OSO_2CH_3, OSO_2CF_3, CHO, $CONH_2$, $S(O)_{0-2}CH_3$, $S(O)_{0-2}CF_3$, SO_2NH_2 vai $NHSO_2CF_3$; un R^3 ir ūdeņraža atoms, CF_3, CH_2CF_3, C_1-C_8alkilgrupa, C_3-C_8cikloalkilgrupa, C_4-C_9cikloalkilmetilgrupa, C_2-C_8alkenilgrupa, C_2-C_8alkinilgrupa, 3,3,3-trifluorpropilgrupa, 4,4,4-trifluorbutilgrupa vai CH_2SCH_3;
vai tā farmaceitiski pieņemams sāls.

2. Savienojums saskaņā ar 1. punktu, kur R^1 ir OSO_2CF_3, CN, SO_2NH_2, SO_2CF_3, SCH_3 vai SO_2CH_3.

3. Savienojums saskaņā ar 1. punktu, kur R^1 ir CN.

4. Savienojums saskaņā ar 1. punktu, kur R^1 ir OSO_2CF_3 vai SO_2CH_3.

5. Savienojums saskaņā ar jebkuru no iepriekšējiem punktiem, kur R^3 ir alkilgrupa.

6. Savienojums saskaņā ar 5. punktu, kur R^3 ir n-propilgrupa.

7. Savienojums saskaņā ar 1. punktu, kas ir S-(-)-3-(3-ciānfenil)-N-n-propilpiperidīns.

8. Savienojums saskaņā ar 1. punktu, kas ir S-3-(3-metilsulfonilfenil)-N-n-propilpiperidīns.

9. Savienojuma saskaņā ar jebkuru no iepriekšējiem punktiem izmantošana medikamenta ražošanai centrālās nervu sistēmas traucējumu, kas saistīti ar dofamīnreceptora aktivitāti, ārstēšanai.

10. Izmantošana saskaņā ar 9. punktu, kur pacientam savienojums tiek nozīmēts daudzumā no 50 līdz 500 mg/70 kg perorāli vai no 0,5 līdz 50 mg/70 kg parenterāli.

11. Izmantošana saskaņā ar 9. punktu geriatrisku traucējumu ārstēšanai, mentālo un kustību funkciju uzlabošanai.

12. Izmantošana saskaņā ar 9. punktu personu, kas pārmērīgi lieto medikamentus, rehabilitācijai.

SUBSTITUTED (S)-3-PHENYLPIPERIDINE DERIVATIVES, THEIR PREPARATION AND THEIR USE AS DOPAMINE AUTORECEPTOR ANTAGONISTS

Description

Field of the Invention

[0001] The present invention is directed to new substituted 3-phenylpiperidine, analogs, processes for preparing such compounds, pharmaceutical preparations of such compounds and the use of such compounds in the manufacture of a pharmaceutical preparation having dopamine receptor activity.

Background of the Invention

[0002] In recent years a large body of pharmacological, biochemical and electrophysiological evidence has provided considerable support in favor of the existence of a specific population of central autoregulatory dopamine (DA receptors) located in the dopaminergic neuron itself and belonging to the D2 receptor subclass of DA receptors. These receptors are part of a homeostatic mechanism that modulates nerve impulse flow and transmitter synthesis and regulates the amount of DA released from the nerve endings. Recently, Sokoloff, et al., Nature, 347 146-51 (1990) presented evidence for the existence of a new type of dopamine receptor called D3. In a series of screened classical and atypical neuroleptics, the preferential dopamine autoreceptor antagonists (+)-AJ76 and (+)-UH232 possessed the highest preference for the D3 site. The D3 receptor appears to occur both pre- and postsynaptically, and the regional distribution (high preference in limbic brain areas) differs from that of the D1 and D2 receptors.

[0003] Drugs acting as agonists or antagonists on central DA transmission are clinically effective in treating a variety of central nervous system disorders such as parkinsonism and schizophrenia. In parkinsonism, for example, the nigroneostriatal hypofunction can be restored by an increase in postsynaptic DA receptor stimulation. In schizophrenia, the condition can be normalized by achieving a decrease in postsynaptic DA receptor stimulation. Classical antipsychotic agents directly block the postsynaptic DA receptor. The same effect can be achieved by inhibition of intraneuronal presynaptic events essential for the maintenance of adequate neurotransmission, transport mechanism and transmitter synthesis.

[0004] Direct DA receptor agonists, like apomorphine, are able to activate the DA autoreceptors as well as the postsynaptic DA receptors. The effects of autoreceptor stimulation appear to predominate when apomorphine is administered at low doses, whereas at higher doses the attenuation of DA transmission is outweighed by the enhancement of postsynaptic receptor stimulation. The antipsychotic and antidyskinetic effects in man of low doses of apomorphine are likely due to the autoreceptor-stimulator properties of this DA receptor agonist. This body of knowledge indicates DA receptor stimulants with a high selectivity for central nervous DA autoreceptors would be valuable in treating psychiatric disorders.

[0005] Compounds displaying preferential antagonistic effects at DA autoreceptors have been developed, Johansson et al., J. Med. Chem., 28, 1049 (1985). Examples of such compounds are (+)-cis-1S,2R-5-methoxy-1-methyl-2-(N-n-propylamino)tetralin ((+)-1S,2R-AJ76) and (+)-cis-1S,2R-5-methoxy-1-methyl-2-(N,N-di-n-propylamino)tetralin ((+)-1S,2R-UH232). Biochemically these compounds behave as classical DA antagonists, e.g. like haloperidol. Consequently, they raise the Dopa accumulation in normal animals after the blockage of aromatic amino acid decarboxylase by NSD1015 and they raise the levels of the DA metabolites DOPAC and HVA (no NSD1015 treatment). However, functionally, in behavioral testing (photocell motility meters), they display stimulatory properties, e.g. they increase the locomotor activity. In addition, gross behavioral observations show that these compounds, in certain dosages, can induce a weak classical dopaminergic stereotypic behavioral effects like sniffing and rearing in rodents.

[0006] Diseases in which an increase in dopaminergic turnover may be beneficial are geriatrics, for preventing bradykinesia and depression and in the improvement of mental functions. It can have an effect in depressed patients. It can be used in obesitas as an anorectic agent. It can improve minimal brain dysfunction (MBD), narcolepsy and negative symptoms of schizophrenia. Improvement of sexual functions is another indication. Some of the compounds in this invention have both pre- and postsynaptic antagonistic effects. Compounds possessing more of the postsynaptic effects can be used to alleviate the symptoms (both positive and negative) of schizophrenia and for the rehabilitation of drug addicts. Other disturbances of interest in this context are "jet lag", sleep disorders and early stages of Parkinsonism.

Information Disclosure Statement

[0007] A number of 3-phenylpiperidine derivatives are known and described, for example, in Hacksell et al., J. Med. Chem., 24, 1475 (1981), and Wikström et al., J. Med. Chem., 27, 1030 (1984). The reported compounds are 3-substituted 3-phenylpiperidines, most of them being 3-OH substituted and displaying pre- and postsynaptic dopaminergic agonistic effects. Clark et al. have presented two thorough reviews on the model autoreceptoragonist (-)-S-3-(3-hydroxyphenyl-N-n-propyl)piperidine ((-)-S-3-PPP).

[0008] The racemic compound 3-(3-cyanophenyl-N-n-propyl)piperidine has been published by Hacksell et al., J.

Med. Chem., 24, 1475 (1981). In that publication it was found to display no direct receptor agonistic effects in reserpinized rats.

[0009] U.S-A-4,259,337 describes 3-(3-trifluorophenyl)piperidines such as 3-(3-trifluoromethyl-N-n-propyl)piperidine with effects upon DA receptors.

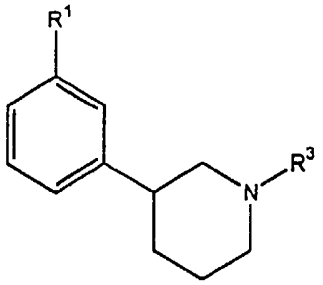
[0010] Bøgesø et al., J. Med. Chem. (1987) 30, 142-150, discloses indolizidine and quinolizidine derivatives of 3-(3-hydroxyphenyl)-N-n-propylpiperidine;

[0011] EP-A-0381235 discloses 3,4-dihydroxyphenyl-3-pyrrolidines and their dopamine 1 agonist activity.

[0012] EP-A-0372776 discloses N-substituted arylpiperidines, the N-substituent being alkyl bearing an aryl or cyclic group. These compounds are disclosed as antipsychotic agents.

Summary of the Invention

[0013] According to the present invention, novel compounds are (S)-enantiomers of formula I



wherein R^1 is CN, OSO_2CH_3, OSO_2CF_3, CHO, $CONH_2$, $S(O)_{0-2}CH_3$, $S(0)_{0-2}CF_3$, SO_2NH_2 or $NHSO_2CF_3$; and R^3 is hydrogen, CF_3, CH_2CF_3, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_4-C_9 cycloalkylmethyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, 3,3,3-trifluoropropyl, 4,4,4-trifluorobutyl or CH_2SCH_3;
and pharmaceutically-acceptable salts thereof.

