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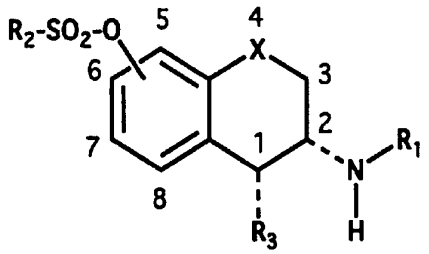

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(57) Abstract

A compound of formula (1) or pharmaceutically acceptable acid addition salts thereof, wherein R_1 is H, (C_1-C_8) alkyl, alkenyl, alkynyl, cyclopropylalkyl or (C_1-C_8) haloalkyl; X is CH_2, O or S; R_2-SO_2-O is in position 5, 6, 7 or 8 and R_2 is CF_3, CF_2CF_3, C_1-C_8 alkyl, substituted aryl (e.g. 4-toluyl); R_3 is H, CH_3 or CH_2CH_3. When R_3 is CH_3 or CH_2CH_3, it is always in a cis-relationship with respect to the 2-amine substituent.

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NEW CENTRALLY ACTING 5-, 6-, 7-, AND 8-SUBSTITUTED SULPHONE ESTERS OF N-MONOSUBSTITUTED 2-AMINOTETRALINS AND RELATED STRUCTURES

Field of the Invention

The present invention is directed toward new 5-, 6-, 7-, and 8-sulphone ester N-monosubstituted 2-aminotetralins and their pharmaceutically acceptable salts, to processes for preparing such compounds, pharmaceutical preparations of such compounds and the use of such compounds in manufacture of a pharmaceutical preparation. Pharmaceutical preparations of these compounds are useful for central nervous system disorders such as for a therapeutic effect on dopamine (DA) and/or 5-HT1A and/or 5-HT1D receptors in mammals.

Background of the Invention.

In depressed patients evidence indicates that the neurotransmission in the central nervous system (CNS) may be disturbed. These disturbances involve the neurotransmitters noradrenaline (NA) and 5-hydroxytryptamine (5-HT). The drugs most frequently used in the treatment of depression are considered to act by improving the neurotransmission of either or both of these physiological agents. The mechanism of action for conventional drugs used to treat mental depression is generally believed to be indirect. It is thought the drugs block the reuptake of the neurotransmitters released from nerve terminals in the CNS,

NA and/or 5-HT, which increases the concentration of these transmitters in the synaptic cleft and restores an adequate neurotransmission. For example, the clinically documented antidepressive drug, zimelidine (dimethy-amino-1-(4-bromo-phenyl)-1-(3-pyridyl)propene) acts as such a reuptake inhibitor with high selectivity for 5-HT neurons.

Available data suggests that the enhancement of 5-HT neurotransmission will primarily improve depressed mood and anxiety, whereas the enhancement of NA neurotransmission will improve retardation symptoms occurring in depressed patients. In recent years many efforts have been made to develop new drugs with high selectivity for the improvement of the 5-HT neurotransmission in the CNS.

A fundamentally different way to improve the neurotransmission in the central 5-HT neurons would be to use a 5-HT receptor agonist acting directly upon the 5-HT receptor, and particularly the 5-HT1A receptor or, alternatively, to use a 5-HT1D receptor antagonist. In order to minimize side effects, a high selectivity for either of these receptor subtypes would be necessary.

Clinically, 5-HT1A agonists have also demonstrated anxiolytic properties. The drug, Buspirone hydrochloride is the only currently available marketed 5-HT1A agonist displaying anxiolytic activity. This compound antagonizes DA receptors at the same dose it stimulates 5-HT1A receptors. A similar drug, Gepirone hydrochloride also has DA antagonist properties. These DA

antagonist properties reduce the clinical utility of these compounds, because long term treatment with DA antagonists can produce tardive dyskinesias.

The search for new CNS active compounds is focused on finding compounds with selective 5-HT1A receptor agonist effects without detrimentally influencing central DA receptors.

Hellstrand et al. have shown that serotonin and 5-HT1A receptor agonists stimulate "killer cell" activity in vitro and in research animals with induced tumors. (Hellstrand, K.; Hermodsson, S. J. Immunol. 1987, 139, 869; Hellstrand, K.; Hermodsson, S. Scand. J. Immunol. 1990, 32, 183; Hellstrand, K.; Hermodsson, S. Cell. Immunol. 1990, 127, 199.)

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 DA receptors located in the dopaminergic neuron itself and belonging to the D2 and/or the D3 receptor subclasses 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.

Drugs acting on central DA transmission are clinically effective in treating a variety of central nervous system disorders such as parkinsonism, schizophrenia, and mano-depressive illness. In

parkinsonism, for example, the nigro-neostriatal 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.

Direct DA receptor agonists, like apomorphine, are able to activate the DA autoreceptors (presynaptic) 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 auto- and/or D3-receptor 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 and extrapyramidal side-effects in patients treated with nuroleptic agents (e.g. with Haloperidol).

Information Disclosure Statement.

The following documents could be important in the examination of this application:

Arvidsson, L-E, et al., J. Med. Chem., 24, 921 (1981), describes hydroxy-2-aminotetralins where the amine is substituted with one n-propyl, one benzyl or two n-propyl substitutents. The 5-, 6-, and 7-hydroxy compounds are described as active central DA-receptor agonists and the 8-hydroxy compound is described as a central 5-HT receptor agonist devoid of DA receptor stimulating activity.

Arvidsson, L-E, et al., J. Med. Chem., 27, 45 (1984), describes 2-aminotetralins where the amine is substituted with one or two methyl, ethyl, n-propyl, i-propyl, n-butyl, or benzyl substituents. The 2-piperidinyltetralin is also described. Several of these compounds were found to be potent 5-HT agonists devoid of DA-mimetic effects.

Arvidsson, L-E, et al., J. Med. Chem., 30, 2105 (1987), describes 8-hydroxy-1-methyl-2-(di-n-propylamino)tetralins. These compounds were 5-HT receptor agonists.

McDermed, et al., (J. Med. Chem., I8, 362 (1975)) deecribes 5,6-dihydroxy-2-aminotetralins. In addition, the 5,8- and 7,8 di-substituted compounds are also disclosed. The amine can be a mono- or di-substituted with simple alkyl groups, benzyl groups, alkylalkoxy groups or the amine can be a 5- or 6-membered hydrocarbon or heterocyclic amine. These compounds are indicated

to have dopaminergic properties although certain compounds are reported to be inactive.

McDermed, et al., (J. Med. Chem., 19, 547 (1976)) describes 5-, 6-, or 7-hydroxy-2-dipropylaminotetralins. These compounds are described as dopaminergic compounds.

Rusterholz, et al., (J. Med. Chem., 19, 99 (1976)) describes 5,8-disubstituted-2-aminotetralins with the amine being substituted with hydrogen, methyl, or cyanopropyl groups. Some of these compounds are potent prolactin inhibitors and believed to be DA agonists.

Ames, et al., (J. Chem. Soc. 2636 (1965)) describes the preparation of a large number of compounds, where the aromatic ring is substituted by methoxy, ethoxy, n- or iso-propoxy, or n-, sec- or tert-butoxy group in the 5 or 8 position and the amine is substituted by hydrogen or alkyl groups having 1-4 carbon atoms. The compounds are indicated to be prepared for pharmacological testing. However, no utility or pharmacological activity is yet known for the compounds just mentioned.

The German patent Number DE-Al-2 803 582 describes 2-aminotetralins where the aromatic ring is substituted on the 5,6,7 or 8 position with the group R1, where R1 is hydrogen, alkanoyl having 1 to 20 carbon atoms or a group $-CO-(CH_2)_n-R_7$, n is a number 0 to 5, R_7 is a phenyl group with substituents as defined further, R_2 is hydrogen, hydroxy, halogen or alkylsulfonylamino, R_3

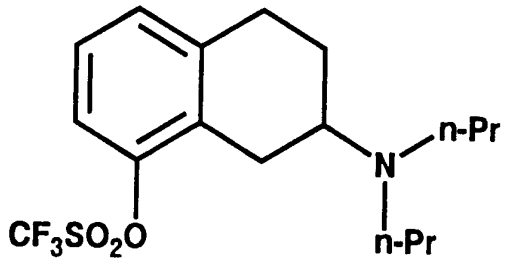
is hydrogen, R_4 is hydrogen, CH_2OH, CH_2O-CO-R_8 or CH_2-O-CO-$(CH_2)_n$-R_7 with further definition and R_5 and R_6 are hydrogen, alkyl or aryl or aralkyl groups further defined or R_5 and R_6 are together an alkylene with 4 to 6 carbon atoms. The compounds are disclosed as having pharmacodynamic activity in particular a stimulating effect on alpha- and beta-adrenoceptors and DA receptors. Among the compounds described are compounds having the group R10 in 8 position and having R2 or R4 other than hydrogen.

The UK Patent Number 1,377,356 describes 2-aminotetralins where the aromatic ring is substituted on the 5, 6, 7 or 8 position by R_1, where R_1 is hydrogen or methyl, the aliphatic ring is substituted by R_2, where R_2 is alkyl having 1-6 carbon atoms, and the amine is substituted by R_3, where R_3 is hydrogen or alkyl having 1-6 carbon atoms are described. Such compounds are stated to possess analgesic activity. 1,1-Dimethyl-2-(N,N-dimethylamino)-7-hydroxytetralin is mentioned as one example of a compound covered by the patent. This compound is also described in Chem. Ab., 79: l46294b as having analgesic and intestinal movement accelerating actions.

J. Pharm. Sci., 67, 880-82 (1978) describes the compound 1-methyl-2-(cyclopropylamino)-5-methoxytetralin and indicates the compound possess local anesthetic activity.

Liu, Y. et al., "C8-Substituted derivatives of 2-(dipropylamino)tetrlain: Palladium-catalyzed synthesis and

interaction with 5-HT1A receptors" have published the triflate derivative of 8-OH-DPAT in Bioorganic & Medicinal Chemistry Letters, 1991, 1, 257-262:



This compound (the racemate has the RN [134394-05-1]) was shown to bind to 5-HT1A receptors with 14 nM affinity. No further pharmacology on this compound has been published as yet. This N,N-di-propylated triflate derivative falls outside the present claim (see below). The same compound appears also in a patent from Andén et al. (EP 399982 A1, November 28, 1990, with priority day May 26, 1989). In addition, the same compound and its enantiomers appear in Liu et al., J. Med. Chem. 1993, 36, 4221-29.

In a patent application from Lin et al. (PCT Int. Pat. Appl., WO 9206967 A1, April 30, 1992, with priority day October 12, 1990) the enantiomers of the 8-triflated DPAT are used as intermediates to produce the enantiomers of 8-CN-DPAT. These 8-TfO-DPAT enantiomers have the following RN numbers: R-(+)-8-TfO-DPAT [136376-13-1] and S-(-)-8-TfO-DPAT [136376-09-5]. Some of the mono-alkylated compounds of this patent application are within the general claim of the Lin et al., WO 9206967 A1 application, but no example of a N-mono-substituted analogue is given in their patent application. In addition, their claim is limited to triflates,

CF_3-SO_2-O-, and does not include other alkyl or aryl sulphone esters, like the R_2-SO_2-O-derivatives of this application. Surprisingly, we found that the N-mono-alkylated sulphone ester analogues of this patent application are more potent and have better biological stability, as measured by their high oral bioavailability, than their corresponding N,N-dialkylated analogues.

The following documents are dealing with biologically active 3-aminochromanes:

Kidd, E. J.; Haj-Dahmane, S.; Jolas, T.; Lanfumay, L.; Fattaccini, C.-M.; Guardiola-Lemaitre, B.; Gozlan, H.; Hamon, M., "New Methoxy-Chroman Derivatives, 4[N-(5-Methoxy-Chroman-3-yl)-N-propylamino]Butyl-Azaspiro-(4,5)-Decane-7,9-Dione[(±)-S20244] and Its Enantiomers, (+)-S20499 and (-)-S20500, with Potent Agonist Properties at Central 5-Hydroxytryptamine$_{1A}$ Receptors.", J. Pharmacol. Exp. Ther., 264(2), 863-72, 1993.

Guillaumet, G.; Guardiola, B., "Preparation of 3-[(imidoalkyl)amino]chromans and analogs as 5-HT1A receptor agonists.", EP 452204 A1 911016, PRAI 900409.

