The present invention comprises the compounds selected from the group of stereoisomers or mixtures thereof of compounds represented by formula (a), wherein R₁ and R₂ are selected from the group consisting of H and OA, wherein A is H or is selected from the group consisting of lower alkyl radicals and aromatic radicals, or A is CO₅R₅, CONHR₅, or COOR₅, wherein R₃ is selected from the group consisting of lower alkyl radicals and aromatic radicals and wherein R₁, R₂ and R₃ are optionally substituted with one or more halogen atoms; R₃ is a lower alkyl radical; X is selected from the group consisting of CH₃, oxygen, sulfur, NH or NR₃, wherein R₃ is a lower alkyl radical; R₄ is selected from the group consisting of (CH₂)₅-COOH, and -(CH₂)₅-<CHEX>(R₁)₂-Ar, wherein R₄ is H or R₅, n is 0 or an integer of 1-4, R₇ is selected from the group consisting of R₅, OR₅, OCOR₅ and H, and Ar is selected from the group consisting of radicals represented by general formulas: (b), (c), (d), (e), (f), (g), (h), wherein Y is selected from the group consisting of hydroxy, nitro, cyano, azido, amino, trifluoromethyl, halogen, and hydrocyclyl, wherein said hydrocyclyl radicals comprise 1-12 carbon atoms, a is 0 or an integer of 1-12 carbon atoms, b is 0 or an integer of from 1 to 2, W is selected from the group consisting of oxygen, sulfur, NH and NR₃, and Z represents two hydrogen radicals, oxygen or sulfur, and pharmaceutical compositions comprising said compounds and a pharmaceutically-acceptable vehicle. Said compounds and compositions are effective for inducing a dopaminergic response in a subject, e.g., a mammal, and are useful for alleviating glaucoma and parkinsonism.


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SUBSTITUTED NAPHTHOXAZINES USEFUL AS DOPAMINERGICS

Field of the Invention:

The invention relates generally to substituted naphthoxazines, processes for preparing such compounds, and their therapeutic use in treating disorders of the central nervous, cardiovascular and endocrine systems. The compound of the invention are also useful for alleviating glaucoma, parkinsonism, and schizophrenia, and for inducing weight loss in mammals.

Background of the Art:


There is continued interest in identifying compounds that are highly potent at the dopamine D-2 receptor, while displaying relatively low affinity at other receptors. The resultant pharmacologic selectivity will improve therapy by minimizing side effects.

SUMMARY OF THE INVENTION

There have now been discovered certain novel compounds displaying dopaminergic activity having the following general structural formula:
dopaminergic activity having the following general structural formula:

![Structural Formula](image)

10 wherein $R_1$ and $R_2$ are selected from the group consisting of $H$ and OA, wherein $A$ is $H$, or is selected from the group consisting of hydrocarbyl radicals having 1-12 carbon atoms, for example, lower alkyl radicals such as methyl, ethyl, propyl, and butyl, or aromatic radicals such as benzyl or phenyl, or $A$ is $-\text{COR}_5$, $-\text{CONHR}_5$, or $-\text{COOR}_5$ wherein $R_5$ is selected from the group consisting of hydrocarbyl radicals having 1-12, preferably 1-9 carbon atoms and further provided that $R_1$, $R_2$ and $R_5$ may be optionally substituted with one or more, e.g., two halogen atoms; $R_3$ is a lower alkyl radical such as methyl, ethyl, propyl or butyl; $X$ is selected from the group consisting of CH$_2$, oxygen, sulfur, NH and NR$_3$, $R_4$ is selected from the group consisting of -(CH$_2$)$_n$-COOR and -(CH$_2$)$_n$-CH(R$_7$)-Ar, wherein $R_6$ is H or R$_3$, n is 0 or an integer of 1-4, $R_7$ is selected from the group consisting of R$_3$, OR$_3$, OCOR$_3$ and H and Ar is selected from the group consisting of radicals represented by the following general formulae:

![Radical Structures](image)
wherein Y is selected from the group consisting of hydroxy, nitro, cyano, azido, amino, acylamino, carboxamido, trifluoromethyl, sulfate, sulfonamido, halogen, hydrocarbnyl and heteroatom-substituted hydrocarbnyl radicals, wherein said heteroatoms are selected from the group consisting of halogen, nitrogen, oxygen, sulfur and phosphorous, and said hydrocarbnyl radicals comprise 1-12 carbon atoms, a is 0 or an integer of from 1 to 2 and W is selected from the group consisting of oxygen, sulfur, NH and NR$_3$ and Z represents two hydrogen radicals, oxygen or sulfur.