[0014] The compounds of this invention possess selective dopamine receptor pharmacological properties, e.g. on the subclasses of DA receptors known as the D2 and D3 receptors. They are useful in treating central nervous system disorders including depression symptoms, geriatric disorders in the improvement of mental and motor functions, schizophrenia, narcolepsy, MBD, obesity, disturbances of sexual functions and rehabilitation of drug abusers.

[0015] The novel compounds have the S absolute configuration, according to the Cahn-Ingold-Prelog priority rules. Depending on the N-substituent, some of these S-enantiomers are dextrorotatory while others are levorotatory.

Description of the Invention

[0016] Preferably, R^1 is OSO_2CF_3, CN, SO_2NH_2, SO_2CF_3, SCH_3 or SO_2CH_3. More preferably, R^1 is CN, OSO_2CF_3 or SO_2CH_3. R^3 is preferably alkyl, and most preferably n-propyl.

[0017] Certain compounds of the invention and *in vitro* binding data are presented in Table 1. "D2-SPIP" refers to DA D2 ([^{3}H]-spiperone, antagonist binding) rat striatum; "5-HT1A" refers to serotonin 5- HT1A ([^{3}H]-8-OH-DPAT, agonist) rat cortex.

TABLE 1

				In vitro binding (IC50 nM)	
Example	**R^1**	**R^3**	**Formula**	**D_2-spip**	**5-HT1A**
1	3-OSO_2CF_3	n-Pr	$C_{15}H_{20}F_3NO_3S$ x HCl	1600	2300
2	3-OSO_2CF_3	Me	$C_{13}H_{16}F_3NO_3S$ x HCl	71000	2800
3	3-OSO_2CF_3	Et	$C_{14}H_{18}F_3NO_3S$ x HCl	7100	1300
4	3-OSO_2CF_3	n-Bu	$C_{16}H_{22}F_3NO_3S$ x HCl	1300	1300
5	3-OSO_2CF_3	allyl	$C_{15}H_{18}F_3NO_3S$ x HCl	28000	4200
6	3-OSO_2CH_3	n-Pr	$C_{15}H_{23}NO_3S$ x HCl	25000	1700
7	3-$CONH_2$	n-Pr	$C_{15}H_{22}N_2O$ x HCl	75000	6300

TABLE 1 (continued)

				In vitro binding (IC50 nM)	
Example	**R^1**	**R^3**	**Formula**	**D_2-spip**	**5-HT1A**
11	3-CN	n-Pr	$C_{16}H_{20}N_2$ x HCl	3500	75000
12	3-CN	H	$C_{12}H_{14}N_2$ x HCl	16000	1000
13	3-CN	Me	$C_{13}H_{16}N_2$ x HCl	50000	14000
14	3-CN	Et	$C_{14}H_{18}N_2$ x HCl	14000	22000
15	3-CN	n-Bu	$C_{17}H_{22}N_2$ x $C_2H_4O_4$	3700	5600
16	3-CN	allyl	$C_{16}H_{18}N_2$ x HCl	8200	12000
17	3-CN	i-Pr	$C_{16}H_{20}N_2$ x HCl	4300	16000
18	3-CN	C_3H_5-CH_2	$C_{17}H_{20}N_2$ x HCl	16000	7900

[0018] As used herein the term C_{n-m} is inclusive such that a compound of C_{1-8} would include compounds of one to 8 carbons and their isomeric forms. The various carbon moieties are defined as follows: Alkyl refers to an aliphatic hydrocarbon radical and includes branched or unbranched forms such as methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl, i-pentyl, neo-pentyl, n-hexyl, i-hexyl, n-heptyl, i-heptyl and n-octyl.

[0019] Alkenyl refers to a radical of an aliphatic unsaturated hydrocarbon having a double bond and includes both branched and unbranched forms such as ethenyl, 1-methyl-1-ethenyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methyl-1-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 1-methyl-4-pentenyl, 3-methyl-1-pentenyl, 3-methyl-2-pentenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 1-methyl-4-hexenyl, 3-methyl-1-hexenyl, 3-methyl-2-hexenyl, 1-heptenyl, 2-heptenyl, 3-heptenyl, 4-heptenyl, 1-methyl-4-heptenyl, 3-methyl-1-heptenyl, 3-methyl-2-heptenyl, 1-octenyl, 2-octenyl or 3-octenyl. Cycloalkyl refers to a radical of a saturated cyclic hydrocarbon such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl.

[0020] It will be apparent to those skilled in the art that compounds of this invention contain one chiral center. The compounds of Formula I contain an asymetric carbon atom in the aliphatic ring moiety (carbon 3 in the heterocyclic ring to phenyl ring junction). The therapeutic properties of the compounds with DA autoreceptor blocking properties relate to compounds that have the S-stereochemistry. One R-enantiomer, (R-3-(3-cyanophenyl-N-n-propyl)piperidine), was prepared and tested and was found to have essentially no affinity for D2 receptors (IC50 = 100000 nM in [3H]-Spiperone binding, as compared to IC50 = 3500 nM for S-3-(3-cyanophenyl-N-n-propyl)piperidine), i.e. the compound of Example II. The R-enantiomer only weakly elevated limbic DOPAC (DA metabolism) levels and, furthermore, it failed to produce locomotor stimulation or to affect the DA synthesis rate in reserpinized rats. This suggests that the R-enantiomer is devoid of direct agonistic or antagonistic actions at central dopamine receptors.

[0021] Both organic and inorganic acids can be employed to form non-toxic pharmaceutically acceptable acid addition salts of the compounds of this invention. Illustrative acids are sulfuric, nitric, phosphoric, hydrochloric, citric, acetic, lactic, tartaric, pamoic, ethanedisulfonic, sulfamic, succinic, cyclohexylsulfamic, fumaric, maleic, and benzoic acid. These salts are readily prepared by methods known in the art.

[0022] The compounds of this invention may be obtained by one of the following methods described below and outlined in Schemes 1-3.

[0023] In clinical practice the compounds of the present invention will normally be administered orally, rectally, or by injection, in the form of pharmaceutical preparations comprising the active ingredient either as a free base or as a pharmaceutically acceptable non-toxic, acid addition salt, such as the hydrochloride, lactate, acetate, sulfamate salt, in association with a pharmaceutically acceptable carrier. The use and administration to a patient to be treated would be readily apparent to a person of ordinary skill in the art.

[0024] In therapeutical treatment an effective amount or a therapeutic amount of the compounds of the invention are from about 1 to about 2000 mg for oral application, preferentially 50-500 mg, and from about 0.1 to about 100 mg for parenteral application, preferentially 0.5-50 mg daily doses. The daily dose will preferably be administered in individual dosages one to 4 times daily and the dosage amounts are based on an individual having a weight of 70 kg.

[0025] The compounds of this invention where R^1 is cyano or O-triflate (OSO_2CF_3) and R^3 is C_{1-8} alkyl are very selective DA receptor antagonists with a preferential action on DA autoreceptors. These compounds are particularly effective central stimulants possibly without self-administration liability. Uses for these compounds include geriatrics, for preventing akinesia and depression and the improvement of mental functions. They can have an effect in depressed patients. They can be used in obesitas as anorectic agents. They can improve minimal brain dysfunction (MBD) and narcolepsy. They can be useful in the rehabilitation of drug addicts. Some of the compounds in this invention have both pre- and postsynaptic antagonistic effects. Such compounds, with more of the postsynaptic effects, can be used to alleviate the symptoms (both positive and negative) of schizophrenia (see above).

[0026] The compounds of this invention also have been shown to have high oral potency and a long duration of action. Both these features are beneficial to effective clinical treatment.

[0027] The utility of the compounds of this invention to treat central nervous system disorders is shown in behavioral and biochemical activity in non-pretreated rats.

Experimental procedures

Locomotor activity in normal non-habituated and habituated animals

[0028] Non-habituated animals: The motor activity was measured (experiments were carried out between 9 a.m. and 1 p.m.) by means of photocell recordings (M/P 40 Fc Electronic Motility Meter, Motron Products, Stockholm) as described in Hacksell et al., J. Med. Chem., 22, 1469 (1979). The different test compounds were administered subcutaneously in the neck region or orally (in animals that had been starved over night) via a syringe equipped with a bent tube (n=4). Immediately after drug administration, the rats were placed in the test cages (one rat/cage) and put into the motility meters. Motor activity was then followed and recorded for the subsequent 30 minutes (Table 2). Observations of gross behavior were made throughout the activity sessions through semi-transparent mirrors.

[0029] Table 2 shows the effects of compounds of the present invention on DA and 5-HT synthesis rates and on motor activity in non-pretreated rats. Values are expressed as % of saline controls, mean ± sem. In the Table, * denotes statistically significantly differences ($p < 0.05$), compared to saline-treated controls.