Cossery, J. M.; Perdicakis, C.; Coudert, G.; Guillaumet, G.; Pichat, L., "Oxygen isosteres of hydroxy(dipropylamino)tetralins. Syntheses of racemic monomethoxy- and monohydroxy-3-[di[3H-propyl]amino]chromans, new radioligands for 5-HT1A and D2-receptor-site labeling.", J. Labelled Compd. Radiopharm., 25(8), 833-54, 1988.

Hall, H. O.; Johansson, L. G.; Thorberg, S.-O., "5-Hydroxy3-aminochroman compounds, processes for their preparation, pharmaceutical compositions containing them and methods of treatment therewith.", WO 8804654 A1 880630, PRAI 861219.

Thorberg, S.-O.; Hall, H.; Åkesson, C.; Svensson, K.; Nilsson, J. L. G., "Aminochromans: potent agonists at central dopamine and serotonin receptors.", Acta Pharm. Suec., 24(4), 169-82, 1987.

During the time from submission of the original application (9301732-5, May 18, 1993) to the Swedish Patent Office (Patent och Registreringsverket), the following documents, relevant to this PCT application, have appeared:

Svensson, Wikström, Carlsson, Boije, Waters, Sonesson, Stjernlöf, Andersson, Hansson, Patent: WO 9218475, PRAI: US 686799, Filing date: 26 Mars, 1992.

Sonesson et al., J. Med. Chem., 1993, 36(21), 3188-96.

Sonesson et al., J. Med. Chem., 1993, 36(22), 3409-16.

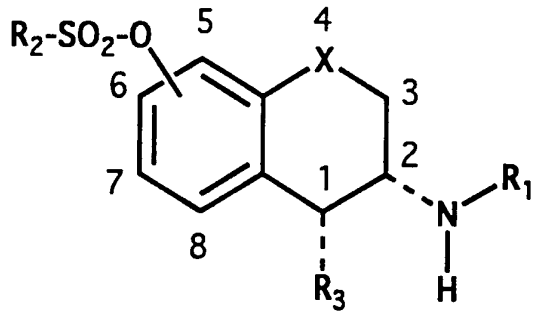
Haadsma-Svensson et al. Bioorg. & Med. Chem. Lett., 1994, 4(5), 689-94.

These documents confirm the statement in this application that aromatic sulfonates, in particular triflates, have beneficial

pharmacokinetic properties. In addition, they confirm that aromatic sulfonates have interesting pharmacodynamic properties.

Summary of the Invention

This invention is related to novel 2-aminotetralin compounds of Formula 1:



Formula 1

or pharmaceutically acceptable acid addition salts thereof, wherein R_1 is H, (C_1-C_8) alkyl, alkenyl, alkynyl, cyclopropylalkyl or (C_1-C_8) haloalkyl; X is CH_2, O or S; R_2-SO_2-O is in position 5, 6, 7 or 8 and R_2 is CF_3, CF_2CF_3, C1-C8 alkyl, substituted aryl (e.g. 4-toluyl); R_3 is H, CH_3 or CH_2CH_3. When R_3 is CH_3 or CH_2CH_3, it is always in a cis-relationship with respect to the 2-amine substituent.

The compounds of this invention possess selective 5-HT1A or 5-HT1D pharmacological properties and are useful in treating hypertension, coughs (antitussive) and central nervous system disorders including depression symptoms, anxiety symptoms, panic attacks, obsessive-compulsive disturbances, senile dementia, emotional disturbances related to dementia disorders, and disturbances of sexual functions. The compounds of this invention

are also useful to alleviate aggressive behavior, confusional delirious states and impotence. In addition, the dopaminergic compounds of this invention are useful for treating disturbances in the CNS such as parkinsonism, schizophrenia, MBD and mano-depressive illness.

In a preferred embodiment, the invention is directed to compounds of Formula 1; wherein R_1 is C_1-C_3, X is CH_2 and R_2 is CH_3 or CF_3 and R_3 is H, CH_3 or CH_2CH_3. A more preferred embodiment are compounds of Formula 1; wherein R_1 is n-Pr, X is CH_2 and R_2 is CH_3 or CF_3 and R_3 is H, CH_3 or CH_2CH_3. An even more preferred embodiment are compounds of Formula 1; wherein R_1 is n-Pr, X is CH_2 and R_2 is CF_3 and R_3 is H. The most preferred positions for the aromatic substituent are 5 and 7 for DA effects and 8 for 5-HT effects.

An object of the invention is to provide compounds for therapeutic use, especially compounds having a therapeutic activity in the central nervous system. Another object is to provide compounds having an effect on the 5-HT1A or 5-HT1D receptors in mammals including man. A further object of this invention is to provide compounds having an effect on the subclasses of DA receptors known as the D_2 and D_3 receptors.

Processes for preparation of these compounds, their pharmaceutical use and pharmaceutical preparations employing such compounds constitute further aspects of the invention.

Detailed Description of the Invention

In appropriate situations, the proper stereochemistry is represented in the structural schemes.

As used herein the term (C_n-C_m) is inclusive such that a compound of (C_1-C_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, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, n-pentyl, isopentyl, neo-pentyl, n-hexyl, isohexyl, n-heptyl, isoheptyl, and n-octyl.

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, l-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. "Halogen" means fluorine, chlorine, bromine or iodide, preferably fluorine.

It will be apparent to those skilled in the art that compounds of this invention may contain chiral centers. The scope of this invention includes all enantiomeric or diastereomeric forms of Formula 1 compounds either in pure form or as mixtures of enantiomers or diastereomers. The compounds of Formula 1 can contain two asymmetric carbon atoms in the aliphatic ring moiety, including the ring carbon atoms adjacent to the nitrogen atom. The therapeutic properties of the compounds may to a greater or lesser degree depend on the stereochemistry of a particular compound. Pure enantiomers as well as enantiomeric or diastereomeric mixtures are within the scope of the invention.

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, methanesulfonic, ethanedisulfonic, sulfamic, succinic, cyclohexylsulfamic, fumaric, maleic and benzoic acid. These salts are readily prepared by methods known in the art.

The compounds of this invention may be obtained by one of the following methods described below, as outlined in the appropriate charts.

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, methanesulfonate, sulfamate salt, in association with a pharmaceutically acceptable carrier. The use and administration to a patient to be treated in the clinic would be readily apparent to a person of ordinary skill in the art.

In therapeutical treatment the suitable daily doses of the compounds of the invention are from about 0.1 mg to 2000 mg for oral application, preferentially 0.5-500 mg, and 0.05 mg to about 100 mg for parenteral application, preferentially 0.05-50 mg daily doses. The daily dose will preferably be administrated in individual dosages 1-4 times daily and the dosage amounts are based on an individual having a weight of 70 kg.

The compounds of Formula 1 of this invention, where R_1 is C_1-C_3 alkyl, R_2-SO_2-O is in the 5, 6 or the 7 position, where R_2 is CH_3, CF_3 or CF_3CF_2 and R_3 is H, are DA D2 and/or D3 receptor agonists. The compounds of Formula 1 of this invention, where R_1 is C_1-C_3 alkyl, R_2-SO_2-O is in the 5 or the 7 position, where R_2 is CH_3, CF_3 or CF_3CF_2 and R_3 is cis-CH_3, are DA D2 and/or D3 receptor antagonists.

The compounds of Formula 1 of this invention, where R_1 is C_1-C_3 alkyl, R_2-SO_2-O is in the 8 position, where R_2 is CH_3, CF_3 or CF_3CF_2 and R_3 is H or cis-CH_3, are very selective 5-HT1A and or 5-HT1D receptor ligands (agonist and/or antagonists), having little or no dopaminergic activity. These compounds are particularly

effective hypotensive, anxiolytic and antidepressant agents. Other uses for these compounds include panic attacks, obsessive-compulsive disturbances, and senile dementia, particularly the emotional disturbances seen in dementia disorders. In addition, central 5-HT receptor activation is believed to be involved in mediating sexual behavior. These compounds would be useful to stimulate sexual activity and to alleviate impotence.

The compounds of this invention with effects of DA receptors are particularly effective in treating psychoses, mano-depressive illness and parkinsonism. The DA autoreceptor antagonists of this invention are stimulants and can be useful in treating parkinsonism, MBD and depression, especially in elderly people.

The compounds of this invention also have high oral potency and a long duration of action, which is different from the 2-aminotetralins known to date (see the references given above). Both these features are beneficial to effective clinical treatment.

The utility of the compounds of this invention to treat central nervous system disorders can be shown in behavioral and biochemical activity in reserpine-pretreated rats.

<u>Antagonism of the reserpine-induced "neuroleptic syndrome" in the rat (gross behavior).</u>

Depletion of the monoamine stores with reserpine brings about a "neuroleptic syndrome" characterized by hypomotility, catalepsy,

muscle rigidity, hunch-backed posture, as well as a number of other central and peripheral signs of monoamine depletion. The whole or parts of this syndrome can be reversed by the administration of drugs that stimulate DA or 5-HT receptors directly or indirectly.

Stimulation of the DA receptors, with apomorphine for example, gives initially rise to yawning (a D3 effect) and later to both locomotion and stereotyped behavior such as sniffing, gnawing and jumping. On the other hand, stimulation of the 5-HT receptors, with 5-hydroxytryptophan (5-HTP) combined with MAO-inhibitors for example, gives rise to a very different behavior, "the 5-HT syndrome". The animals lie flat on the cage floor exhibiting forward movements with extended forepaws padding, "piano-playing," and abducted hindlegs, occasionally with some tremor in the forebody and with Straub tail (stiff tail erection).

In vivo determination of rat brain tyrosine and tryptophan hydroxylation after reserpine pretreatment (biochemically monitored DA and 5-HT receptor activity).

The compounds under evaluation were tested biochemically for central DA and 5-HT receptor (pre- and/or postsynaptic) stimulating activity. The concept of this biochemical screening method is that a DA or 5-HT-receptor agonist will stimulate the receptor and through regulatory feedback systems effect a decline in tyrosine or tryptophan hydroxylating activity, respectively, and a subsequent reduction in the synthesis rate for DA and 5-HT in the presynaptic neuron. DOPAC 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.

Analogous conditions probably exist also for central NA-neurons. Effects on the DA formation in the NA-predominated hemispheral parts (mainly cortex) may thus be considered to reflect NA-receptor mediated changes.

Anti-anxiety models in vivo: 1) Elevated Plus Maze and 2) Defensive Burying.

1) The rats were placed in the middle of an elevated (1 m above the floor) plus maze having two open arms and two closed arms. The total number of entries in either type of arm was scored in drug

treated and saline treated (control) rats. More entries in the open arms is considered to be an expression of diminished anxiety.

2) The rats were placed in a cage equipped with en electrified rod. After the first contact with the rod the rat starts to bury the rod in order to avoid electric chock. The more anxious, the more time the rat devotes to burying and vice versa.

Experimental procedures

Syntheses

Starting materials (the corresponding phenols) for the claimed target compounds may be obtained by the methods known in the art :

L. E. Arvidsson, U. Hacksell, J. L. G. Nilsson, S. Hjorth, A. Carlsson, P. Lindberg, D. Sanchez and H. Wikström, 8-Hydroxy-2-(dipropylamino)tetralin, a new centrally acting 5-hydroxytryptamine receptor agonist, J. Med. Chem., 1981, 24, 921-3, Abstract: Four monophenolic tetralin derivs. I were synthesized and tested in rats for dopamine (DA) and 5-hydroxytryptamine (5-HT) receptor-stimulating activity. I (8-OH-DPAT) [76135-31-4] was a potent and selective 5-HT receptor agonist devoid of DA receptor stimulating activity. (+)-I (8-OH-DPAT) [78095-19-9] was a more active 5-HT receptor agonist than (-)-I (8-OH-DPAT) [78095-20-2]. I (5-OH-DPAT) [71787-83-2], I (6-OH-DPAT) [76135-29-0], and I (7-OH-DPAT) [76135-30-3] were potent DA

receptor agonists and lacked 5-HT receptor stimulating activity. Structure-activity relations are discussed.).

L. E. Arvidsson, U. Hacksell, A. Johansson, J. L. G. Nilsson, P. Lindberg, D. Sanchez, H. Wikström, K. Svensson, S. Hjorth and A. Carlsson, 8-Hydroxy-2-(alkylamino)tetralins and related compounds as central 5-hydroxytryptamine receptor agonists, J. Med. Chem., 1984, 27, 45-51, Abstract: The title compds. I (R1 = H, OH, or OMe; R2 = OH or OMe; R3 = H or C1-4 alkyl; R4 = C1-4 alkyl, etc.; R3R4 = (CH2)5; HBr or HCl salts) were prepd. and tested as dopamine and 5-hydroxytryptamine-receptor agonists in reserpinized rats. (R)-(+)-8-Hydroxy-2-(dipropylamino)tetralin-HCl[(R)-(+)-I; R1 = H, R2 = OH, R3 = R4 = Pr.HCl] showed the highest activity. Structure-activity relations are discussed.