One of the more preferred substituents for R$_1$ is H, for R$_2$ is -OH, for R$_3$ is propyl, and for R$_4$ is -(CH$_2$)$_n$CH(R$_7$)Ar. The most preferred ring fusion is trans and the most preferred substituent for R$_4$ is benzyl; i.e., n is 0, R$_7$ is H, and Ar is phenyl. It has been found that trans-3,4,4a,5,6,10b-hexahydro-2-(phenylmethyl)-4-propyl-2H-naphth[1,2-b]-1,4-oxazin-9-ol is especially preferred for its high affinity and selectivity for binding to dopamine D$_2$ receptors.

**DETAILED DESCRIPTION OF THE INVENTION**

The compounds used in the present invention are selected from the group of stereoisomers or mixtures thereof of compounds having dopaminergic activity represented by the above formula.

In the formula, preferably R$_1$ is H and R$_2$ is OA, wherein A is H or is selected from the group consisting of phenyl and alkyl radicals having 1-12 carbon atoms, or A is -COR$_5$, -CONHR$_5$, or -COOR$_5$, wherein R$_5$ is an alkyl or aryl radical that would serve to extend the activity of the compound in the body, for example, methyl, t-butyl, phenyl, o-methylphenyl, o-chlorobenzyl, p-isopropylphenyl or o,p-dichlorophenyl. These derivatives would serve to prevent rapid metabolism of the biologically active species by blocking sites of inactivation, thereby extending the duration of action of the parent drug. Slow removal of these protecting groups in the body would provide prolonged delivery of the active species.

Preferably, R$_3$ is selected from the group consisting of methyl, ethyl and propyl. Preferably X is O or S and most preferably X is O. Preferably Z is O or two hydrogen radicals. The more preferred groups for R$_4$ are benzyl, phenethyl, naphthylmethyl, naphthylethyl, 2-thienylmethyl, 2-thienylethyl and 2,5-
dimethylpyrrolylethyl, and even more preferably, \( R_4 \) is benzyl, phenethyl or 2,5-dimethylpyrrolylethyl.

The preferred stereochemistry for ring fusion is trans. In the trans conformation, the most preferred substituent for \( R_1 \) is H, for \( R_2 \) is -OH, for \( R_3 \) is propyl, and for \( R_4 \) is one of the aryl radicals set forth in the paragraph immediately above. (The alkaryl radicals are even more preferred.) The most preferred substituent for \( R_4 \) is benzyl. In particular, it has been found that trans-3,4,4a,5,6,10b-hexahydro-2-(phenylmethyl)-4-propyl-2H-naphth[1,2-b]-1,4-oxazin-9-ol is especially preferred for its high affinity and selectivity for binding to dopamine D₂ receptors.

The compounds of the invention may exist as stereoisomers or mixtures thereof, having positive, negative or zero optical activity, and exhibit potent and selective dopamine receptor agonist activity when administered to mammals. Thus, these compounds are useful, as demonstrated by standard animal tests, for the treatment of disorders of the central nervous system, especially those related to the dopaminergic systems.

Particularly preferred compounds are as follows:

trans-3,4,4a,5,6,10b-hexahydro-2-(phenylmethyl)-4-propyl-2H-naphth[1,2-b]-1,4-oxazin-9-ol;

trans-3,4,4a,5,6,10b-hexahydro-2-[(2,6-dimethylphenyl)methyl]-4-propyl-2H-naphth[1,2-b]-1,4-oxazin-9-ol;

trans-3,4,4a,5,6,10b-hexahydro-2-[(3,5-dimethylphenyl)methyl]-4-propyl-2H-naphth[1,2-b]-1,4-oxazin-9-ol;

trans-3,4,4a,5,6,10b-hexahydro-2-(phenylethyl)-4-propyl-2H-naphth [1,2-b]-1,4-oxazin-9-ol;