[0030] In the experimental procedure, the animals were injected with test drugs and, five minutes later, they were put into photocell motility boxes. The activity (accumulated counts/ 30 min) was then measured and expressed as % of saline controls (230±20 counts /30 min), mean ± sem, n = 4. Gross behavioral observations were made. After the activity session, the rats were injected with NSD 1015 (100 mg/kg,i.p.) and then killed 30 min later. DOPA accumulation in the DA-rich striatal region and in the NE-rich cortical regions, and 5-HTP accumulation in the limbic forebrain, are shown.

[0031] Table 3 reports the effects of compounds of the present invention on DA and 5-HT metabolism in habituated rats. Values are expressed as % or saline-treated controls, mean ± sem (n = 4).

[0032] These experiments were performed as described above for non-habituated animals, but the animals were habituated in the test cages one hour before the injection of the test compound or saline (controls). The habituation resulted in a locomotor activity of about 10% of that seen in non-habituated animals. The locomotor activity after the test compound was then recorded for 60 minutes. Control levels were 44 ± 15 counts/60 minutes (mean ± sem, n = 4).

[0033] Striatal and limbic levels of DOPAC and 5-HIAA were measured by HPLC-EC.

TABLE 2

Example (dose µmol/kg)	DOPA acc striatum	cortex	5-HTP acc limbic region	Motor act.	Gross behavioral observations
3(100 sc)	286±33*	80±4	76±9	103±19	No change
4(100 sc)	234±10*	89±9	82±5	116±21	No change
13(25 sc)	132±9*	91±5	98±7	128±27	No change
13(100 sc)	215±6*	109±12	78±2*	79±2*	Weak hypomot.
14(25 sc)	282±11*	108±7	83±3	157±7*	Weak stimulat.
14(100 sc)	318±19*	137±7	77±3*	113±7	No change
11(50 sc)	285±3*	156±9*	144±6*	154±20*	Activation
11(100 sc)	268±16*	158±8*	148±10*	165±8*	Activation
11(200 sc)	294±26*	148±16*	80±12	159±24*	No change

TABLE 3

Example (µmol/kg)	DOPAC striatum	DOPAC limbic	5-HIAA limbic	Motor activity	Behavioral observations
2(100 sc)	172±11*	138±10	109±2	135±14	No change
3(100 sc)	293±29***	223±39***	98±33	404±205*	Activation
1(6.2 sc)	118±10	134±10	132±9	91±24	No change

TABLE 3 (continued)

Example (µmol/kg)	DOPAC striatum	DOPAC limbic	5-HIAA limbic	Motor activity	Behavioral observations
1(25 sc)	175±8*	145±11*	126±5	128±33	No change
1(100 sc)	217±3*	196±16*	140±11	445±131*	Activation
4(100 sc)	192±4***	186±2***	109±4	345±39**	Activation
5(100 sc)	222±12***	159±18**	93±6	195±13*	Activation
6(100 sc)	276±12***	209±11***	118±11	550±50**	Activation
12(100 sc)	167±8***	153±15**	-	431±80*	Activation
13(100 sc)	120±5	110±6	-	277±68*	Weak slim.
10(100 sc)	167±8***	153±15**	-	431±80*	Activation
11(100 sc)	362±25*	226±11*	-	653±41*	Activation
11(25 po)	167±10	138±13	-	231±31*	Activation
11(400 po)	259±31	246±10	-	338±52*	Activation
17(100 sc)	251±18***	335±12***	-	336±33*	Activation
16(100 sc)	298±11***	205±17***	-	679±***	Activation
18(100 sc)	272±12***	221±8***	-	518±153**	Activation

[0034] In-vivo determination of rat brain monoamine metabolites and tyrosine and tryptophan hydroxylation (biochemically monitored DA and 5-HT receptor agonist or antagonist activity).

[0035] The compounds under evaluation were tested biochemically for central DA and 5-HT receptor (pre- and/or postsynaptic) stimulating and/or blocking activity. The concept of this biochemical screening method is that a DA or 5-HT receptor agonist will stimulate the receptor and through regulatory negative feed-back systems induce a decline in tyrosine or tryptophan hydroxylating activity, respectively, and a subsequent reduction in the synthesis rate of DA and 5-HT in the presynaptic neuron. Dopa and 5-HTP formation, as determined after in-vivo inhibition of the aromatic L-amino acid decarboxylase with NSD 1015 (3-hydroxybenzylhydrazine hydrochloride) are taken as indirect measures of DA and 5-HT synthesis rates, respectively, as described by Wikström et al., J. Med. Chem., 27, 1030 (1984). The biochemical experiments and the determinations of Dopa and 5-HTP by means of HPLC with electrochemical detection were performed. The antagonistic effects were seen as increases in the synthesis rate (n=4), as a result of the positive feed-back upregulation of synthesis. The effects on Dopa and 5-HTP accumulation are expressed as % of controls, which were: DOPA limbic system=447±23 ng/g and DOPA striatum=1045±47 ng/g, 5-HTP limbic region 241 ±2 ng/g (Table 2).

[0036] In the experiments with habituated rats no NSD was administered and the animals were killed one hour after drug administration. The brains were dissected and the levels of DA, DOPAC (control levels: limbic 304 ±11 ng/g and striatum 843 ±24 ng/g), HVA (control levels: 175±9 ng/g and striatum 651 ±16 ng/g), 5-HT and 5-HIAA (control levels: limbic region: 388 ±45 ng/g) were measured by means of HPLC with electrochemical detection. The levels were expressed as % of controls (DOPAC and 5-HIAA see Table 3). The in vivo brain microdialysis experiments were performed in conscious rats as described by Waters et al., Eur. J. Pharm., 187, 425-34 (1990).

[0037] Animals used in the biochemical and motor activity experiments were male rats of the Sprague-Dawley strain (ALAB, Sollentuna, Sweden), weighing 200-300 g. The rats were kept 5 per cage with free access to water and food (except for the starved animals for the experiments with per oral administration, who were only allowed water the last 18 hours before testing), at least one week from arrival until used in the experiments.

[0038] All substances to be tested were dissolved in saline immediately before use, occasionally with the addition of a few drops of glacial acetic acid and/or moderate heating in order to obtain complete dissolution. Injection volumes were 5 mL/kg.

[0039] Analysis of variance (ANOVA) followed by Fischer's test was used for the statistical calculations. P values less than 0.05 were regarded statistically significant.

[0040] D2 antagonist binding. Preparation of rat striatal membranes for [3H]-spiperone (specific activity 21-24 Ci/mmol) binding was carried out in a similar manner as described for D1-binding, Hyttel et al., J. Neural. Transm., 68, 171 (1987). The final pellets were homogenized in 1300 volumes of 50 mM K-phosphate buffer and the membrane suspension was incubated with 0.5 nM (3H]-spiperone in a final volume of 4.2 mL (3 mg original tissue) for 10 minutes at 37°C. Specific binding was 70-80% of total binding and was obtained by adding 10 µM 6,7-ADTN to the membrane suspension.

[0041] 5-HT1A radioligand binding. Male Sprague-Dawley rats (160-225 g) were killed by decapitation and the whole

brain with the exception of the brainstem and cerebellum was rapidly removed, weighed and chilled in ice-cold 0.9% NaCl. Each brain was homogenized (Ultra-Turrax, 20 s) in 10 mL ice-cold 50 mM Tris buffer (pH 8.0 at 25°C) containing 120 mM NaCl, 4 mM CaCl2 and 4 mM MgCl2 and centrifuged at 20,000 g's at 4°C for 10 minutes. Pellets were resuspended in 10 mL fresh buffer and preincubated for 10 minutes in a 37°C waterbath and then recentrifuged. Final pellets were homogenized in 100 volumes (w/v) of Tris buffer (as described above) containing 10 µM pargyline. The incubation tubes were kept on ice in triplicates and received 100 µL drug solution in water (or water for total binding) and 1000 µL membrane suspension (corresponds to 10 mg original tissue). The binding experiment was initiated by addition of 100 µL of (3H)-8-OH-DPAT (specific activity 143-158 Ci/mmol) in ascorbic acid (the final incubation concentration was 1nM (3H)-8-OH-DPAT in 0.1% ascorbic acid). After incubation for 15 minutes at 37°C the reaction was terminated by separation of the free radioligand from bound by rapid vacuum filtration using a cell harvester equipment (O.M. Teknik, Denmark). The tubes were rinsed with 4 mL and the filters (Whatman GF/F 25 mm) were washed twice with 4 mL ice-cold 0.9% NaCl.

[0042] The radioactivity of the filters was measured in a liquid scintillation counter (efficiency 41%) in 5 mL Picofluor®. Specific binding (70-75% of total binding) was defined as the radioactivity displaced by 10 µM 5-HT. IC50 values were calculated by semi-log plot and linear regression analysis.

[0043] The absence of significant decreases/increases in the DA metabolite levels in the hemispheral brain parts suggests that none of the compounds possess central NE receptor stimulating/blocking effects at the dosage under consideration.