L. E. Arvidsson, A. M. Johansson, U. Hacksell, J. L. G. Nilsson, K. Svensson, S. Hjorth, T. Magnusson, A. Carlsson, B. Andersson and H. Wikström, (+)-cis-8-Hydroxy-1-methyl-2-(di-n-propylamino)tetralin: a potent and highly stereoselective 5-hydroxytryptamine receptor agonist, J. Med. Chem., 1987, 30, 2105-9, Abstract: C(1)-methylated derivs. of the potent 5-hydroxytryptamine (5-HT) receptor agonist 8-hydroxy-2-(dipropylamino)tetralin (I) were synthesized and tested for central 5-HT and dopamine receptor activity by use of a biochem. test method in rats. cis-8-Hydroxy-1-methyl-2-(dipropylamino)tetralin (II) was found to be a 5-HT receptor agonist. The (+)-enantiomer of II had a potency equal to that of I, whereas (-)-II and the trans isomer (.+-.)-III were inactive.

H. Wikström, B. Andersson, D. Sanchez, P. Lindberg, L. E. Arvidsson, A. M. Johansson, J. L. G. Nilsson, K. Svensson, S. Hjorth and A. Carlsson, Resolved monophenolic 2-aminotetralins and 1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolines: structural and stereochemical considerations for centrally acting pre- and postsynaptic dopamine-receptor agonists, J. Med. Chem., 1985, 28, 215-25, The resolved title compds. 2-(dipropylamino)-5-hydroxy- and -7-hydroxytetralins I (R = 5- or 7-OH) and cis- and trans-propylbenzo[f]quinolinols (II) prepd. by demethylation of the appropriate methoxy compd. were evaluated for a detailed structure-activity relationship of their pre- and postsynaptic dopamine receptor-agonist activity. Male rats were used in the biochem. and motor activity expts. (S)-2-(Dipropylamino)-5-hydroxytetralin (I; R = 5-OH-DPAT) [68643-08-3] and (R)-2-(dipropylamino-7-hydroxytetralin (I; R = 7-OH-DPAT) [82730-72-1] were the most active compds.

Other relevant references (journals and patent applications) are:

Al, N. M.; Reynaud, D.; Podona, T.; Ou, L.; Perdicakis, C.; Coudert, G.; Guillaumet, G.; Pichat, L.; Gharib, A.; Sarda, N. Methoxy and hydroxy derivatives of 3,4-dihydro-3-(di-n-propylamino)- 2H-1-benzopyrans: new synthesis and dopaminergic activity□. *Eur. J. Med. Chem.* **1991**, *26,*

Chen, J.; Hutchison, A. J. EP 267878 A1 880518: N9-Cyclopentyl-substituted adenine derivatives, procedure for their preparation,

pharmaceutical compositions containing them, and their use as adenosine receptor agonists. *Ep* **1988**,

Chen, J.; Hutchison, A. J. US 4954504 A 900904: Preparation of n9-cyclopentyl-substituted adenine derivatives having adenosine-2 receptor stimulating activity. *Us* **1990**,

Ciba, G. A.; G JP 62059273 A2 870314 Showa: Preparation of 3-aminodihydro[1]benzopyran and benzothiopyran derivatives as serotoninergic agonists. *Jp* **1987**,

Cossery, J. M.; Gozlan, H.; Spampinato, U.; Perdicakis, C.; Guillaumet, G.; Pichat, L.; Hamon, M. The selective labelling of central 5-HT1A receptor binding sites by [3H]5-methoxy-3-(di-n-propylamino)chroman. *Eur. J. Pharmacol.* **1987**, *140*, 143-55.

Cossery, J. M.; Perdicakis, C.; Coudert, G.; Guillaumet, G.; Pichat, L. Oxygen isosteres of hydroxy(dipropylamino)tetralins. Syntheses of racemic monomethoxy- and monohydroxy-3-[di[3H-propyl]amino]chromans: new radioligands for 5-HT1A- and D2-receptor-site labeling. *J. Labelled Compd. Radiopharm.* **1988**, *25*, 833-54.

Guillaumet, G.; Guardiola, B. EP 452204 A1 911016: Preparation of 3-[(imidoalkyl)amino]chromans and analogs as 5-HT1A receptor agonists. *Ep* **1991**,

Guillaumet, G.; Coudert, G.; Podona, T.; Guardiola, L. B.; Renard, P.; Adam, G.; Caignard, D. H. EP 571243 A1 931124: Preparation of (aminoalkoxy)thiochromans as psychotropics. *Eur. Pat. Appl.* **1993**,

Hall, H. O.; Johansson, L. G.; Thorberg, S. O. WO 8804654 A1 880630: 5-hydroxy-3-aminochroman compounds, processes for their preparation, pharmaceutical compositions containing them and methods of treatment therewith. *Pct Int. Appl.* **1988**,

Hammarberg, E. M.; Johansson, L. G.; Ross, S. B.; Thorberg, S. O. EP 538222 A1 930421: 3-(N-isopropyl-N-propylamino)-5-(N-isopropyl)carbamoylchroman as a selective 5-hydroxytryptamine receptor stimulant. *Eur. Pat. Appl.* **1993**,

Hutchison, A. J. EP 277917 A2 880810: Preparation of adenosine-5'-carboxamide derivatives as adenosine-2 receptor agonists, antipsychotics, and antihypertensives and pharmaceutical compositions containing them. *Ep* **1988**,

Hutchison, A. J. EP 280269 A1 880831: Preparation of 3-aminodihydro-2H-[1]benzopyrans and -thiopyrans as neurotransmitter agonists. *Ep* **1988**,

Hutchison, A. J. US 4968697 A 901106: Preparation of 2-substituted adenosine-5'-carboxamides as antihypertensive agents. *Us* **1990**,

Larsson, L. G.; Noreen, R.; Renyi, L. A.; Ross, S. B.; Sohn, D. D.; Svensson, B. E.;
Thorberg, S. O. WO 9109853 A1 910711: Preparation of 3-(alkylamino)chroman and -thiochroman derivatives and pharmacological activity thereof. *Pct Int. Appl.* **1991**,

Thorberg, S. O.; Hall, H.; Aakesson, C.; Svensson, K.; Nilsson, J. L. G. Aminochromans: potent agonists at central dopamine and serotonin receptors. *Acta Pharm. Suec.* **1987**, *24*, 169-82.

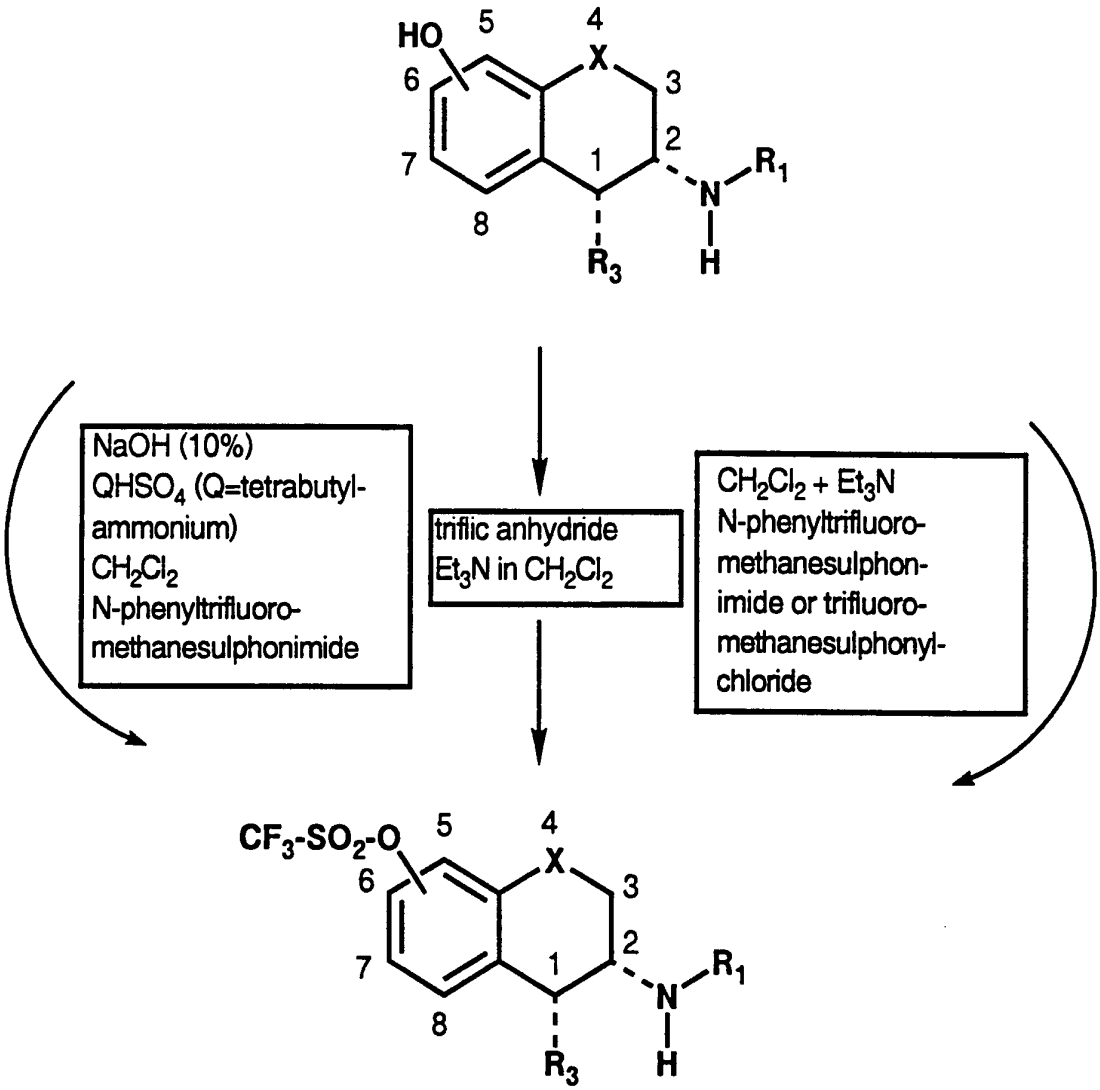
Experimental Section

1H and 13C NMR spectra were recorded at 200 and 50.3 MHz, respectively, on a Varian Gemini 200 spectrometer. CDCl3 was employed as the solvent unless otherwise stated. Chemical shifts are given in units (ppm) and relative to TMS or deuterated solvent. IR spectra were obtained on a ATI-Mattson spectrometer. Elemental analyses were performed in the Micro Analytical Department of the University of Groningen. The chemical ionization (CI) mass spectra were obtained on a Finnegan 3300 system or a UNICAM Automass 150 GC/MS system, equipped with a UNICAM GC, 610 Series. Melting points were determined on a Electrothermal digital melting point apparatus and are uncorrected. Specific optical rotations were measured in methanol (c = 1.0) at 21 °C on a Perkin Elmer 241 polarimeter.

All monomethoxylated aminotetralins were prepared according to the literature procedures. Chemicals used were commercially available (Aldrich and/or Sigma) and were used without further purification. R- and S-2-Chlocyphos were obtained from Syncom B.V, The Netherlands.

Parts of the synthetic methods for forming the sulphone esters from the corresponding phenols are exemplified in Scheme 1:

Scheme 1



Suitable starting materials (either the phenols or the OMe-analogues, which can be dealkylated to the corresponding phenols in refluxing (2 h) 48% HBr or in CH_2Cl_2 with BBr_3) for this invention are known:

(±)-8-OH-2-(N-n-propylamino)tetralin; RN [105578-37-8]

(±)-8-OMe-2-(N-n-propylamino)tetralin; RN [87395-00-4] or [3902-22-5]

R-(+)-8-OMe-2-(N-n-propylamino)tetralin; RN [81185-23-1]

S-(-)-8-OMe-2-(N-n-propylamino)tetralin; RN [133267-79-5]

(±)-7-OMe-2-(N-n-propylamino)tetralin; RN [136559-47-2] and [148258-42-8]

(+)-7-OMe-2-(N-n-propylamino)tetralin; see Wikström et al. J. Med. Chem., 28, 215-25, 1985.