trans-3,4,4a,5,6,10b-hexahydro-2-(2,5-dimethylpyrrolylmethyl)-4-propyl-2H-naphth[1,2-b]-1,4-oxazin-9-ol;

trans-3,4,4a,5,6,10b-hexahydro-2-(2,5-dimethylpyrrolylethyl)-4-propyl-2H-naphth[1,2-b]-1,4-oxazin-9-ol;

trans-3,4,4a,5,6,10b-hexahydro-9-methoxy-2-(phenylmethyl)-4-propyl-2H-naphth[1,2-b]-1,4-oxazin-3-one;

trans-3,4,4a,5,6,10b-hexahydro-2-(phenylmethyl)-4-propyl-2H-naphth[1,2-b]-1,4-oxazin-
9-ol-3-one;

trans-3,4,4a,5,6,10b-hexahydro-2-(phenylethyl)-4-propyl-2H-naphth[1,2-b]-1,4-oxazin-9-ol-3-one;

trans-3,4,4a,5,6,10b-hexahydro-2-(2-thienylmethyl)-4-propyl-2H-naphth[1,2-b]-1,4-oxazin-9-ol;

trans-3,4,4a,5,6,10b-hexahydro-2-(2-thienylethyl)-4-propyl-2H-naphth[1,2-b]-1,4-oxazin-9-ol;

trans-3,4,4a,5,6,10b-hexahydro-2-(2-methoxyphenylethyl)-4-propyl-2H-naphth[1,2-b]-1,4-oxazin-9-ol;

trans-3,4,4a,5,6,10b-hexahydro-2-(carboxy)-4-propyl-2H-naphth[1,2-b]-1,4-oxazin-9-ol;

trans-3,4,4a,5,6,10b-hexahydro-2-(carbethoxy)-4-propyl-2H-naphth[1,2-b]-1,4-oxazin-9-ol;

trans-3,4,4a,5,6,10b-hexahydro-2-(carbobenzyloxy)-4-propyl-2H-naphth[1,2-b]-1,4-oxazin-9-ol;

trans-3,4,4a,5,6,10b-hexahydro-2-(naphthylmethyl)-4-propyl-2H-naphth[1,2-b]-1,4-oxazin-9-ol.

The compounds of the invention may contain up to 4 asymmetric carbon atoms. Three of these asymmetric carbon atoms are marked with asterisks (*) in the following structural formula:

![Structural formula]

The remaining asymmetric carbon may be in the \( R_4 \) radical. The therapeutic properties of the compounds may to a greater or lesser degree be ascribed to any of the stereoisomers. Thus, the pure enantiomers of the cis and trans forms, as well as
mixtures thereof, are within the scope of the invention.

The invention also encompasses (A) a method of preparation of the subject compounds and a method for inducing a dopaminergic response by administering the subject compounds to a patient, (B) pharmaceutical compositions comprising the foregoing compounds in combination with an inert pharmaceutical carrier, and (C) pharmaceutical compositions in dosage forms containing a clinically effective amount of one of the foregoing dopaminergic compounds.

The process for preparing the novel compounds of the present invention may be represented by the general method outlined below:

**GENERAL SYNTHETIC METHOD**

The 1,2,3,4-tetrahydro-2-alkylamino-1-naphthalenols (Compound I) are known [see Jones, et al., J. Med. Chem., 27, 1607 (1984)]. The preparation of the novel compounds of this invention is shown in the general reaction scheme shown below where \( R_1, R_2, R_3 \) and \( R_4 \) are as defined above, \( X \) is illustrated by \( O \) and \( Z \) is illustrated by \( O \) (II and III) or two hydrogen radicals (IV). The reaction of compound I with an appropriate \( R_4 \)-substituted (alpha)-halogenated acetic acid derivative [i] (where \( X' \) represents halogen, e.g., Cl, Br, or I) results in intermediates which can be converted to naphthoxazine derivatives (II) using sodium hydride or sodium hydroxide.

![Chemical structure](image)

Alternatively, alkylation of the naphthoxazine compound III [see Jones, et al., J. Med. Chem., 27, 1607 (1984)] using a strong base (e.g., lithium diisopropyl amide)
with an appropriate alkylating agent $R_4X''$, wherein $R_4$ is not hydrogen and $X''$ is a suitable halogen leaving group (e.g., Cl, Br or I) results in a substituted naphthoxazine (Compound II).