[0044] The following detailed examples describe how to prepare the various compounds and/or perform the various processes of the invention. Those skilled in the art will promptly recognize appropriate variations from the procedures both as to reactants and as to reaction conditions and techniques.

Pharmacological Results

[0045] In vivo biochemical data, as exemplified with the prototypical test compound of Example 11:

[0046] DOPA accumulation (DA synthesis rate) in non-pretreated rats (Table 2). After the locomotor activity session (see Table 2, above) the rats were injected with the decarboxylase inhibitor NSD 1015 (100 mg/kg, sc) and killed 30 minutes later. The DOPA accumulation in the DA -rich limbic and striatal and the NE-rich cortical (mainly hemispheres) brain areas were expressed as % of saline treated controls.

[0047] The DOPA accumulation was dose-dependently (3.1-200 µmol/kg, s.c.) elevated in the limbic (limb.) and striatal (stri) brain regions with a maximal response equal to that observed for classical neuroleptics such as haloperidol. The cortical (cort) DOPA formation was slightly, but statistically significantly increased. High doses (25 µmol/kg, sc and above) also weakly elevated (+45-50%) brain 5-HTP formation (Table 2). However, no statistical significant effects on brain 5-HIAA levels were observed (Table 3).

[0048] DOPA accumulation, time course after s.c. and p.o. administration (Table 2). The animals were injected with S-(-)-34 50 µmol/kg and killed after various time intervals (sc: 1.0, 2.5 and 4.5 hours; po 1.0 and 2.5 hours). NSD 1015 (100 mg/kg, sc) was injected 30 minutes before death. The data are expressed as % of saline treated controls.

[0049] The duration of the increase in brain DOPA accumulation was 2.5-4.5 hours after s.c. administration and 1.5-2.5 hours after po administration.

[0050] The effects on DOPA accumulation in the GBL-model is considered to reflect an event at the presynaptic dopamine autoreceptors (for further details, see Svensson et al., Naunyn-Schmiedeberg's Arch. Pharm., 334, 234 (1986)). GBL (750 mg/kg, i.p. 35 minutes before death) elevated the limbic and striatal DA synthesis rate. This effect was completely reversed by the dopamine agonist apomorphine (0.16 mg/kg, sc, 40 minutes before death).

[0051] S-(-)-34 (200 µmol/kg, sc, 40 minutes) blocked the effect of apomorphine but was inactive per se. A lower dose (100 µ mol/kg, sc) of S-(-)-34 produced only a partial blockade of the apomorphine effect (data not shown). These data strongly indicate DA autoreceptor blocking effects of S-(-)-34 and no direct agonistic effects of the compound on central DA autoreceptors.

[0052] After the activity session the rats were killed and the brain levels of HVA and DOPAC were measured (data are expressed as means ± SEM). A pronounced and dose-dependent increase in brain DA metabolism was noted after sc administration of Example 11. No effects on the brain levels of 5-HIAA were observed (Table 3).

[0053] The dialysis was performed in conscious rats implanted with a dialysis probe (Carnegie Medicin, Stockholm) in the caudate. Example 11 (50 µmol/kg, sc) was injected when a stabile baseline was obtained. The perfusion media was a Ringer solution with a Ca2+ concentration of 1.2 mM. The perfusion rate was 2.0 µL/min and samples were collected every 20 minutes and analyzed on HPLC/EC. Effects on striatal DA release in the in vivo microdialysis model, time course are shown in Table 4. Data are expressed as % of controls, means ± SEM, n = 4.

[0054] The increase in release of DA and in the levels of the DA metabolite DOPAC (Table 4) was similar to that noted for (+)-AJ76 27 and classical DA receptor antagonists like haloperidol (unpublished data from this lab.). The duration of the effect was approximately 2.5 hours. The duration for the increase in DOPAC and HVA appears to be

at least 4 hours. No consistent changes in the levels of 5-HIAA were noted (Table 4).

TABLE 4

Table 4. Microdialysis in rat striatum (% of control) for Example 11 at 50 μ mol/kg s.c., n=4

MINUTES	DA	HVA	DOPAC	5-HIAA
0	100	100	100	100
20	180	140	180	110
40	240	200	250	115
60	280	250	295	120
80	300	280	300	115
100	280	300	295	115
120	275	310	280	110
140	225	300	260	105
160	200	305	250	110
180	190	280	230	110
200	180	220	215	110
220	160	230	190	100

[0055] In the in vitro binding assays (Table 1), Example 11 had an IC50 of 3500 nM for the dopamine D2 receptor sites while the affinity for the 5-HT1A sites was much lower (IC50 = 75000 nM).

[0056] In vivo behavioral data was obtained with rats injected with drug and 5 minutes later put into the motility chambers for the first time. The motor activity was measured for the subsequent 30 minutes (accumulated counts/30 minutes) and expressed as % of saline treated controls. Example 11 produced a dose-dependent (25-200 μmol/kg, sc) monophasic increase in motor activity with a maximal effect of +60%.

[0057] Locomotor activity was measured in rats which were habituated 60 minutes to the activity meters before drug injection. The activity was measured for the subsequent 60 minutes and expressed as % of controls (means ± SEM, n = 4). The activity of the habituated rats were approximately 10% of the activity of the non-habituated rats.

[0058] Example 11 produced a strong locomotor stimulation (+600%) in the habituated rats. Stereotyped sniffing and rearing was also observed. The efficacy of Example 11 is lower than that of d-amphetamine but similar or even somewhat higher than that of the preferential DA autoreceptor antagonists (+)-AJ76 and (+)-UH232 5.

[0059] It was shown that Example 11-induced hypermotility in habituated rats is blocked by haloperidol, raclopride, reserpine and alpha-methyl-para tyrosine. The hypermotility induced by 50 μmol/kg s.c. of Example 11 was blocked by the DA receptor blockers haloperidol and raclopride. The test compounds were administered consecutively at the same time. These results strongly suggests that the stimulation produced by Example 11 was mediated via central dopamine receptors.

[0060] The catecholamine synthesis inhibitor alpha-methyl-para-tyrosine (Sigma, alpha-MT;100 mg/kg, i.p.) was administered 60 minutes before Example 11 (50 mol/kg, s.c.). Alpha-MT alone did not affect the motor activity while it partially inhibited the locomotor stimulation produced by Example 11. This suggests that the behavioral activation is indirectly mediated via an increase in the release of DA. The monoamine depleting agent reserpine (5 mg/kg, 18h before) completely prevented the locomotor stimulation produced by Example 11 (50 μmol/kg, sc). The corresponding R-enatiomer (50 μmol/kg, sc) failed to activate the reserpinized rats: 6±2 counts/30 min.

[0061] Effects on d-amphetamine-induced hyperactivity in habituated rats was measured where the rats were habituated to the motility meters for 60 minutes before injection of test drugs (d-amphetamine 0.5 or 5.0 mg/kg, sc ; (+)-AJ76 14 mg/kg, sc and Example 11, 14 mg/kg, sc. The activity was measured for the subsequent 60 minutes and was expressed as accumulated counts/60 min (means ± SEM).

[0062] Example 11, per se, produced a locomotor stimulation in habituated rats. Example 11 failed to affect the strong activation induced by a high dose (5 mg/kg, sc) of d-amphetamine while (+)-AJ76 clearly blocked the stimulation produced by d-amphetamine. When combined with a lower dose of d-amphetamine (0.5 mg/kg, sc), Example 11 produced an additive stimulatory effect. Also a higher dose (64 mg/kg, sc = 200 μmol/kg) of Example 11 failed to block the hyperactivity induced by d-amphetamine (5.0 mg/kg, sc) in habituated rats :d-amphetamine 871±68 %; S-(-)-34 + d-amphetamine: 773 ± 158%; NaCl: 100 ± 14% (% of NaCl controls), no statistical significant difference between d-amphetamine and d-amph.plus Example 11 was observed.

[0063] These results suggest that Example 11 even at very high doses lacks detectable blocking properties at post-synaptic dopamine receptors. This is in contrast to the actions of the preferential dopamine autoreceptor antagonists (+)-AJ76 and (+)-UH232 5. The blood levels of Example 11 were measured after oral (40 μmol/kg) and iv (5 μmol/kg)

administration of the drug to male Sprague -Dawley rats (250-300g) that were cannulated with catheters in the jugular vein and the arteria carotis. The levels of Example 11 were measured in whole blood by means of GC-MS. A comparison of the areas under the curves yields an oral bioavailability of approximately 78%. The half-life was approximately 3 hours (i.v. curve). The oral availability is considerably better than the values obtained for (+)-UH232 and (+)-AJ76 (approximately 6 and 3%, respectively).