(-)-7-OMe-2-(N-n-propylamino)tetralin; ; see Wikström et al. J. Med. Chem., 28, 215-25, 1985.

(±)-6-OMe-2-(N-n-propylamino)tetralin; RN [82763-23-3]

(±)-5-OMe-2-(N-n-propylamino)tetralin; RN [3899-07-8] and [78598-91-1]

R-(+)-5-OMe-2-(N-n-propylamino)tetralin; RN [101403-25-2]

S-(-)-5-OMe-2-(N-n-propylamino)tetralin; RN [101403-24-1]

(±)-5-OH-2-(N-n-propylamino)tetralin; RN [78598-89-7] or [78950-82-0]

R-(+)-5-OH-2-(N-n-propylamino)tetralin; RN [101470-24-0]

S-(-)-5-OH-2-(N-n-propylamino)tetralin; RN [101470-23-9]

(±)-2H-Benzopyran-3-amine, 3,4-dihydro-5-methoxy-N-propyl-, or 5-Methoxy-3-(N-propylamino)chromane; RN [119755-71-4] and RN [112904-79-7]

(±)-2H-Benzopyran-3-amine, 3,4-dihydro-5-methoxy-, or 5-Methoxy-3-aminochromane; RN [119755-62-3] and [110927-03-2]

R-2H-Benzopyran-3-amine, 3,4-dihydro-5-methoxy-, or R-5-Methoxy-3-aminochromane; RN [117444-30-1]

S-2H-Benzopyran-3-amine, 3,4-dihydro-5-methoxy-, or S-5-Methoxy-3-aminochromane; RN [117422-50-1]

(-)-2H-Benzopyran-3-amine, 3,4-dihydro-5-methoxy-, or (-)-5-Methoxy-3-aminochromane; RN [117422-48-7]

2H-1-Benzothiopyran-5-ol, 3,4-dihydro-3-(propylamino)-, or 5-hydroxy-3-(N-propylamino)-dihydro-2H-[1]benzothiopyran; RN [112904-80-0]

2H-1-Benzothiopyran-5-methoxy, 3,4-dihydro-3-amino-, or 5-methoxy-3-dihydro-2H-[1]benzothiopyran; RN [109140-19-4]

Resolution 8-methoxy-2-(N-n-propylamino)tetralin

Resolution of 8-OMe-2-(N-n-propylamino)tetralin (first description).

8-OMe-2-(N-n-propylamino)tetralin (11.11 g; 50.7 mmol) was dissolved in EtOH (100 mL) and (+)-R-2-Chlosyphos (14.00 g; 50.7 mmol) was dissolved in EtOH (100 mL) and the two solutions were merged. The solvent was evaporated under reduced pressure. The residue was refluxed in acetone (300 mL) and white crystals were filtered after cooling. This costitutes a purification process and not an actual resolution crystallization. The white crystals (5.0 g) were recrystallized two times from refluxing i-PrOH and gave crystals (3.7 g) with an $[\alpha]_D^{21}$ = +60.1° (c=1.0 in MeOH). These crystals (3.7 g) were basified with 10% KOH and extracted with CH_2Cl_2, yielding a colorless oil (1.6 g; 14%) with an $[\alpha]_D^{21}$ = +76.4° (c=1.0 in MeOH), the R-enantiomer according to the literature.

The residueal filtrate from the acetone crystallization (above) (11.24 g) was basified with 10% KOH and extracted with CH_2Cl_2, yielding a colorless oil (4.8 g), which was dissolved in EtOH (100 mL) and mixed with (-)-S-2-Chlosyphos (6.0 g; 21.7 mmol) dissolved in EtOH (100 mL). The solvent was evaporated under reduced pressure. The residue was refluxed in acetone (200 mL) and white crystals were filtered after cooling. This costitutes a purification process and not an actual resolution crystallization. The white crystals were recrystallized two times from refluxing i-PrOH and gave crystals (4.0 g) with an $[\alpha]_D^{21}$ = -61.2° (c=1.0 in MeOH). These crystals (3.9 g) were basified with 10% KOH and extracted with CH_2Cl_2, yielding a colorless oil (1.7 g; 15%) with an $[\alpha]_D^{21}$ = -77.6° (c=1.0 in MeOH), the S-enantiomer according to the literature.

R-(+)-8-OH-2-(N-n-propylamino)tetralinxHBr

R-(+)-8-OMe-2-(N-n-propylamino)tetralin (1.7 g; 6.8 mmol) was refluxed for 2 h in 48% HBr (50 mL) under N_2(g). After cooling to room temprature the excess HBr was evaporated under reduced pressure yielding a white solid, which was dried in a desiccator, yielding 1.88 g (97%; $[\alpha]_D^{21}$ = +63.5° (c=1.0 in MeOH)), which was used in the triflation step without further purification.

S-(-)-8-OH-2-(N-n-propylamino)tetralinxHBr

S-(-)-8-OMe-2-(N-n-propylamino)tetralin (1.9 g; 7.5 mmol) was refluxed for 2 h in 48% HBr (75 mL) under N_2(g). After cooling to

room temprature the excess HBr was evaporated under reduced pressure yielding a white solid, which was dried in a desiccator, yielding 2.17 g (100%; $[\alpha]_D^{21}$ = -64.5° (c=1.0 in MeOH)), which was used in the triflation step without further purification.

R-(+)-8-OSO_2CF_3-2-(N-n-propylamino)tetralinxHCl

R-(+)-8-OH-2-(N-n-propylamino)tetralinxHBr (0.92 g; 3.2 mmol) was dissolved in CH_2Cl_2 (50 mL) and 10% NaOH (50 mL) was added. Thereafter was added QHSO4 (Q=NBu_4^+; 109 mg, 10 mol %) and $PhN(SO_2CF_3)_2$ (1.26 g; 3.5 mmol) (see Scheme 1 above) and the reaction mixture was stirred vigurously to give an optimal phase contact. After 3 h the organic phase was separated and the water phase was extracted once with another portion of CH_2Cl_2 (50 mL). The organic phases were pooled and the solvent was evaporated and the residue was redissolved in ether (50 mL). The ether phase was washed with water and extracted with 5 % HCl. The ether phase was separated and the acidic water phase was basified with Na_2CO_3(s) and the product was extracted over in ether (3x100 mL). The ether phases were pooled, dried (Na_2SO_4) and the solvent was evaporated under reduced pressure to give a colorless oil (0.43 g; 40%). This oil (0.33 g) was dissolved in ether and converted to its HCl salt with ethereal HCl, yielding white crystals (347 mg; 38%) melting at 235-238 °C and having $[\alpha\ ]_D^{21}$ = +61.5° (c=1.0 in MeOH).

S-(-)-8-OSO_2CF_3-2-(N-n-propylamino)tetralinxHCl

S-(-)-8-OH-2-(N-n-propylamino)tetralinxHBr (0.88 g; 3.1 mmol) was dissolved in CH_2Cl_2 (100 mL) and 10% NaOH (50 mL) was added. Thereafter was added $QHSO_4$ (107 mg, 10 mol %) and $PhN(SO_2CF_3)_2$ (1.25 g; 3.5 mmol) (see Scheme 1 above) and the reaction mixture was stirred vigurously to give an optimal phase contact. After 2 days the organic phase was separated and the water phase was extracted once with another portion of CH_2Cl_2 (50 mL). The organic phases were pooled and the solvent was evaporated and the residue was redissolved in ether (50 mL). The ether phase was washed with water and extracted with 5 % HCl. The ether phase was separated and the acidic water phase was basified with Na_2CO_3(s) and the product was extracted over in ether (3x100 mL). The ether phases were pooled, dried (Na_2SO_4) and the solvent was evaporated under reduced pressure to give a colorless oil (1.0 g; 97%). This oil (0.91 g) was dissolved in ether and converted to its HCl salt with ethereal HCl, yielding white crystals (760 mg; 73%) melting at 235-238 °C and having $[\alpha]_D^{21}$ = -61.6° (c=1.0 in MeOH).

The synthetic sequence described above has been rewritten and more experimental details and physical data have been added according to the following:

Resolution of 8-Methoxy-2-(n-propylamino)tetralin (second description).

A mixture of racemic amine (11.1 g, 50.7 mmol) and R-(+)-2-chlocyphos (14.0 g, 50.7 mmol) in abs. ethanol (200 mL) was refluxed until all material was dissolved after which the solvent was removed in vacuo giving an off-white solid. The salt (24.1 g, 48.7 mmol) was recrystallized from 2-propanol yielding 5.16 g (10.42 mmol, 21%) of white crystals with $[\alpha]_D^{21}$= +53.1. A second recrystallization gave 3.74 g (7.56 mmol, 16%) salt with $[\alpha]_D^{21}$= +60.1 (c = 1.0 in MeOH). This salt (3.65 g, 7.37 mmol) was converted to the free base by stirring in 10% KOH (50 mL), extraction with ether and drying over Na2SO4. Evaporation of the solvent in vacuo yielded R-(+)-8-methoxy-2-(n-propylamino)tetralin (1.58 g, 15%) as a colorless oil with $[\alpha]_D^{21}$= +76.4 (c = 1.0 in MeOH) (lit1 $[\alpha]_D^{22}$ = +78.3 (c=1.05)). The residual salt (11.2 g, 22.7 mmol) was converted to the free base described as above using 10% KOH (100 mL). Repeating the above procedure with the enriched (-)-enantiomer of 8-methoxy-2-(n-propylamino)tetralin (4.57 g, 21,7 mmol) with S-(-)-chlocyphos (5.99 g, 21.7 mmol) gave S-(-)-8-methoxy-2-(n-propylamino)tetralin (1.65 g, 15%) as a colorless oil with $[\alpha]_D^{21}$ = -77.6 (c = 1.0 in MeOH) (lit1 $[\alpha]_D^{22}$ = -77.0 (c=1.03)).

R-(+)-8-Hydroxy-2-(n-propylamino)tetralin hydrobromide.

R-(+)-8-Methoxy-2-(n-propylamino)tetralinxHCl salt (1.74 g, 6.82 mmol) was refluxed in 48% HBr (50 mL, freshly distilled) for 2 h under N_2-atmosphere. The reaction mixture was allowed to cool to room temperature and evaporated to dryness giving 1.88 g (97%) of the product as a pale-brown solid, of which 445 mg was recrystallized from ethanol/ether for purification (374 mg, 78%): mp 283-286 °C; IR (KBr) 3275 cm-1; 1H NMR (CD3OD) 1.07 (t, J = 7.69, 3H), 1.70-1.91 (m, 3H), 2.33 (m, 1H), 2.60 (dd, J1 = 10.25, J2 = 16.23, 1H), 2.91 (m, 2H), 3.08 (m, 2H), 3.26-3.37 (m, 1H), 3.43-3.58 (m, 1H), 6.61 (d, J = 7.7, 1H) 6.62 (d, J = 8.12, 1H) 6.97 (dd, J1 = 7.69, J2 = 8.12, 1H); 13C NMR (CD3OD) 11.0, 20.7, 26.6, 27.2, 28.3, 47.5, 55.8, 112.6, 120.0, 120.3, 127.8, 136.9, 156.0; MS (CI with NH3) m/e 206 (M+1); Anal. Calcd for C13H19NOxHBr: C, H, N; $[\alpha]_D^{21}$ = +63.5 (HBr) (c = 1.0 in MeOH).

S-(-)-8-Hydroxy-2-(n-propylamino)tetralin hydrobromide.

Demethylation of S-(-)-8-methoxy-2-(n-propylamino)tetralin (1.92 g, 7.53 mmol) was performed according to procedure as described for R-(+)-8-methoxy-2-(n-propylamino)tetralin as above giving S-(-)-8-hydroxy-2-(n-propylamino)tetralinxHBr in a quantitative yield. Part of the salt (1.06 g) was recrystallized from ethanol/ether yielding 0.80 g (76%) of off-white crystals: mp 273-277 °C; IR (KBr) 3275 cm-1; 1H NMR (CD3OD) 1.07 (t, J = 7.69, 3H), 1.70-1.91 (m, 3H), 2.33 (m, 1H), 2.60 (dd, J1 = 10.25, J2 = 16.23, 1H), 2.91 (m, 2H), 3.08 (m, 2H), 3.26-3.37 (m, 1H), 3.43-3.58

(m, 1H), 6.61 (d, J = 7.7, 1H) 6.62 (d, J = 8.12, 1H) 6.97 (dd, J1 = 7.69, J2 = 8.12, 1H); 13C NMR (CD3OD) 11.1, 20.7, 26.6, 27.2, 28.3, 47.5, 55.8, 112.6, 120.0, 120.3, 127.8, 136.9, 156.0; MS (CI with NH3) m/e 206 (M+1); Anal. Calcd for C13H19NO.HBr: C, H, N; $[\alpha]_D^{21}$ = -64.5 (HBr) (c = 1.0 in MeOH).