The above reaction may be effected by contacting III with an appropriate base in a polar solvent, e.g., tetrahydrofuran. Conveniently, the base is added to a solution of III in such polar solvent with stirring at a temperature of less than 0°C, e.g., -78°C, and the resulting reaction product recovered by raising the temperature of the reaction mixture to room temperature, quenching and extracting a crude reaction product for subsequent separation by flash chromatography, utilizing a silica gel column and a mixture of ethyl acetate and petroleum ether.

Reduction of Compound II with an appropriate reducing agent, such as lithium aluminum hydride, provides the compound series of this invention wherein Z is two hydrogen radicals (see General Formula IV). This reduction may also be effected in a polar solvent, e.g., tetrahydrofuran or diethyl ether, and the resulting product recovered as discussed above. Furthermore, aryl ether cleavage (not shown), wherein $R_1$ and/or $R_2$ is OA and A is a suitable leaving group (e.g., a lower alkyl group), provides another of the series of novel compounds herein claimed wherein $R_1$ and/or $R_2$ is -OH.
Prodrug esters, ethers and carbamates (wherein $R_1$ and/or $R_2$ is OA and A is -COR$_5$, a hydrocarbyl radical or CONHR$_5$, respectively) are prepared by derivatization of the resultant phenols, resorcinols, or catechols in the conventional manner [see, e.g., Horn, et al., J. Med. Chem., 25, 993 (1982), Thorberg, et al., J. Med. Chem., 30, 2008 (1987)]. Alternatively, prodrug ethers will result from isolation of the above-described intermediate (wherein $R_1$ or $R_2$ is not H) before aryl ether cleavage. Furthermore, by starting with the thiols corresponding to the above-mentioned 1,2,3,4-tetrahydro-2-alkylamino-1-naphthalenols, the compounds of this invention (wherein $X$ is sulfur) are prepared by the above synthetic method.

**PHARMACEUTICAL FORMULATION**

The esters and acid addition salts of the compounds of the general formula are prepared in the conventional manner. As acid additional salts, the salts derived from a therapeutically acceptable acid (such as hydrochloric acid, acetic acid, propionic acid) and, more particularly, from a di- or poly-basic acid (such as phosphoric acid, glutaric acid, citraconic acid, glutaconic acid, tartaric acid, malic acid, and ascorbic acid) are suitable.

A preferred embodiment of this invention is a method of treatment which comprises the administration of a therapeutically effective amount of the compounds of the above formula. In general, the daily dose can be from 0.01 mg/kg to 10 mg/kg per day and preferably from 0.2 mg/kg to 4 mg/kg per day, bearing in mid,
of course, that in selecting the appropriate dosage in any specific case, consideration must be given to the patient’s weight, general health, metabolism, age and other factors which influence response to the drug.

In another embodiment of this invention, there are provided pharmaceutical compositions in dosage unit form which comprise from about 1 mg to about 150 mg of a compound of the above formula, and preferably from about 5 mg to about 100 mg.

The pharmaceutical composition may be in any form suitable for oral use, such as tablets, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents, and preserving agents in order to provide a pharmaceutically elegant and palatable preparation. Tablets may contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for manufacture of tablets. These excipients may be inert diluents, for example, calcium carbonate, sodium carbonate, lactose, calcium phosphate; granulating and disintegrating agents, such as corn starch, or alginic acid; binding agents, for example, starch, gelatin or acacia; and lubricating agents, such as magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with an oil medium, for example, arachis oil, liquid paraffin or olive oil.

The present invention also comprehends aqueous suspensions containing the active compound in admixture with suitable pharmacologically-acceptable excipients. Such excipients are suspending agents, for example, sodium carboxymethylcellulose,
methylcellulose, hydroxypropylmethyl-cellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents such as naturally-occurring phosphatides, for example, lecithin, or condensation products of an alkylene oxide with fatty acids, for example, polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol, for example, polyoxyethylene sorbitol monooleate, or condensation product of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example, polyoxyethylene sorbitan monooleate. The said aqueous suspensions may also contain one or more preservatives, for example, ethyl, n-propyl-p-hydroxy benzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose, saccharin, aspartame, mannitol, sorbitol, or sodium or calcium cyclamate.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent, and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example, sweetening, flavoring, and coloring agents, may also be present.