[0064] The biochemical actions of Example 11 on indices of presynaptic dopaminergic autoreceptor activity indicate a profile indistinguishable from that of classical neuroleptics. Example 11 stimulates DA synthesis rate (DOPA) accumulation and metabolism (DOPAC and HVA levels) in limbic and striatal brain regions. An increased release of DA is evident from the microdialysis study. These effects of Example 11 are likely to be the result of a blockade of the presynaptic dopamine autoreceptors. This is also strengthened by the fact that Example 11 blocks apomorphine in the GBL-model (considered to reflect activity at dopamine autoreceptors). In vitro, Example 11 possesses, albeit weak, affinity to the dopamine D2 receptor site. Furthermore, as expected, the compound failed to affect the DOPA accumulation in reserpinized (5mg/kg, 18h) rats. This strongly indicates a lack of direct agonistic effects at central dopamine receptors.

[0065] In non-pretreated rats, Example 11 elevated brain 5-HTP levels indicating an antagonistic affect also at central 5-HT1A receptors. However, it is likely that this response is of an indirect nature since Example 11 failed to affect brain levels of 5-HIAA (both in habituated rats and in the microdialysis model) and also displayed a very low affinity for the 5-HTIA receptors in vitro. The slight increase in cortical DOPA accumulation suggest that Example 11 might block central alpha 2-receptors.

[0066] In sharp contrast to classical neuroleptics, Example 11 displayed stimulant effects on the locomotor activity in the behavioral assays. The degree of locomotor stimulation depend largely on the baseline activity of the rats. A pronounced activation with weak stereotypies (sniffing and rearing) was observed in habituated rats. The maximal degree of stimulation is lower than that observed after classical stimulants like d-amphetamine and apomorphine but higher than that produced by the preferential dopamine autoreceptor antagonists (+)-UH232 and (+)-AJ765.

[0067] The latter difference is most likely explained by the fact that Example 11 appears to lack the ability to block postsynaptic DA receptors; Example 11 failed to block d-amphetamine- induced hyperactivity even at high doses. Thus, Example 11 appears to have an even higher preference for the dopamine autoreceptors than have (+)-UH232 and (+)-AJ76.

[0068] Example 11 is likely to exert its effects via a selective blockade of the presynaptic dopamine autoreceptors. As a result of this the synthesis and release of dopamine is increased. The newly released dopamine will activate the postsynaptic DA receptors and produce a behavioral stimulation. The fact that the behavioral stimulation is blocked by raclopride and haloperidol strongly suggest that the effects of Example 11 is mediated via central dopamine receptors. It is most likely that the DA autoreceptor blockade of Example 11 results in an increased release of dopamine from the granular storage pool since the locomotor stimulation also is blocked by pretreatment with reserpine and alpha-MT.

[0069] The pharmacokinetic experiments show that Example 11 clearly has a higher oral availability (78%) than both (+)-UH232 and (+)-AJ76 in the rat. When comparing the effects on DOPA accumulation e.g. in the striatum (Table 2) after sc and po administration an estimated availability of 50% is obtained.

[0070] Taken together, the available pharmacological data strongly indicate that Example 11, the prototype compound, selectively blocks central dopamine autoreceptors and has favorable pharmacokinetic properties.

[0071] The following Examples illustrate compounds of the invention.

Example 1 S-(-)-3-((3-(Trifluoromethyl)sulfonyl)oxyphenyl-N-n-propyl)-piperidine

[0072] A solution of S-(-)-3-(3-hydroxyphenyl-N-n-propyl)piperidine (3.3 g, 15.07 mmol), 2,6-lutidine (2.42 g, 22.6 mmol) and 4-dimethylaminopyridine (0.368 g, 3.01 mmol) in 300 ml CH_2Cl_2 was cooled to -30°C. Then triflic anhydride (9.65 g, 34.2 mmol) in 30 ml CH_2Cl_2 was added dropwise. The reaction mixture was allowed to warm to room temperature and stirred for 2 hours at 25°C. The reaction was quenched with cold water. The layers were separated, and the organic phase was washed with 2 portions of cold 5% HCl-solution. Following a wash of the organic portion with brine and drying ($MgSO_4$). The solvent was removed under reduced pressure and the residue was used without any further purification, except for 200 mg, which was chromatographed on a silica column with MeOH:CH_2Cl_2 (1:19) as eluent. Evaporation of the solvent, addition of ether to the remaining solid, filtration of the insoluble SiO_2, and addition of ethereal HCl to the ether solution afforded the title compound x HCl: m.p. 156-158°C.

Example 2 S-(+)-3-((3-(Trifluoromethyl)sulfonyl)oxyphenyl-N-methyl)-piperidine

[0073] This product was prepared as described for Example 1.

Example 3 S-(-)-3-((3-(Trifluoromethyl)sulfonyl)oxyphenyl-N-ethyl)-piperidine

[0074] This product was prepared as described for Example 1.

Example 4 S-(-)-3-((3-(Trifluoromethyl)sulfonyl)oxyphenyl-N-n-butyl)-piperidine

[0075] This product was prepared as described for Example 1.

Example 5 S-3-((3-(Trifluoromethyl)sulfonyl)oxyphenyl-N-allyl)piperidine (S-17)

[0076] This product was prepared as described for Example 1.

Example 6 S-3-((3-Methylsulfonyl)oxyphenyl-N-n-propyl)piperidine

[0077] A solution of S-(-)-3-(3-hydroxyphenyl-N-n-propyl)piperidine (200 mg, 0.91 mmol), triethylamine (101 mg, 1 mmol) in 15 ml CH_2Cl_2 was cooled to 0°C. Then CH_3SO_2Cl (136 mg, 1.19 mmol) in 5 ml CH_2Cl_2 was added dropwise. The reaction mixture was allowed to warm to room temperature and stirred for 2 hours at 25°C. The reaction was quenched with water, the layers were separated, and the organic phase was washed with 10% HCl and 10% Na_2CO_3. The organic phase was dried ($MgSO_4$) and the solvent was removed under reduced pressure. The residue was chromatographed on a silica column with MeOH:CH_2Cl_2 (1:12) as eluent. The solvents from the collected fractions containing pure S-22 were evaporated and addition of fumarate salt afforded the title compound fumarate (200 mg, 66%): m.p. 164-165°C (fumarate salt).

Intermediate 1 S-3-(3-Methoxycarbonyl)phenyl-N-n-propyl)piperidine

[0078] A mixture of Example 1 (5.5 g), triethylamine (3.17 g, 31.34 mmol), MeOH (20 g, 626.8 mmol), $Pd(OAc)_2$ (0.105 g, 0.47 mmol), 1,3-Bis(diphenylphosphino)propane (0.194 g, 0.47 mmol) in 60 ml DMSO was stirred at room temperature for 15 minutes or until all particles were dissolved in the solution. A stream of CO was passed into the solution for 4-5 minutes, then the reaction vessel and contents were placed in a 70°C oil bath under CO balloon. After 6 hours GC revealed complete absence of starting triflate S-15 and a 90 % yield of the title ester. The reaction mixture was allowed to cold to room temperature. Water (200 ml) was then added. The water solution was extracted with 5 portions of Et_2O. The combined organic phases were washed with water until neutral, dried ($MgSO_4$), and evaporated. The residue was used without any further purification: m.p. 166-167°C (HC salt).

Example 7 S-(-)-3-(3-Carbamoylphenyl-N-n-propyl)piperidine

[0079] A suspension of S-25 (3.5 g, 13.4 mmol) in 10% NaOH solution (110 ml) and MeOH (30 ml) was refluxed until reaction was completed as shown by T.L.C (2.5 hours). The reaction mixture was acidified by 10 % HCl and evaporated in vacuo. The solid residue was triturated with EtOH and filtered. Evaporation of the EtOH afforded the crude aminoacid hydrochloride as slight brown crystals.

[0080] The amino acid was heated in thionyl chloride (10 ml) at 50°C for 1.5 hours. After the addition of more thionyl chloride (5 ml), the heating was continued for 1.5 hours. Evaporation of the excess thionyl chloride gave an oil which crystallized on standing. The solid acyl chloride that fanned was dissolved in $CHCl_3$ (100 ml) and NH_3 (g) was slowly bubbled through the solution for 1 hour. The reaction mixture was evaporated, and the solid residue was triturated with CH_2Cl_2 (50 ml). The NH_4Cl was filtered off, and the solvent was evaporated to afford the title compound x HCl as light-brown crystals. This product was chromatographed on silica column with MeOH as eluent. Collection of the pure fractions of the product and evaporation of the solvent afforded pure title compound x HCL (2g): m.p. 130°C.

Example 8 S-3-(3-Carbamoylphenyl-N-methyl)piperidine

[0081] This product was prepared as described for Example 7.

Example 9 S-3-(3-Carbamoylphenyl-N-ethyl)piperidine

[0082] This product was prepared according to Example 7.

Example 10 S-3-(3-Carbamoylphenyl-N-n-butyl)piperidine

[0083] This product was prepared as described for Example 7.