R-(+)-8-[[(Trifluoromethyl)sulfonyl]oxy]-2-(n-propylamino)tetralin.

A mixture of R-(+)-8-hydroxy-2-(n-propylamino)tetralinxHBr (200 mg, 0.70 mmol), N-phenyltrifluoromethanesulfonimide (376 mg, 1.05 mmol) and tetrabutylammoniumhydrogensulfate (24 mg, 10 mol%) in dichloromethane (8 mL) and 10% NaOH (3 mL) was stirred at room temperature for 24 h. The reaction mixture was quenched with 5% HCl solution (v/v) until pH1, diluted with H2O (25mL) and washed with ether (50 mL). The ether layer was extracted with H2O and 5% HCl solution (20 mL). The combined aquous layers were basified with solid Na2CO3 until pH 9, extracted with ether (3X30 mL) after which the organic phase was washed with brine and dried over Na2SO4. Evaporation in vacuo yielded the product as a colorless oil, which was converted to the HCl salt and recrystallized from methanol/ether (177 mg, 68%): mp 238-240 °C (HCl); IR (KBr) 1217 cm-1; 1H NMR 0.96 (t, J = 7.5, 3H), 1.35 (br s, NH), 1.55 (m, 2H), 1.63 (m, 1H), 2.05 (m, 1H), 2.53 (dd, J1 = 8.55, J2 = 16.24, 1H), 2.69 (t, J = 7.5, 2H), 2.83-3.04 (m, 3H), 3.12 (dd, J1 = 4.71, J2 = 16.24, 1H), 7.05-7.18 (m, 3H); 13C NMR 11.8, 23.4, 27.8, 28.6, 30.7, 49.0, 52.5, 118.3, 118.6 (q, J = 321, CF3), 126.7, 128.6, 128.7, 139.9, 148.4; MS (CI with NH3) m/e 338 (M+1); Anal. Calcd

for C14H18NO3SF3xHCl: C, H, N, F, S; $[\alpha]_D^{21}$ = +61.5 (HCl) (c = 1.0 in MeOH).

S-(-)-8-[[(Trifluoromethyl)sulfonyl]oxy]-2-(n-propylamino)tetralin.

Triflation of S-(-)-8-hydroxy-2-(n-propylamino)tetralinxHBr (880 mg, 3.08 mmol) was performed according to the procedure given for the synthesis of R-(+)-8-[[(trifluoromethyl)sulfonyl]oxy]-2-(n-propylamino)tetralin above giving an oil (1.0 g, 97%) after extractive workup. Conversion of this oil (0.91 g) to the HCl salt and subsequent recrystallization from methanol/ether gave 760 mg (73%) of white crystals: mp 235-238 °C (HCl); IR (KBr) 1217 cm-1; 1H NMR 0.95 (t, J = 7.7, 3H), 1.32 (br s, NH), 1.54 (m, 2H), 1.64 (m, 1H), 2.06 (m, 1H), 2.53 (dd, J1 = 8.55, J2 = 16.24, 1H), 2.69 (t, J = 7.69, 2H), 2.82-3.02 (m, 3H), 3.12 (dd, J1 = 4.7, J2 = 16.24, 1H), 7.04-7.20 (m, 3H); 13C NMR 11.7, 23.4, 27.7, 28.6, 30.7, 49.0, 52.5, 118.3, 118.6 (q, J = 321, CF3), 126.7, 128.6, 128.7, 139.9, 148.4; MS (CI with NH3) m/e 338 (M+1); Anal. Calcd for C14H18NO3SF3.HCl: C, H, N, F, S; $[\alpha]_D^{21}$ = -61.6 (HCl) (c = 1.0 in MeOH).

Resolution 5- and 7-methoxy-2-(N-n-propylamino)tetralins. The amines have been resolved with the two enantiomers of 4-(2-chlorophenyl)-5,5-dimethyl-2-hydroxy-1,3,2-dioxaphosphorane-2-oxide (Chlocyphos).

Resolution of 5-methoxy-2-(N-n-propylamino) tetralin

A mixture of 6.23 g (28.4 mmol) racemic amine and 7.8 g (28.4 mmol) (+)-chlocyphos was dissolved in of ethanol (30 mL) and of H_2O (10 mL). The solution was allowed to cool to room temperature with stirring. After 6 h crystals were collected and washed, first with ethanol/ether and then with ether. The yield was 43% salt with $[\alpha]_D^{21}$ = -1.5 (c =1.0 in MeOH). The salt was stirred for 1 h with sodium hydroxide (1 g) in H_2O (50 mL) and then chloroform was added. The mixture was stirred for another 30 min. The layers were separated and the aqueous layer was extracted with chloroform. The chloroform layers were washed with water, dried over Na_2SO_4 and evaporated to give an oil. Treatment with dry HCl-ether and recrystalliazation from ethanol/ether gave 3.1 g (43%) of a white salt melting at 279-283 °C and having an $[\alpha]_D^{21}$ = -65.2 (c=1.0 in MeOH; lit -63.0). The filtrate was, after evaporation of the solvent, also treated with NaOH and gave impure amine. Treatment of this amine with (-)-chlocyphos afforded 2.5 g (35 %) optically pure (+)-amine $[\alpha]_D^{21}$ = +68.2 (c=1.0 in MeOH; lit +69.7). The e.e. was determined by ^{31}P-NMR (0.33 ppm) using the adduct of the acid chloride of chlocyphos.

Resolution of 7-methoxy-2-(N-n-propylamino) tetralin

A mixture of 6.36 g (29 mmol) racemic 7-methoxy-2-(N-n-propylamino)tetralin (RN [136559-47-2]) and 8.0 g (29 mmol) of (-)-chlocyphos was dissolved in of 2-propanol (450 mL). The solid was allowed to cool to room temperature with stirring. During the first hour optically pure seeding crystals were added. After 4

hours a white solid was filtered off. It displayed a rotation of $[\alpha]_D^{21}$ = +0.5 (c=1.0 in MeOH). A second recrystallization from propanol-2 gave 6.0 g (42%) salt with $[\alpha]_D^{21}$ = +14.6 (c=1.0 in MeOH). This salt was stirred with sodium hydroxide in water (50 mL) and the aqueous layer was extracted with ethyl acetate. The organic layer was dried over $MgSO_4$. After filtration and evaporation of ethylacetate, a HCl salt was prepared. Recrystallization from ethanol/ether gave 2.5 g (33.7 %) $[\alpha]_D^{21}$ = +75.2 (c=1.0 in MeOH; lit. +70.2)

The filtrates from the two crystallizations were combined, concentrated, made alkaline and extracted with CH_2Cl_2, dried over Na_2SO_4 and concentrated to give 4.1 g (> 50%) of the remaining 7-methoxy-2-(N-n-propylamino)tetralin after the first resolution above. This amine, (+)-chlocyphos (5 g, 18 mmol) and 2-propanol (200 mL) were heated to solution. The heating mantle was removed and the solution was allowed to cool to room temperature with stirring. After 6 h the salt was filtered off and washed with ether to give 6.4 g (12.9 mmol) with $[\alpha]_D^{21}$ = - 14.3 (c=1.0 in MeOH). This salt was converted into the HCl salt, and recrystallization from ethanol yielded 2.8 g (37.7%) S-(-)-7-methoxy-2-(N-n-propylamino)tetralin with an $[\alpha]_D^{21}$ = -75.1 (c=1.0 in MeOH; lit. -72.6).

(-)-5-Hydroxy-2-(N-n-propylamino)tetralinxHBr

The hydrochloride salt of 5-methoxy-2-(N-n-propylamino)tetralin (0.5 g, 1.96 mmol) was refluxed with 48% HBr (20 mL) under

nitrogen atmosphere for 3 h. Addition of H_2O gave a crystalline material, which on recrystallization from ethanol/ether yielded 350 mg (62.4%) product melting at 249-251 °C and with an $[\alpha]_D^{21}$ = -58.4 (c=0.76 in MeOH).

The procedure described above was also followed for the other enantiomer and the 7-methoxy isomers. The data for those reactions were:

(R)-(+)-5-OH-PATxHBr (72%)

(R)-(+)-5-OH-PATxHBr (72%)

(S)-(-)-7-OH-PATxHBr (61%)

R-(+)-7-Hydroxy-2-(n-propylamino)tetralin hydrobromide

Demethylation of R-(+)-7-methoxy-2-(n-propylamino)tetralin (see Wikström et al. J. Med. Chem., 28, 215-25, 1985; 537 mg, 2.11 mmol) was performed according to procedure as described for R-(+)-8-methoxy-2-(n-propylamino)tetralin above, giving R-(+)-7-hydroxy-2-(n-propylamino)tetralin as a pale-brown solid. The title compound was purified by recrystallization from ethanol/ether (478 mg, 79%): mp 215-224 °C; IR (KBr) 3315 cm-1; 1H NMR (CD3OD) 1.07 (t, J = 7.41, 3H), 1.70-2.00 (m, 3H), 2.36 (m, 1H), 2.91-3.16 (m, 5H), 3.30-3.42 (m, 1H), 3.51-3.65 (m, 1H), 7.13-7.33 (m, 3H); 13C NMR (CD3OD) 11.0, 20.6, 26.4, 27.6, 32.5, 47.6, 54.8, 120.3, 122.5, 131.5, 136.0, 136.9, 148.9; MS (CI with NH3) m/e 206

(M+1); Anal. Calcd for C13H19NO.HBr: C, H, N; $[\alpha]_D^{21}$ = +57.8 (HBr) (c = 1.0 in MeOH).

R-(+)-7-[[(Trifluoromethyl)sulfonyl]oxy]-2-(n-propylamino)tetralin.

Triflation of R-(+)-7-hydroxy-2-(n-propylamino)tetralin (302 mg, 1.06 mmol) was performed according to the procedure given for the synthesis of R-(+)-8-[[(trifluoromethyl)sulfonyl]oxy]-2-(n-propylamino)tetralin above giving a colorless oil after extractive workup. Conversion to the HCl salt and subsequent recrystallization from methanol/ether gave 107 mg (34%) as a white crystalline material: mp 206-208 °C (HCl); IR (KBr) 1211 cm-1; 1H NMR (CD3OD) 1.00 (t, J = 7.31, 3H), 1.54-1.77 (m, 3H), 2.13-2.27 (m, 1H), 2.64-3.23 (m, 7H), 7.06-7.26 (m, 3H); 13C NMR (CD3OD) 11.6, 22.7, 28.1, 28.5, 35.2, 48.9, 54.2, 119.6, 119.8 (q, J = 319, CF3), 122.3, 131.3, 137.7, 138.1, 148.7; MS (CI with NH3) m/e 338 (M+1); Anal. Calcd for C14H18NO3SF3.HCl: C, H, N; $[\alpha]_D^{21}$ = +50.6 (HCl) (c = 1.0 in MeOH).

S-(-)-5-Hydroxy-2-(n-propylamino)tetralin hydrobromide

Demethylation of S-(-)-5-methoxy-2-(n-propylamino)tetralinxHCl (617 mg, 2.42 mmol) was performed according to procedure as described for R-(+)-8-methoxy-2-(n-propylamino)tetralinxHCl above, giving the title compound as a pale-brown solid. Recrystallization from ethanol/ether gave white crystals (312 mg, 45%): mp 249-251 °C; IR (KBr) 3327 cm-1; 1H NMR (CD_3OD) 1.07

(t, J = 7.45, 3H), 1.69-1.92 (m, 3H), 2.30-2.43 (m, 1H), 2.56-2.74 (m, 1H), 2.82-3.35 (m, 5H), 3.41-3.55 (m, 1H), 6.63 (d, J = 7.69, 2H) 6.97 (t, J = 7.69, 1H); 13C NMR (CD3OD) 11.0, 20.7, 22.4, 26.5, 32.9, 47.4, 55.5, 113.2, 120.8, 122.7, 127.6, 134.1, 155.9; MS (CI with NH3) m/e 206 (M+1); Anal. Calcd for C13H19NOxHBr: C, H, N; $[\alpha]_D^{21}$ = -58.4 (c=0.76 in MeOH).