Syrups and elixirs may be formulated with sweetening agents, for example, glycerol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative, and flavoring and coloring agents.

The pharmaceutical compositions may also be in the form of a sterile injectable preparation, for example, as a sterile injectable aqueous suspension. This suspension may be formulated as is conventional using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butanediol.

The pharmaceutical compositions may be tabulated or otherwise formulated so that for every 100 parts by weight of the composition there are present between
5 and 95 parts by weight of the active ingredient and preferably between 25 and 85 parts by weight of the active ingredient. The dosage unit form for humans will generally contain between about 1 mg and about 100 mg of the active ingredient of the formula stated above.

The pharmaceutical compositions may also be in the form of topical preparations formulated to allow transdermal delivery of the active agent. These can include conventional preparations optionally employing penetration enhancers such as n-dodecylazacycloheptan-2-one or conventional polymeric delivery devices (e.g., patch devices).

From the foregoing formulation discussion, it is apparent that the compositions of this invention can be administered orally, topically or parenterally. The term parenteral as used herein includes subcutaneous injection, intravenous, intramuscular, or intrasternal injection or infusion techniques.

**EXAMPLES**

Details of the synthesis, together with modifications and variations specifically tailored for particular compounds, are set out more fully in the specific examples which follow:

**EXAMPLE 1**

Preparation of trans-4a,5,6,10b-tetrahydro-9-methoxy-2-(phenylmethyl)-4-propyl-2H-naphth[1,2-b]-1,4-oxazin-3(4H)-one.

To a stirred solution of lithium diisopropylamide (2.9 mL, 4.36 mmol) in 40 mL THF at -78°C was added a solution of 1.0 g of trans-1a,2,4,4a,5,6-hexahydro-9-methoxy-4-propynaphth[1,2-b]-1,4-oxazin-3-one (prepared according to J. Med. Chem., 1984, 27, 1607) in THF. After 30 min. additional stirring at that temperature, 0.48 mL (3.99 mmol) of benzyl bromide was added and the solution was brought to r.t. After workup and purification by flash chromatography (Silica, 9:1 petroleum ether/EtOAc) the product was isolated as a white solid. NMR (300 MHz, CDCl₃) showed characteristic peaks at δ 7.4 - 7.2 (m, 5H), 7.0 (m, 2H), 6.8 (m, 1H), 4.6 (dd, 1H), 4.5
(d, 1H), 3.8 (m, 1H), 3.75 (s, 3H), 0.8 (t, 3H).

**EXAMPLE 2**

Preparation of trans-3,4,4a,5,6,10b-hexahydro-9-methoxy-2-(phenylmethyl)-4-propyl-2H-naphth[1,2-b]-1,4-oxazine.

To a suspension of excess lithium aluminum hydride in THF at 0°C was added dropwise a solution of the product of Example 1 (100 mg, 0.27 mmol) in THF and brought to a reflux for one hour. After workup the mixture was purified by flash chromatograph (Silica, 9:1 petroleum ether/EtOAc) and the desired product was isolated as a white solid. NMR (300 MHz, CDCl₃) showed characteristic peaks at δ 7.3 (m, 5H), 6.95 (m, 2H), 6.7 (m, 1H), 4.3 (d, 1H), 4.0 (m, 1H), 3.75 (s, 3H), 0.9 (t, 3H).

**EXAMPLE 3**

Preparation of trans-3,4,4a,5,6,10b-hexahydro-2-(phenylmethyl)-4-propyl-2H-naphth[1,2-b]-1,4-oxazin-9-ol.

The product of Example 2 and an excess of pyridine hydrochloride was heated to 200-220°C under nitrogen for 30 minutes. After workup the reaction mixture was purified by flash chromatograph (Silica, 95:5 petroleum ether/EtOAc) to obtain the product. NMR (300 MHz, CDCl₃) showed characteristic peaks at δ 7.3 (m, 5H), 6.9 (m, 2H), 6.6 (m, 1H), 4.3 (d, 1H), 4.1 (m, 1H), 0.9 (t, 3H). The product was dissolved in ether and converted to its hydrochloride salt by the addition of dry ether-HCl.