Example 11 S-(-)-3-(3-Cyanophenyl-N-n-propyl)piperidine

[0084] A solution of Example 7 x HCl (1.42 g, 5.02 mmol) and 1.8 ml $POCl_3$ in dry DMF (10 ml) was heated at 80°C for 3 hours in argon-atmosphere. Evaporation of the reaction mixture gave a dark oily residue, which was dissolved in H_2O. The water solution was basified with saturated Na_2CO_3 solution and extracted several times with CH_2Cl_2. The combined organic layers were evaporated under reduced pressure and the residue was dissolved in Et_2O and insoluble particles were filtered off. The solvent was evaporated and the residue was chromatographed on a silica column with MeOH:CH_2Cl_2 (1:9) as eluant. Collection of the pure fractions and evaporation of the solvent, addition of Et_2O to the remaining solid, filtration of insoluble SiO_2, and addition of ethereal HCl to the Et_2O solution afforded crystals of the title compound x HCl. Recrystallization from ethanol/isopropyl ether gave pure crystals (1 g, 75%): m.p. 190-191°C.

Example 12 S-3-(3-Cyanophenyl)piperidine

[0085] A solution of Example 11 (1.6 g, 7.02 mmol) in 30 ml of dichloroethane was cooled to 0°C. Then α-chloroethyl chloroformate (1.49 g, 10.5 mmol) in 10 ml dichloroethane was added dropwise at 0°C. The reaction mixture was refluxed for 10 hours. Three portions (1 ml) of α-chloroethyl chloroformate were added during three days. After this period the heating was interrupted and the volatiles were evaporated in vacuo. The residue was triturated with 75 ml MeOH and refluxed for 1.5 hours. The solvent was evaporated to afford the title compound x HCl as light-brown crystals. The product was chromatographed on a silica column with MeOH as eluent. Evaporation of the solvent afforded pure S-31x HCl (1.0 g, 76 %): m.p. 123-124°C (fumarate salt).

Example 13 S-(+)-3-(3-Cyanophenyl-N-methyl)piperidine

[0086] This product was prepared as described for Example 11: m.p. 210-212°C.

Example 14 S-(-)-3-(3-Cyanophenyl-N-ethyl)piperidine

[0087] This product was prepared as described for Example 11: m.p. 192-194°C.

Example 15 S-3-(3-Cyanophenyl-N-n-butyl)piperidine

[0088] This product was prepared as described for Example 11: m.p. 117-119°C.

Example 16 S-3-(3-Cyanophenyl-N-allyl)piperidine

[0089] A suspension of Example 12 (173 mg, 0.778 mmol) and ground K_2CO_3 (330 mg) was stirred in 10 ml of CH_3CN at room temperature. Allyl bromide (97.5 mg, 0.806 mmol) dissolved in 1 ml of CH_3CN was added dropwise over a period of 2 hours. The mixture was stirred overnight. The reaction mixture was filtered, and the volatiles were evaporated in vacuo. The oily residue was chromatographed on a silica column with MeOH:CH_2Cl_2 (1:19) as eluent. Evaporation of the solvent afforded pure title compound. The amine was converted into the hydrochloride and recrystallized from ethanol/isopropyl ether (131 mg, 64%): m.p. 183-185°C.

Example 17 S-3-(3-Cyanophenyl-N-iso-propyl)piperidine

[0090] This product was prepared as described for Example 16: m.p. 185-186°C.

Example 18 S-3-(3-Cyanophenyl-N-cyclopropylmethyl)piperidine

[0091] This product was prepared as described for Example 16.

Example 19 S-(-)-3-(3-Acetylphenyl)-N-n-propylpiperidine

[0092] To a stirred solution of Example 1 (1.87 g, 5.34 mmol) in DMF (18 mL) under an argon atmosphere at room temperature were sequentially added Et_3N (1.63 g, 16 mmol), butylvinyl ether (4.01 g, 40 mmol), DPPP (309 mg, 0.749

mmol), and $Pd(OAc)_2$ (129 mg, 0.575 mmol). The reaction flask was heated to 80 °CC. After 0.5 h the conversion was complete (GLC). The reaction mixture was cooled to room temperature, 5% HCl (30 mL) was added and after another 0.5 h of stirring the mixture was poured into CH_2Cl_2 (60 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL), and the combined organic layers were washed with water until neutrality, dried (anhydrous $MgSO_4$), filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography (CH_2Cl_2/MeOH, 9/1 by volume), affording the title compound (964 mg, 74%). The amine was converted into the hydrochloride salt and recrystallized from ethanol/isopropyl ether: m.p. 151-56°C (HCl); MS *m/e* 245.15 (M^+, 3.3), 217.05(15.8), 216.05 (100), 133.05 (5.0), 130.95 (5.6), 114.95 (4.8), 100.55 (6.1), 86.05 (6.2); $a)_D^{20}$ -5.1°C (c=1.0, MeOH).

Example 20 S-(-)-3-(3-Cyanophenyl)-N-propargylpiperidine

[0093] This compound was prepared as described for Example 16 from Example 12 (363 mg, 1.95 mmol) and propargyl bromide (237 mg, 1.99 mmol). Purification of the crude reaction mixture by flash chromatography (CH_2Cl_2/MeOH, 25/1 by volume) afforded 302 mg (69%) of pure title compound as an oil. The amine was converted to the hydrochloride salt with HCl-saturated ethanol and recrystallized from ethanol/ isopropyl ether: m.p. 195-96°C (HCl); $a)_D^{20}$ -7.6°C (c=1.0, MeOH); Analysis calc'd for $C_{15}H_{16}N_2$ x HCl: C, 69.09; H, 6.57; N, 10.74; found: C, 69.0; H, 6.6; N, 10.5.

Example 21 S-(-)-3-(3-Cyanophenyl)-N-2-butylpiperidine

[0094] This compound was prepared as described for Example 16 from Example 12 (0.7 g, 3.76 mmol) and 2-iodobutane (0.7 g, 3.8 mmol). Purification of the crude reaction mixture by flash chromatography (CH_2Cl_2/MeOH, 19/1 by volume) afforded 700 mg (77%) of pure title campound as an oil. The amine was converted into the fumarate salt, and recrystallized from ethanol/isopropyl ether: m.p. 153-57°C (fumarate); MS *m/e* 242.25 (M^+, 1.1), 227.25 (8.2), 214.25 (15.9), 213.25 (100), 142.2 (4.4), 129.1 (5.0), 116.1 (10.6);)a)$_D^{20}$-19.9°C (c=1.0, MeOH).

Intermediate 2 S-3-(3-Aminophenyl)-N-n-propylpiperidine

[0095] To a solution of Intermediate 1 (10 g, 38.31 mmol) in concentrated sulphuric acid (240 mL) and CH_2Cl_2 (400 mL) was added carefully NaN_3 (15 g, 231 mmol). After the addition was completed, the mixture was refluxed (50 °CC). Over a period of 6 h small portions of NaN_3 (3 x 2 g) were added to the reaction mixture. After refluxing for 20 h, the reaction was cooled to room temperature and quenched with ice water. The aqueous solution was basified with 50% NaOH and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 200 mL), and the combined organic phases were dried with $MgSO_4$, filtered, and concentrated *in vacuo* to give 6.2 g (28.44 mmol, 74%) of crude Intermediate 2 (95% purity according to G.L.C), which was used without further purification. : MS *m/e* 218.45 (M^+, 13.2), 190.4 (13.4), 189.4 (100), 120.25 (19.1), 119.25 (13.6), 106.2 (13.4), 86.30 (10.9), 70.15 (19.0).

Intermediate 3 S-(-)-3-(3-Bromophenyl)-N-n-propylpiperidine

[0096] To a solution of the amine hydrochloride Intermediate 2 (16.28 g, 55.96 mmol) in 100 mL of 48% aqueous HBr at 0°C was added dropwise with stirring a solution of $NaNO_2$ (4.2 g, 60.96 mmol) in 4 mL H_2O. The reaction mixture was stirred for 1 h at 0 °C under Ar-atmosphere. Cuprous bromide (8.2 g, 57.16 mmol) dissolved in 20 mL of 48% HBr was added, and the solution was heated at 80 °C for 40 min. After cooling, 100 mL of water was added and the reaction mixture was made alkaline with concentrated ammonia. The aqeous solution was extracted with CH_2Cl_2 (3 x 60 mL). The combined organic phases were dried ($MgSO_4$), filtered, and the solvent was evaporated *in vacuo* to give 13.6 g (85%) of crude Intermediate 3. The residue, was purified by flash chromatography using CH_2Cl_2/MeOH (9/1) as eluent, affording pure Intermediate 3 (9.05 g, 57.3 %). The amine was converted to the hydrochloride salt with ethereal HCl. The Intermediate 3 x HCl was recrystallized in ethanol:isopropyl ether: m.p. 209-11°C (HCl); MS *m/e* 283.05 ($M^+ + 1$, 2.8), 282.05 (M^+, 1.9), 281.05 ($M^+ - 1$, 3.4), 254.95 (12.1), 253.95 (94.2), 251.95 (100), 129.95 (30.8), 128.95 (31.7), 115.95 (20.6), 114.95 (23.7);)a)$_D^{20}$ -7.9°C (c=1.0, MeOH); Analysis calc'd for $C_{14}H_{21}NBrCl$: C, 52.77; H, 6.64; N, 4.40; found: C, 52.9; H, 6.8; N, 4.6.