S-(-)-5-[[(Trifluoromethyl)sulfonyl]oxy]-2-(n-propylamino)tetralin

Triflation of S-(-)-5-Hydroxy-2-(n-propylamino)tetralinxHBr (246 mg, 0.86 mmol) was performed according to the procedure given for the synthesis of R-(+)-8-[[(Trifluoromethyl)sulfonyl]oxy]-2-(n-propylamino)tetralin above, giving of an oil (248 mg) after extractive workup which was purified on a silica column, eluting with CH_2Cl_2/MeOH (1:1). Conversion to the HCl salt and subsequent recrystallization from methanol/ether gave white crystals (190 mg, 59%): mp 232-233 °C (HCl); IR (KBr) 1213 cm-1; 1H NMR (CD3OD) 1.00 (t, J = 7.5, 3H), 1.54-1.73 (m, 3H), 2.19-2.32 (m, 1H), 2.65-2.86 (m, 4H), 2.97-32.26 (m, 3H), 7.12-7.28 (m, 3H); 13C NMR (CD3OD) 11.0, 20.6, 23.1, 25.7, 32.4, 47.8, 54.6, 119.7 (q, J = 319, CF3), 120.2, 128.7, 129.2, 130.4, 137.1, 148.9; MS (CI with NH3) m/e 338 (M+1); Anal. Calcd for C14H18NO3SF3xHCl: C, H, N; $[\alpha]_D^{21}$ = -62.4 (HCl) (c = 1.0 in MeOH).

5-Methoxy-3-(N-propylamino)chromane; RN [119755-71-4] and RN [112904-79-7]

5-Methoxy-3-aminochromanexHCl (RN [119755-62-3] and [110927-03-2]; described in Thorberg et al., Acta Pharm. Suec., 24 (4), 169-82, 1987) (26 mg, 0.12 mmol) was propionylated with propionylchloride (16 μL, 1.5 equiv.) in CH_2Cl_2 (2 mL) in the presence of Et_3N (34 μL, 1.5 equiv.). The reaction was quenched after 2 h with MeOH (0.5 mL) and the mixture was worked up by adding CH_2Cl_2 (20 mL) and washing the organic layer with water (10 mL). The organic layer was separated, dried ($MgSO_4$) and filtered and the solvent was evaporated under reduced pressure yielding an oil (28 mg, 98%).

This amide (32 mg, 0.14 mmol) was dissolved in dry THF (2 mL) and reduced with $LiAlH_4$ (27 mg, 5 equiv.) under $N_2(g)$ at room temperature. After 3 h the reaction was stopped by the addition of 30 μL H_2O, 30 μL 10% NaOH and 90 μL H_2O. The solid material was filtered and the solvent of the filtrate was evaporated under reduced pressure, yielding a colourless oil (28 mg, 93%). Conversion to the HCl salt gave white crystals (32 mg, 89%). GC/MS shows: M^+ (also base peak) at m/e = 221. Other prominent peaks were found at: m/e = 192 (M-29; CH2CH3) and m/e = 163 (M-NHCH2CH2CH3).

5-Methoxy-3-(N-butylamino)chromane

5-Methoxy-3-aminochromanexHCl (RN [119755-62-3] and [110927-03-2]; described in Thorberg et al., Acta Pharm. Suec., 24 (4), 169-82, 1987) (100 mg, 0.47 mmol) was amidated with buturylchloride (75 μL, 1.5 equiv.) in CH_2Cl_2 (6 mL) in the presence of Et_3N (130

μL, 2.0 equiv.). The reaction was quenched after 3 h with MeOH (0.5 mL) and the mixture was worked up by adding CH_2Cl_2 (20 mL) and washing the organic layer with water (10 mL). The organic layer was separated, dried ($MgSO_4$) and filtered and the solvent was evaporated under reduced pressure yielding a brownish solid (113 mg, 97%). GC/MS shows: M^+ (also base peak) at m/e = 249. Another prominent peak (base peak) was found at: m/e = 162 (M-H-NHCH2CH2CH2CH3, i.e. elimination of the amide functionality).

This amide (104 mg, 0.42 mmol) was dissolved in dry THF (5 mL) and reduced with $LiAlH_4$ (75 mg, 1.97 mmol) under N_2(g) at room temperature. After 3 h the reaction was stopped by the addition of 75 μL H_2O, 75 μL 10% NaOH and 150 μL H_2O. The solid material was filtered and the solvent of the filtrate was evaporated under reduced pressure, yielding a yellow oil (93 mg, 94%). GC/MS shows: M^+ (also base peak) at m/e = 235. Other prominent peaks were found at: m/e = 192 (M-CH2CH2CH3) and m/e = 163 (M-NHCH2CH2CH2CH3).

<u>5-Hydroxy-3-(N-butylamino)chromane</u>

5-Methoxy-3-(N-butylamino)chromanexHCl (105 mg, 0.39 mmol) was dissolved in HOAc (2 mL) and 48% HBr (1 mL) was added. The rection mixture was refluxed under N_2(g) for 2 h and was then allowed to cool to room temperature. The reaction mixture was poured into saturated Na2CO3 (50 mL) and the product was extracted with CH_2Cl_2 (1x50 mL and 2x25 mL). The combined organic layers were dried (Na_2SO_4), filtered and the solvent was

evaporated under reduced pressure to give a brown oil (77 mg, 84%), which was chromatographed on SiO_2, using CH_2Cl_2/MeOH (2:1) as eluent. The fraction containing pure product were poole and the solvent was evaporated under reduced pressure to give a colourless oil (48 mg, 56%). GC/MS shows: M^+ at m/e = 221. Other prominent peaks were found at: m/e = 178 (M-CH2CH2CH3) and m/e = 149 (M-NHCH2CH2CH2CH3).

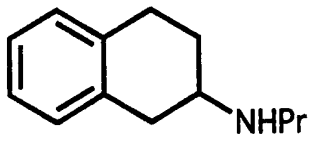
5-Hydroxy-3-(N-propylamino)chromane

5-Methoxy-3-(N-propylamino)chromanexHCl was hydrolyzed in HOAc and 48% HBr , as described for the preparation of 5-hydroxy-3-(N-butylamino)chromane above. GC/MS shows: M^+ at m/e = 221. Other prominent peaks were found at: m/e = 192 (M-CH2CH3) and m/e = 163 (M-NHCH2CH2CH3).

The following compounds (sulphonates), all racemic, have been synthesized from the corresponding phenols under phase transfer catalyst conditions ($QHSO_4$, CH_2Cl_2 and 10% NaOH in room temperature), using the appropriate sulphonylchlorides (purchased from Aldrich).

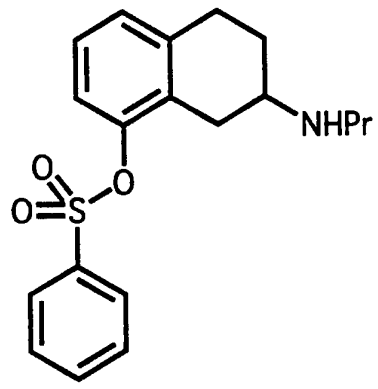
structure	direct inlet (CI) or GC/MS (EI-PI)

TETRALINS

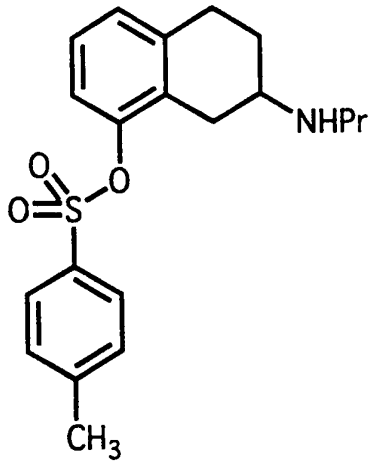


OSO_2CH_3

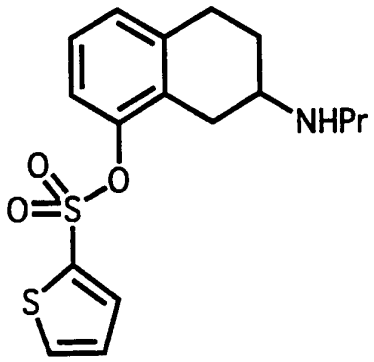
M^+ at m/e=283, base peak at m/e=254 (M-CH2CH3) and other peaks at m/e=225 (M-NHCH2CH2CH3) and m/e=204 (M-CH3SO2).



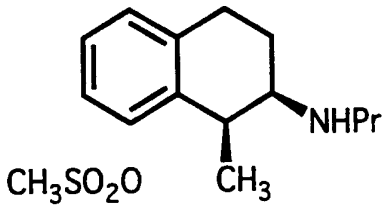
CI: M+1 at m/e=346



CI: M+1 at m/e=362

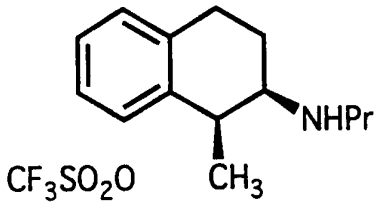


CI: M+1 at m/e=354



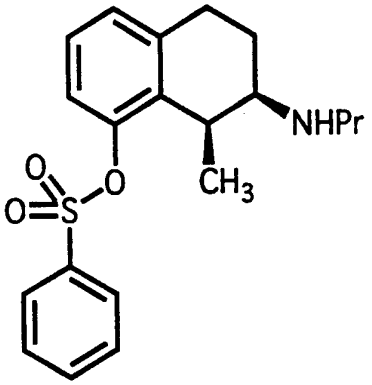
cis

CI: M+1 at m/e=298.



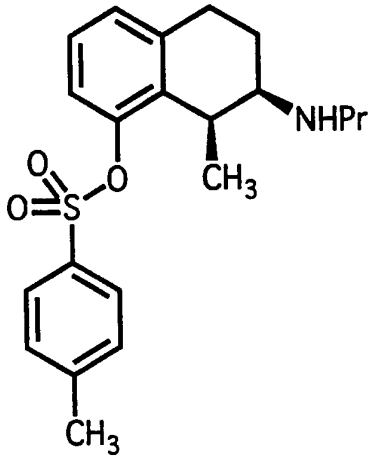
cis

CI: M+1 at m/e=352.



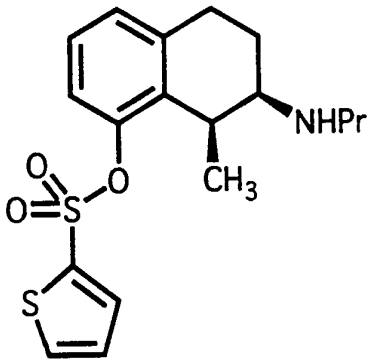
cis

CI: M+1 at m/e=360.



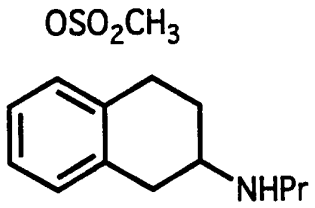
cis

CI: M+1 at m/e=374.

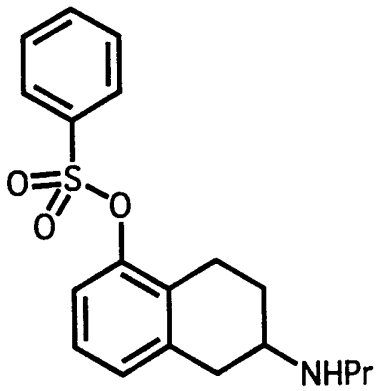


cis

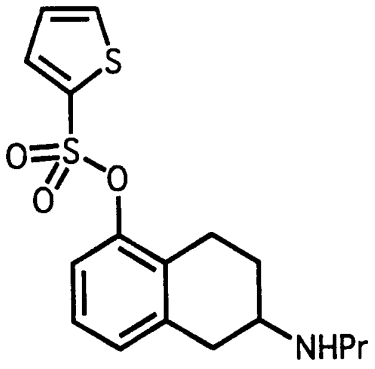
Cl: M+1 at m/e=298.