Anal. Calc'd for C₂₂H₂₇NO₂·HCl: C, 70.67; H, 7.55; N, 3.74. Observed: C, 70.54; H, 7.54; N, 3.73.
EXAMPLE 4
Preparation of trans-4a,5,6,10b-tetrahydro-9-methoxy-2-(phenylethyl)-4-propyl-2H-naphth[1,2-b]-1,4-oxazin-3(4H)-one.

As in Example 1, phenethyl bromide is substituted for benzyl bromide to provide the desired compound.

EXAMPLE 5
Preparation of trans-3,4,4a,5,6,10b-hexahydro-9-methoxy-2-(phenylethyl)-4-propyl-2H-naphth[1,2-b]-1,4-oxazine.

The product of Example 4 was reduced with lithium aluminum hydride as in Example 2 to provide the desired compound.

EXAMPLE 6
Preparation of trans-3,4,4a,5,6,10b-hexahydro-2-(phenylethyl)-4-propyl-2H-naphth[1,2-b]-1,4-oxazin-9-ol.

The product of Example 5 was treated with pyridine hydrochloride as in Example 3 and the final product was isolated.

EXAMPLE 7
To test the selectivity and specifically of the present compounds for binding to dopamine receptors, tests were conducted using the following standard procedures.

To test binding to dopamine receptors, the bovine caudate nuclei assay was employed. Bovine brains were obtained fresh from a local slaughterhouse. The caudate nuclei were dissected out and homogenized in Buffer A (50 mM Tris; 1 mM Na$_2$-EDTA; 5 mM KCl; 1 mM MgCl$_2$; 2 mM CaCl$_2$; pH 7.4) using a Brinkman Polytron. The homogenate was centrifuged at 40,000 x g for 20 minutes and washed once. The pellet was resuspended in Buffer A, incubated at 37°C for 15 minutes, then centrifuged. The pellet was washed once more, resuspended to a protein
concentration of 5-10 mg/ml in Buffer A and frozen at -70°C until used.

To test binding of the compounds to α₂-adrenergic receptors, the rat cerebral cortex assay was employed. Male Sprague Dawley rats were killed by decapitation and the brains removed. The cerebral cortices were homogenized in 50 mM Tris; 2 mM MgCl₂ (pH 7.4), and centrifuged at 40,000 x g for 10 minutes. The pellet was washed once, resuspended in Tris/MgCl₂ and incubated with 8 units/ml adenosine deaminase at 37°C for 30 minutes. The homogenate was centrifuged, washed once, resuspended to a protein concentration of 5-10 mg/ml and frozen at -70°C until used.

The following tritiated drugs were used as radioligands for each of the receptors tested: [³H]-Spiperone 21-24 Ci/mmol for dopamine D₂ receptors, [³H]-SCH23390 75-85 Ci/mmol for dopamine D₁ receptors, and [³H]-Para aminooclindine 48-52 Ci/mmol for α₂-adrenergic receptors. The radioligands were incubated with various concentrations of competing drug and the appropriate membrane source for periods of time as follows: 75 minutes at room temperature for D₂ receptors, 15 minutes at 37°C for D₁ receptors, or 30 minutes at room temperature for α₂ receptors. Specific binding was defined using 1 μM butaclamol (D₂), 1 μM SCH23390 (D₁), or 1 μM yohimbine (α₂). In addition the D₂ assays contained 30 nM ketaserin in order to block the binding of [³H]-spiperone to 5-HT₂ receptors.

The assays were terminated by filtration using a 24-port Brandell cell harvester over filters that had been previously soaked in 0.1% polyethyleneimine, and the filters were washed three times by filtration of cold buffer. The filters were then placed in 5 ml scintillation vials to which 4 ml of Beckman Ready-Protein was then added, and each vial was counted for 2 minutes in a Beckman 3801 scintillation counter calibrated for conversion of cpm to dpm. Binding data were analyzed using the Ligand program of Munson and Rodbard (1980). The results are presented as Ki values if the data were best fitted to a one-site model, or as KH and KL values if a two-site model produced the better fit.