Example 22 S-3-(3-Thiomethylphenyl)-N-n-propylpiperidine

[0097] To a solution of Intermediate 3 (1.0 g, 3.56 mmol) in dry diethyl ether (20 mL) at -78 °C were added a solution of s-butyllitium in hexane (1.4 M, 3.56 mL, 4.98 mmol). The solution was stirred at -78 °C for 15 min., allowed to warm to 0 °C, stirred for additional 30 min. at 0 °C, brought to -78 °C, and then was treated with dimethyl disulfide (502 mg, 5.34 mmol). The reaction mixture was allowed to warm to room temperature and stirred for lh. The reaction mixture was then diluted with 10% Na_2CO_3 and the phases were separated. The aqueous phase was extracted with diethyl

ether (3 x 30 mL) and the combined organic phases were washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give 980 mg (110%) of crude title compound. The residue was purified by flash chromatography using CH_2Cl_2/MeOH (12/1) as eluent, affording pure title compound (560 mg, 63%). The amine was converted to the hydrochloride salt with ethereal HCl. The title campound x HCl was recrystallized in ethanol:isopropyl ether: MS *m/e* 249.25 (M^+, 7.9), 221.15 (15.3), 220.15 (100), 150.15 (5.2), 129.15 (7.3), 115.05 (6.9).

Example 23 S-3-(3-Methylsulfonylphenyl)-N-n-propylpiperidine

[0098] To a solution of Example 22 (560 mg, 2.25 mmol) in trifluoroacetic acid (5 mL) was added a solution of m-chloroperbenzoic acid (970 mg, 3.62 mmol) in trifluoroacetic acid (3 mL). The solution was stirred at room temperature for 3 h and poured into ice water. The resulting mixture was made alkaline with 15% NaOH, and extracted with CH_2Cl_2 (3 x 25 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The oily residue as purified by flash chromatography using CH_2Cl_2/ MeOH (9/1) as eluent, affording pure title campound (537 mg, 85%). The amine was converted into the fumarate salt and recrystallized in ethanol : isopropyl ether: m.p. 105-08°C (fumarate); MS *m/e* calc'd for $NO_2SC_{15}H_{23}$: 281.145, found 281.143; 281.25 (M^+, 2.9), 253.15 (16.1), 252.15 (100), 129.15 (9.6), 70.15 (6.4).

Example 24 S-3-(3-Trifluoromethylsulfonylphenyl)-N-n-propylpiperidine

[0099] To a solution of Intermediate 3 (1.0 g, 3.56 mmol) in dry diethylether (20 mL) at -78°C was added a solution of s-butyllitium in hexane (1.4 M, 3.56 mL, 4.98 mmol). The solution was stirred at-78 °C for 15 min., and allowed to warm to 0°C. After an additional 30 min. at 0 °C the mixture was brought to -78 °C and treated with trifluoromethanesulfonic anhydride (1.1 g, 3.91 mmol). The reaction mixture was allowed to warm to room temperature and stirred for lh. The reaction mixture was then diluted with 10% Na_2CO_3 and the phases were separated. The aqueous phase was extracted with diethyl ether (3 x 30 mL) and the combined organic phases were washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo.*: MS *m/e* calc'd for $F_3NO_2SC_{15}H_{20}$: 335.117, found 335.099; 335.1 (M^+, 5.0), 202.25 (10.7), 144.15 (17.3), 129.15 (18.2), 117.15 (35.9), 115.15 (21.1), 91.15 (25.9), 72.15 (100).

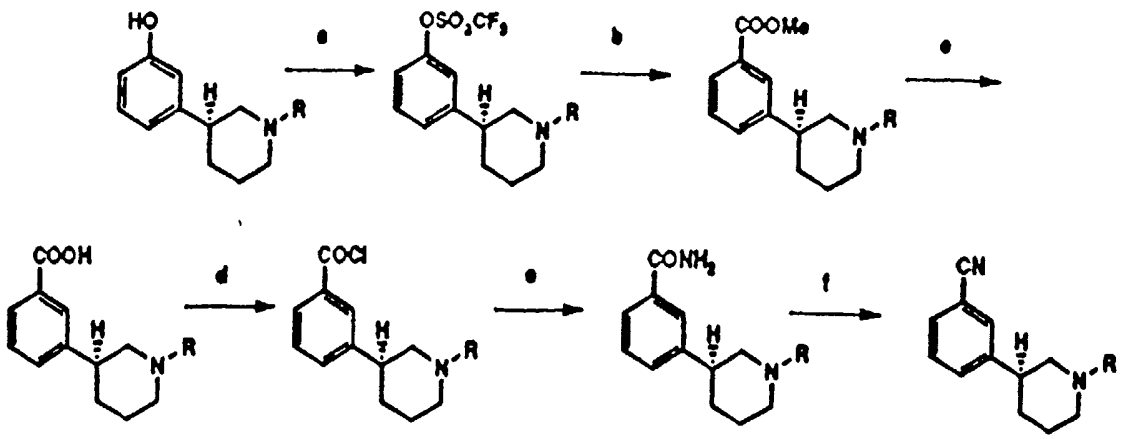
Example 25 S-3-(3-Aminosulfonylphenyl)-N-n-propylpiperidine

[0100] To a solution of Intermediate 3 (700 mg, 2.49 mmol) in dry THF (20 mL) at -78 °C was added a solution of s-butyllitium in hexane (1.4 M, 2.66 mL, 3.73 mmol). The solution was stirred at-78 °C for 15 min.and allowed to warm to 0 °C. After an additional 30 min. at 0 °C the solution was brought to -78 °C, at which time dry sulfur dioxide gas was passed into the reaction vessel via a needle positioned just above the surface of the solution for 20 min. to give a copious precipitate. The reaction mixture was allowed to warm to room temperature and stirred for lh under SO_2 (g). The reaction mixture was then concentrated *in vacuo* and pretreated with CH_2Cl_2 (25 mL). The suspension was cooled to 0 °CC and SO_2Cl_2 (3 mL) was added dropwise. After 2 h the mixture was concentrated *in vacuo* to remove excess of $SOCl_2$.The oily residue was dissolved in CH_2Cl_2 (35 mL) and cooled to 0 °CC. Ammonia gas was bubbled through the solution for 20 min. The suspension was filtered through a pad of celite and washed several times with CH_2Cl_2. The organic phase was washed with brine. dried ($MgSO_4$), filtered and concentrated in *vacuo.*: MS *m/e* calc'd for $N_2O_2SC_{14}H_{22}$: 282.140, found 282.139; 282.25 (M^+, 2.9), 254.15 (13.5), 253.15 (100), 129.15 (9.9), 128.15 (7.3), 115.15 (6.9).

Example 26 S-3-3-(((Trifluoromethyl)sulfonyl)amino)phenyl)-N-n-propy 1-piperidine

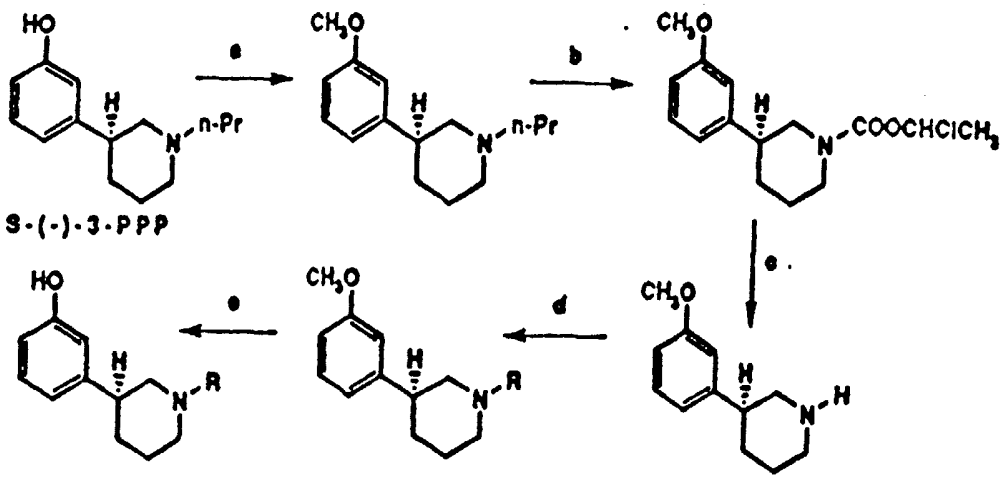
[0101] This compound was prepared as described for Example 1 from Intermediate 2 (230 mg, 1.05 mmol) and triflic anhydride (326 mg, 1.16 mmol). Purification of the crude product by flash chromatography (CH_2Cl_2/MeOH, 9/1 by volume) afforded 176 mg (48%) of pure title compound as crystals: m.p. 124-28°C (base) MS *m/e* 350.2 (M^+, 2.6), 322.15 (16.2), 321.15 (100), 188.25 (12.3), 187.25 (20.0), 160.15 (9.2), 144.15 (10.0).