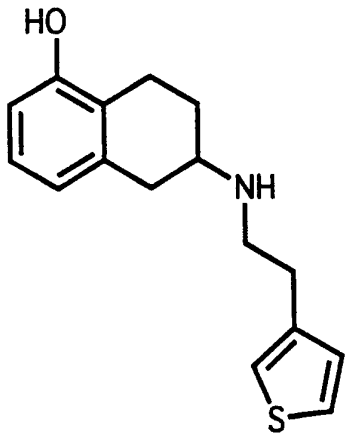
Cl: M+1 at m/e=284.



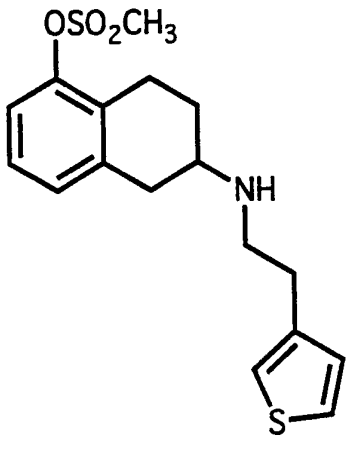
Cl: M+1 at m/e=346.



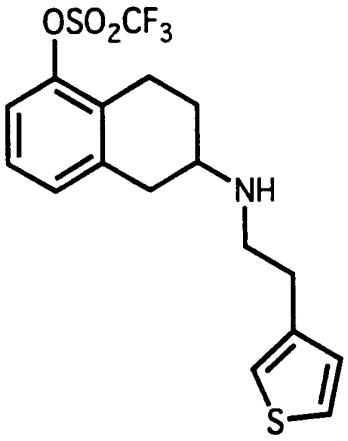
CI: M+1 at m/e=352.



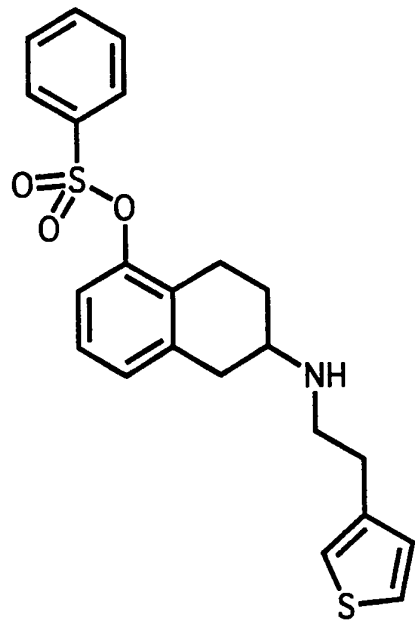
M^+ at m/e=273, base peak at m/e=176 (M-CH2C4H3S) and another peak at m/e=147 (M-NHCH2CH2C4H3S).



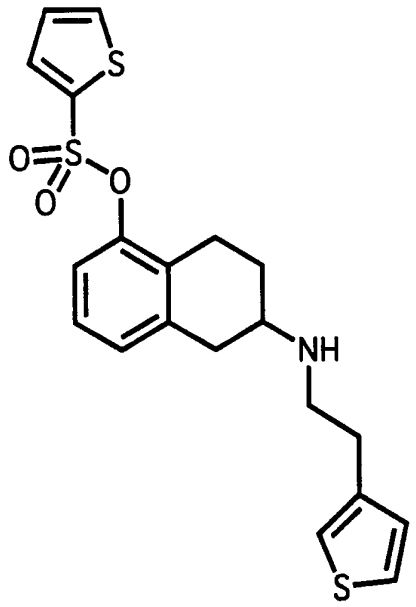
M+ at m/e=351, M-1 at 350, base peak at m/e=254 (M-CH2C4H3S) and another peak at m/e=225 (M-NHCH2CH2C4H3S).



M+ at m/e=405, M-1 at 404, base peak at m/e=308 (M-CH2C4H3S) and anotner peak at m/e=279 (M-NHCH2CH2C4H3S).



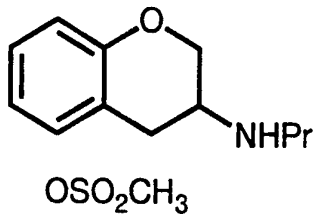
No M+ peak, base peak at m/e=316 (M-CH2C4H3S) and another peak at m/e=287 (M-NHCH2CH2C4H3S); Cl gave M+1=414.



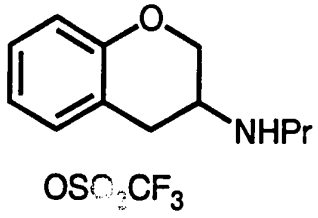
CI: M+1 at m/e=420.

5

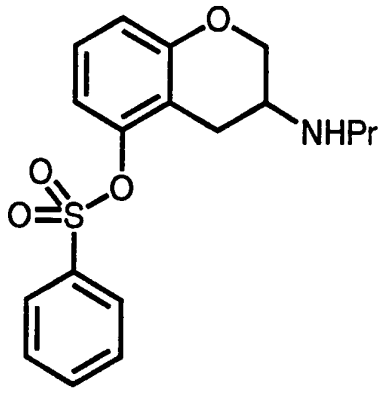
CHROMANES



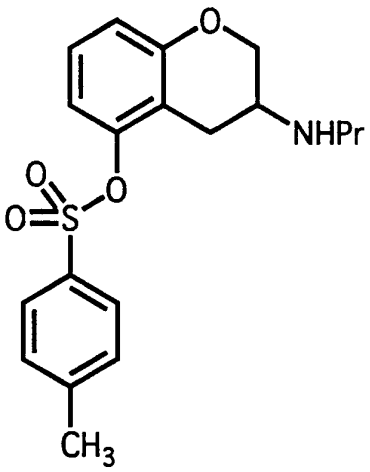
Cl: M+1 at m/e=286.



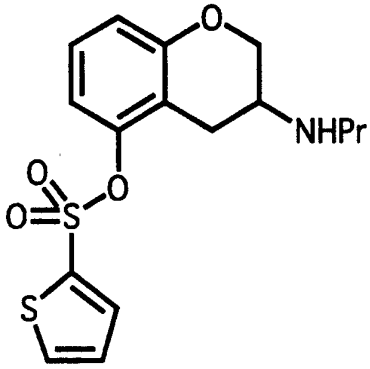
Cl: M+1 at m/e=340.



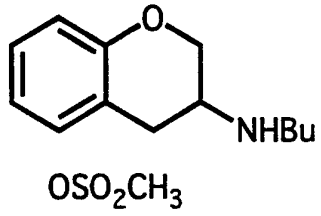
Cl: M+1 at m/e=348



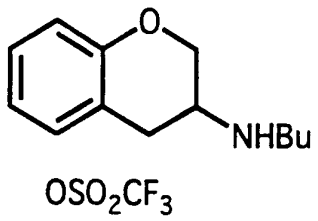
Cl: M+1 at m/e=362.



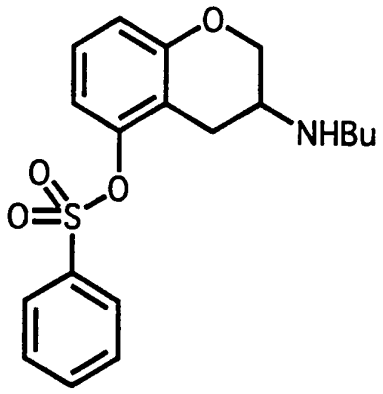
Cl: M+1 at m/e=354.



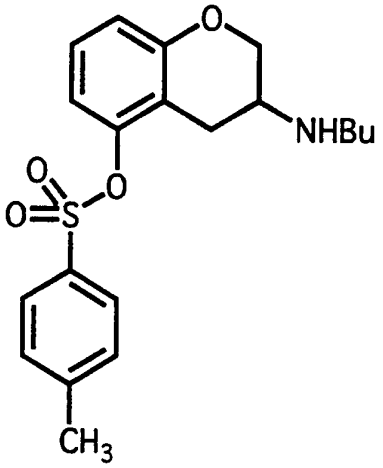
M^+ at m/e=299, base peak at m/e=256 (M-CH2CH2CH3) and another peak at m/e=220 (M-SO2CH3).



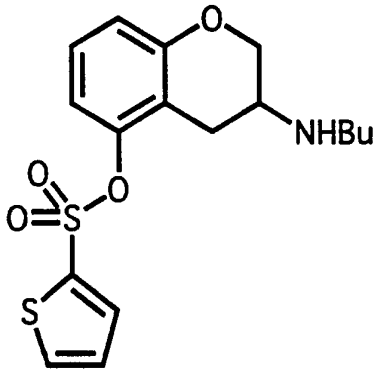
M+ at m/e=353, base peak at m/e=220 (M-SO2CF3) and other peaks at m/e=310 (M-CH2CH2CH3) and m/e=281 (M-NHCH2CH2CH2CH3).



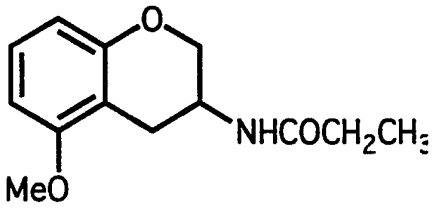
M+ at m/e=361, base peak at m/e=220 (M-SO2C6H6) and other peaks at m/e=318 (M-CH2CH2CH3) and m/e=289 (M-NHCH2CH2CH2CH3).



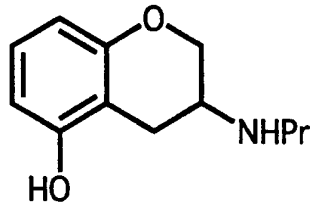
M^+ at m/e=375, base peak at m/e=220 (M-SO2C6H4CH3) and other peaks at m/e=332 (M-CH2CH2CH3) and m/e=303 (M-NHCH2CH2CH2CH3).



M^+ at m/e=367, base peak at m/e=220 (M-SO2C4H3S) and other peaks at m/e=324 (M-CH2CH2CH3) and m/e=295 (M-NHCH2CH2CH2CH3).



CI: M+1 at m/e=236.



CI: M+1 at m/e=208.

Pharmacology

Biochemsitry. Rats (150-300 g) pretreated with reserpine (5 mg/kg, 18 hours before) are given the test compounds. Gross behavioral observations (changes in motility, hindleg abduction, etc.) are made. Subsequent administration of NSD 1015, decapitation, brain dissection (corpora striata, the limbic forebrain and the remaining hemispheral portions (mainly cortex) or rat brain), homogenization, centrifugation, ion-exchange chromatography and spectrofluorimetric measurements (all as described in detail by Wikström, et al., J. Med. Chem., 21, 864-867, 1978 and references cited therein), or by HPLC/EC, gave the actual DOPAC and 5-HTP levels. Several doses (n=4-6) are tested for each compound and brain area. The dose of a compound giving 50% of the maximal reduction of the 5-HTP level in the rat brain part is then estimated.

The compounds of this invention are both behaviorally and biochemically active, producing the above mentioned effects, indicating either central DA or 5-HT receptor stimulation. The absence of significant decreases in the DOPAC levels in the hemispheral brain parts suggests that the compounds do not possess central NA receptor stimulating effects at the dosage under consideration.

Biochemical and behavioral effects of 5-, 6-, 7- and 8-OTf-PAT have been published in Sonesson et al. in J. Med. Chem., 1993, 36, 3409-16. Biochemical and behavioral effects of cis-(+)-1-Me-5-OTf-PAT has been published in Haadsma-Svensson et al. in Bioorg. & Med. Chem. Let., 1993, 36, 3409-16.

Behavioral anti-anxiety tests.

Behavioral approaches to studying the role of 5HT in anxiety involves animal models that are based on simple adaptions to aversive or threatening stimuli. One example is the 'elevated plus-maze test' (Pellow et al., 1985). Normally, rats restrict their activity to the enclosed area of the plus-maze, avoiding the two open arms. This behavior can be suppressed by anxiolytic drugs and enhanced by anxiogenics. The plus-maze is relatively insensitive to drugs other than anxiolytics and anxiogenics and provides a simple test of anxiety in rats (Griebel et al., 1993). Prior exposure to an emotional stressor produces higher emotionality in the animals which is reflected by reduced exploration of the open maze arms in favor of enclosed maze arms (Heinrichs et al.,1992).

A second simple animal model of anxiety is the 'conditioned defensive burying test' (Treit et al., 1981). In this test, rats are exposed to an electrified shock-probe, and the duration of burying behavior is the major index of anxiety. Standard anti-anxiety agents suppress this burying response in a dose-related manner.

The combination of these tests is particularly important (Treit et al., 1993). In the plus-maze test, passive avoidance of novel, elevated, open platforms is the major index of 'anxiety', while in the conditioned defensive burying test, the major index of 'anxiety' is the active burying of the shock-probe.

Animals

Male Wistar rats (n=5-9) weighing 300-500 g at the beginning of the experiments were used. They were housed individually in clear Plexiglass cages (25 x 25 x 30 cm) on a 12 h light-dark regime (light on between 08.00 and 20.00). All animals had free access to standard rat chow (Hope Farms) and tapwater. The experiments were carried out between 10.00 and 14.00.

R-(+)-8-[[(Trifluoromethyl)sulfonyl]oxy]-2-(n-propyl-amino)tetralin (Sonesson et al., 1993) was dissolved in saline which, alone, served for control injections. The compound was given intraperitoneally (i.p.) 30 min before the test session in a dose range of 1.0-3.0 mg/kg . Cited doses refer to the HCl salt, and neither of these doses did produce the 5HT-syndrome in the rats.

Conditioned defensive burying

The Shock-probe defensive burying test was performed in the home cage of the animals. The floor was covered with wood shavings (height 2 cm). A removable teflon probe (6.5 cm long, 1 cm in diameter) was positioned 2 cm above the bedding. The probe was

inserted through a small hole in the center of the longest wall of the cage. Two exposed wires (0.5 mm in diameter) were each wrapped (25 times) independently around the probe. Whenever the animal touched both wires simultaneously, with any part of its body, an electric current of 1.5 mA was delivered to the animal. During the entire period the shock circuit was left on, i.e. "repeated shock probe procedure" was used (Treit and Fundytus, 1988). Shock intensity was adjusted with a variable resistor in series with a 1000 8V shock source. On day 2 vehicle or drug was injected 30 min before introduction of the non-electrified probe in the home cages of the rats. Thus the procedure investigated the conditioned emotional consequence of former punishment rather than the direct effect of shock. All animals were observed for 10 min. Animals burying less than 25% of total time on day 1 were not tested for day 2.

Fear of footshock

The rats were trained in a passive avoidance apparatus in which the electric shock would be applied (Korte et al., 1990). Rats were exposed to a dark compartment where they were allowed to stay for 5 min. During the trial an inescapable scrambled footshock (0.6 mA, AC for 3 s) was given after the minutes 1 and 4. On the next day the animals are reexposed to the dark compartment in which no further footshock was given.

Elevated Plus-Maze

Directly after the 5 min period exposure to the shock compartment (above), the animals were placed in the elevated Plus-maze. The elevated Plus-maze (wood, painted black) consisted of two open, 50x10 cm, and two enclosed arms, 50x10x40 cm, with an open roof, arranged such that the two arms of each type were opposite to each other (Pellow et al., 1985), connected by an open central area (10 10 cm) . The maze was elevated to a height of 50 cm above the floor. Rats were individually placed in the centre of the maze facing an enclosed arm. The maze was cleaned after each rat.

Behavioral Measurements

During the exposure to the former shock compartment time spent immobile, i.e. when the animal is completely motionless, was measured. Time spent in the open arms relative to the time spent in the open plus the closed arms, is used as an index for the anxiolytic or anxiogenic effects (Pellow et al., 1985; Wahlestedt et al., 1993). Furthermore, the activity score, i.e. number of arm entries, the closed arm entries and the open arm entries were measured. The observations were recorded by trained observers who were unaware the the treatment schedule.

The behaviour in the defensive burying paradigm was classified in five categories: (a) defensive burying - moving toward the probe and spraying or pushing bedding material toward the probe with rapid movements of the snout or forepaws as described earleir by Pinel and Treit (1983).; (b) eating, chewing chow or faeces; (c) rearing, standing or sitting on hindlegs, mostly making sniffing

movements, pointing the nose up into the air; (d) resting, the hindlimbs, the forelimbs, and the belly of the rat touched the floor and supported its body weight; (e) exploring, investigation of any part of the home cage.

Statistics

The data were analyzed with oneway ANOVA's. The ANOVA's were followed by the Dunnett's t-test in order the compare the vehicle group to each of the other groups.

Results

Conditioned defensive burying

The burying behavior after 3 mg/kg, but not after 1 mg/kg administration of R-(+)-8-[[(trifluoromethyl)sulfonyl]oxy]-2-(n-propyl-amino)tetralin (Sonesson et al., 1993), is completedly abolished ($F(2,18)=3.46$, $p=0.057$) whereas the % rearing is also dose-dependently decreased. Interestingly, both the 1 mg/kg and the 3 mg/kg dose dramatically increased the food intake.

Elevated plus-maze

One-factor ANOVA revealed a significant effect of R-(+)-8-[[(trifluoromethyl)sulfonyl]oxy]-2-(n-propyl-amino)tetralin (Sonesson et al., 1993) on the number of open arm entries at 3 mg/kg ($F(2,21)=15.27$; $p<0.01$) and on the total number of entries ($F(2,21)=3.97$; $p<0.05$). Furthermore, the number of open arm entries between the non-stressed and stressed animals is also significantly different ($p<0.05$, T-test). The % time L/L+D shows the same trend as the open arm and total entries whereas the number of enclosed arm entries is not significantly changed at the applied dose-range.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, practice the present invention to its fullest extent. The above mentioned examples describe how to prepare the various compounds and/or perform the

various processes of the invention and are to be construed as merely illustrative, and not limitations of the preceding disclosure in any way whatsoever. Those skilled in the art will promptly recognize appropriate variations from the procedures both as to reactants and as to reaction conditions and techniques.

References for the Pharmacology section

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Kennett, G.A., Marcou, M., Dourish, C.T. and Curzon, G., 1987, Single administration of $5HT_{1A}$ agonists decreases $5HT_{1A}$ presynaptic, but not postsynaptic receptor-mediated responses: relationship to antidepressant-like action, European J. Pharmacol. 138, 53.

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Sonesson, C., Boije, M., Svensson, K., Ekman, A., Carlsson, A., Romero, A.G., Martin, I.J., Duncan, J.N., King, L.J. and Wikström, H., 1993, Orally active central dopamine and serotonin receptor ligands: 5-, 6-, 7-, and 8-[[(Trifluoromethyl)sulfonyl]oxy]-2-(di-n-propylamino)tetralins and the formation of active metabolites in vivo, J. Med. Chem. 36, 3409.

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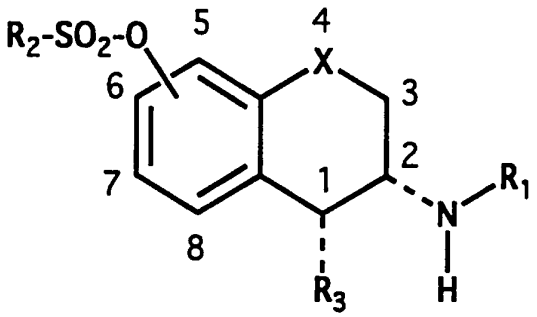
Wahlestedt, 1993

WHAT IS CLAIMED:

1. Compounds of Formula 1:



Formula 1

or pharmaceutically acceptable acid addition salts thereof, wherein R_1 is H, (C_1-C_8) alkyl, alkenyl, alkynyl, cyclopropylalkyl or (C_1-C_8) haloalkyl; X is CH_2, O or S; R_2-SO_2-O is in position 5, 6, 7 or 8 and R_2 is CF_3, CF_2CF_3, C1-C8 alkyl, substituted aryl (e.g. 4-toluyl); R_3 is H, CH_3 or CH_2CH_3. When R_3 is CH_3 or CH_2CH_3, it is always in a cis-relationship with respect to the 2-amine substituent.

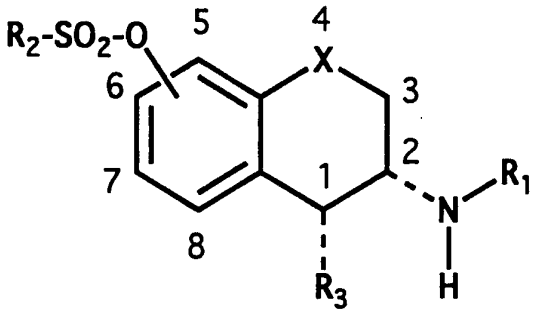
2. A compound of claim 1, Formula 1, wherein R_1 is chosen from C_1-C_3 alkyl, R_2 is CH_3 or CF_3, R_3 is H or cis-CH_3 and X is CH_2.

3. A compound according to claim 2 wherein R_1 is n-Pr.

4. A compound according to claim 3 wherein R_2 is CF_3 .

5. A compound according to claim 4 wherein R_3 is cis-CH_3.

6. A method for treating DA, 5-HT1A or 5-HT1D disorders of the central nervous system comprising the administration to a mammal of a therapeutic amount of a compound of Formula 1:



Formula 1

or pharmaceutically acceptable acid addition salts thereof, wherein R_1 is H, (C_1-C_8) alkyl, alkenyl, alkynyl, cyclopropylalkyl or (C_1-C_8) haloalkyl; X is CH_2, O or S; R_2-SO_2-O is in position 5, 6, 7 or 8 and R_2 is CF_3, CF_2CF_3, C1-C8 alkyl, substituted aryl (e.g. 4-toluyl); R_3 is H, CH_3 or CH_2CH_3. When R_3 is CH_3 or CH_2CH_3, it is always in a cis-relationship with respect to the 2-amine substituent.

7. The method of claim 6 wherein said compound is administered in an amount of from about 0.1 to about 2000 mg oral daily dose, or from 0.01 to about 100 mg parenteral daily dose.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 94/00465

A. CLASSIFICATION OF SUBJECT MATTER

IPC : C07C 309/63, C07D 311/58, C07D 335/06, A61K 31/13, A61K 31/35, A61K 31/38
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC : C07C, C07D, A61K

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

SE,DK,FI,NO classes as above

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

CA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	Chemical Abstracts, Volume 119, No 21, 22 November 1993 (22.11.93), (Columbus, Ohio, USA), Sonesson, Clas et al, "Orally active central dopamine and serotonin receptor ligands: 5-,6-,7-, and 8- (trifluoromethyl)sulfonyl oxy -2-(di-n-propylamino)tetralins and the formation of active metabolites in vivo", page 20, THE ABSTRACT No 216755y, J. Med. Chem. 1993, 36 (22), 3409-3416 --	1-5
X	WO, A1, 9109853 (AKTIEBOLAGET ASTRA), 11 July 1991 (11.07.91), page 23, line 7 - line 22; page 31, line 10 - line 26, the claims --	1-5

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 August 1994	26 -08- 1994
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Gerd Strandell Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 94/00465

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO, A1, 9206967 (THE UPJOHN COMPANY), 30 April 1992 (30.04.92), page 7, line 4 - line 20; page 30, the claims	1-5
X	WO, A1, 9014330 (AKTIEBOLAGET ASTRA), 29 November 1990 (29.11.90), page 9, line 1 - line 22; page 16, line 1 - line 28; page 22, line 11 - line 36, the claims	1-5
X	WO, A1, 8804654 (ASTRA LÄKEMEDEL AKTIEBOLAG), 30 June 1988 (30.06.88), page 6, line 27 - page 7, line 4, the claims	1-5
X	EP, A1, 0385658 (ELI LILLY AND COMPANY), 5 Sept 1990 (05.09.90), page 11, line 34 - page 12, line 1, the claims	1-5

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 94/00465

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

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 6,7
because they relate to subject matter not required to be searched by this Authority, namely:

See PCT Rule 39.1(iv): Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

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

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

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

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

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

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

02/07/94

International application No.
PCT/SE 94/00465

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A1- 9109853	11/07/91	AU-B-	641204	16/09/93
		AU-A-	6977091	24/07/91
		CA-A-	2047237	23/06/91
		CN-A-	1052669	03/07/91
		EP-A-	0460169	11/12/91
WO-A1- 9206967	30/04/92	AU-A-	8752591	20/05/92
		EP-A-	0552246	28/07/93
		JP-T-	6502165	10/03/94
WO-A1- 9014330	29/11/90	AU-B-	644081	02/12/93
		AU-A-	5818590	18/12/90
		CA-A-	2032498	27/11/90
		CN-A-	1047494	05/12/90
		EP-A-	0399982	28/11/90
WO-A1- 8804654	30/06/88	AU-A-	1082988	15/07/88
		EP-A-	0279150	24/08/88
EP-A1- 0385658	05/09/90	AU-B-	630671	05/11/92
		AU-A-	5014490	25/10/90
		CA-A-	2010542	27/08/90
		JP-A-	2268151	01/11/90