Scheme 1



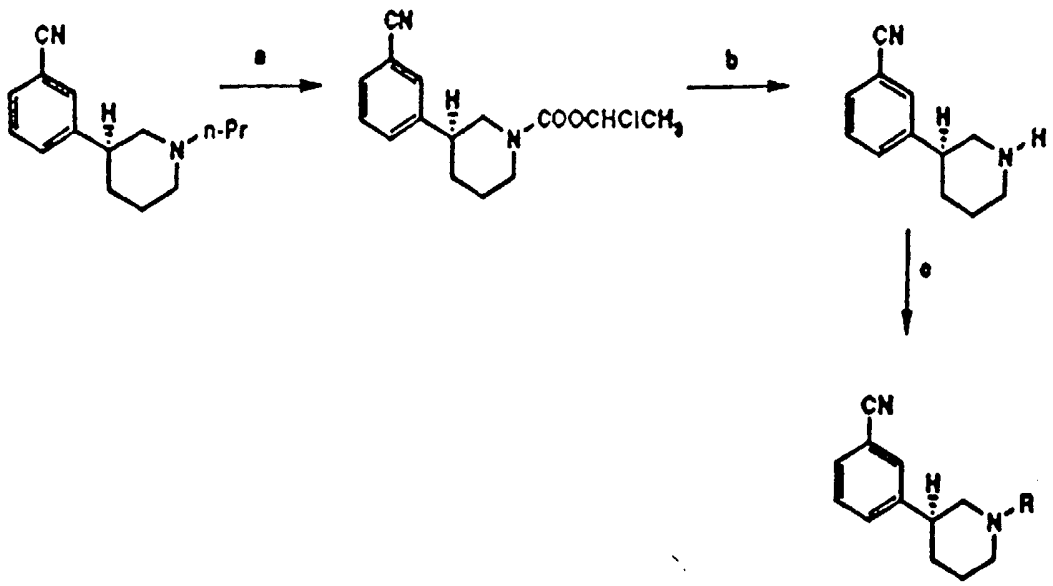
Reagents: a) $(CF_3SO_2)_2O$ b) $Pd(OAc)_2$ and CO(g) c) 10% NaOH d) $SOCl_2$ e) NH_3 f) $POCl_3$

Scheme 2

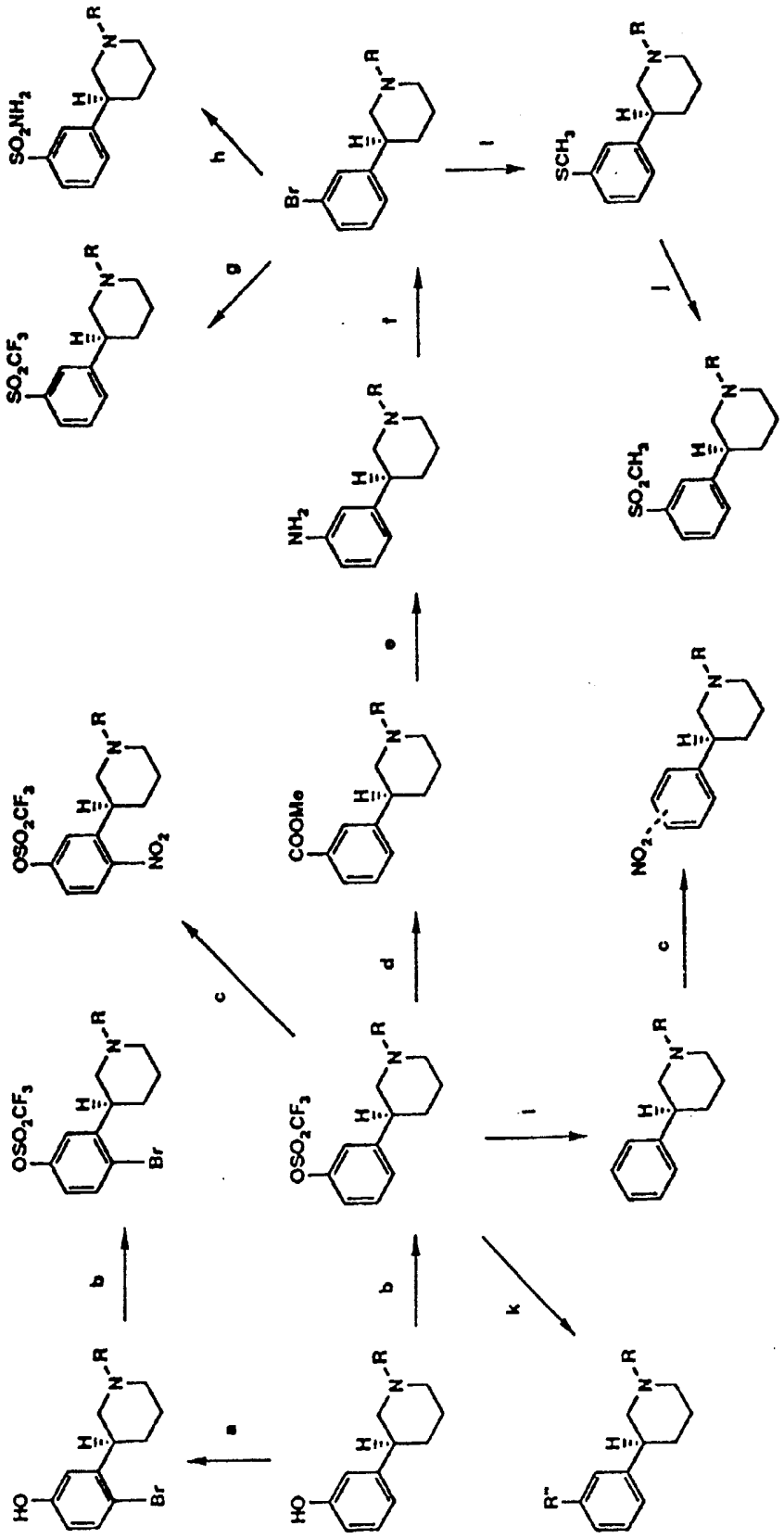


Reagents: a) NaOH, $(CH_3)_2SO_4$ b) $CH_3CHClOCOCl$ c) MeOH
d) R_1CHO (where $R = R_1CH_2$) and $NaBH_3CN$ e) 48% HBr

Scheme 3



Reagents: a) $CH_3CHClOCOCl$ b) MeOH c) K_2CO_3, RX

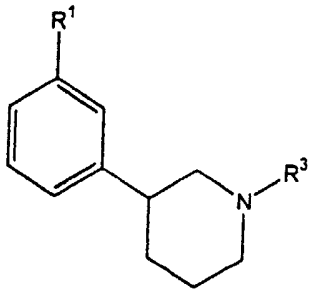


Scheme 4

Reagents: a) Pyridinium bromide perbromide b) $(CF_3SO_2)_2O$ c) HNO_3/H_2SO_4 d) $Pd(OAc)_2$, CO(g) e) H_2SO_4, NaN_3 f) CuBr, $NaNO_2$ g) BuLi, $(CF_3SO_2)_2O$ h) BuLi, SO_2(g), NH_3(g) i) BuLi, CH_3SSCH_3 j) MCPBA, CF_3COOH k) "Pd", R_3SnR' l) $Pd(OAc)_2$, HCO_2H

Claims

1. A compound that is a (S)-enantiomer of formula I



wherein R^1 is CN, OSO_2CH_3, OSO_2CF_3, CHO, $CONH_2$, $S(O)_{0-2}CH_3$, $S(0)_{0-2}CF_3$, SO_2NH_2 or $NHSO_2CF_3$; and R^3 is hydrogen, CF_3, CH_2CF_3, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_4-C_9 cycloalkylmethyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, 3,3,3-trifluoropropyl, 4,4,4-trifluorobutyl or CH_2SCH_3;
or a pharmaceutically-acceptable salt thereof.

2. A compound of claim 1, wherein R^1 is OSO_2CF_3, CN, SO_2NH_2, SO_2CF_3, SCH_3 or SO_2CH_3.

3. A compound of claim 1, wherein R^1 is CN.

4. A compound of claim 1, wherein R^1 is OSO_2CF_3 or SO_2CH_3.

5. A compound of any preceding claim, wherein R^3 is alkyl.

6. A compound of claim 5, wherein R^3 is n-propyl.

7. A compound of claim 1, which is S-(-)-3-(3-cyanophenyl)-N-n-propylpiperidine.

8. A compound of claim 1, which is S-3-(3-methylsulfonylphenyl)-N-n-propylpiperidine.

9. Use of a compound of any preceding claim, for the manufacture of a medicament for treating central nervous system disorders associated with dopamine receptor activity.

10. The use of claim 9, wherein the compound is administered to a patient in an amount of 50-500 mg/70 kg orally or 0.5 to 50 mg/70 kg parenterally.

11. The use of claim 9, for treating geriatric disorders for improvement of mental and motor functions.

12. The use of claim 9, for the rehabilitation of drug abusers.