Results of the binding tests are summarized in the following table:
### TABLE

<table>
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<tr>
<th>EXAMPLE</th>
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<th>D&lt;sub&gt;2&lt;/sub&gt;(pK)</th>
<th>D&lt;sub&gt;1&lt;/sub&gt;(pK)</th>
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<td>(±)</td>
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<td><strong>Comparative 2</strong></td>
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</table>

This table shows the high dopamine D₂ receptor affinity of the compound of Example 3 chosen from the examples above, with unexpectedly high degree of selectivity. Comparative 1 compound is described in Jones U.S. 4,420,480 and Comparative 2, 2-(N-n-propyl-N-thienylethyl-amino)-5-hydroxytetralin, is described in U.S. Patent No. 4,564,628; they are included as reference compounds for comparative purposes.

There is currently much interest in the utility of dopaminergic agonists selective for the D₂ receptor, as abnormalities with this receptor function are thought to be involved in disease states. It is desirable to minimize the effects of these compounds on D₁ receptors in order to lessen side effects seen with these drugs.
Claims

1. The compounds selected from the group of stereoisomers or mixtures thereof of compounds represented by the formula:

\[
\text{R}_1 \quad \text{R}_2 \quad \text{R}_3 \quad \text{R}_4 \quad \text{Z}
\]

wherein \( \text{R}_1 \) and \( \text{R}_2 \) are selected from the group consisting of H and OA, wherein A is H or is selected from the group consisting of lower alkyl radicals and aromatic radicals, or A is \(-\text{COR}_5\), \(-\text{CONHR}_5\), or \(-\text{COOR}_5\), wherein \( \text{R}_5 \) is selected from the group consisting of lower alkyl radicals and aromatic radicals and wherein \( \text{R}_1 \), \( \text{R}_2 \) and \( \text{R}_5 \) are optionally substituted with one or more halogen atoms; \( \text{R}_3 \) is a lower alkyl radical; X is selected from the group consisting of \( \text{CH}_2 \), oxygen, sulfur, NH or NR\(_3\), wherein \( \text{R}_3 \) is a lower alkyl radical; \( \text{R}_4 \) is selected from the group consisting of \(-\text{(CH}_2)_n\text{-COOR}_6\) and \(-\text{(CH}_2)_n\text{-CH(R}_7\text{-Ar)}\), wherein \( \text{R}_6 \) is H or \( \text{R}_3 \), \( n \) is 0 or an integer of 1-4, \( \text{R}_7 \) is selected from the group consisting of \( \text{R}_3 \), OR\(_3\), OCO\(_3\) and H, and \( \text{Ar} \) is selected from the group consisting of radicals represented by the following general formulae:
wherein Y is selected from the group consisting of hydroxy, nitro, cyano, azido, amino, trifluoromethyl, halogen, and hydrocarbyl, wherein said hydrocarbyl radicals comprise from 1-12 carbon atoms, a is 0 or an integer of from 1-12 carbon atoms, a is 0 or an integer of from 1 to 2, W is selected from the group consisting of oxygen, sulfur, NH and NR₃, and Z represents two hydrogen radicals, oxygen or sulfur.

2. The compound of claim 1, wherein R₁ is H; R₂ is OA, wherein A is H or is selected from the group consisting of phenyl and alkyl radicals, or A is -COR₃, -CONHR₃ or -COOR₃, wherein R₃ is selected from the group consisting of methyl, t-butyl, phenyl, o-methylphenyl, o-chlorobenzyl, p-isopropylphenyl and o,p-dichlorophenyl; R₃ is selected from the group consisting of methyl, ethyl, and propyl radicals; X is O or S; Z is oxygen or two hydrogen radicals and R₄ is selected from the group consisting of benzyl, phenethyl, naphthylmethyl, naphthylethyl, 2-thienylmethyl, 2-thienylethyl, and 2,5-dimethylpyrrolylethyl.

3. The compound of claim 2 wherein X is oxygen.

4. The compound of claim 3, wherein R₄ is selected from the group
consisting of benzyl, phenethyl, and 2,5-dimethylpyrrolylethyl.

5. The compound of claim 4, wherein R₃ is propyl.

6. The compound of claim 5, wherein R₁ is H and R₂ is OH.

7. The compound of claim 6, wherein R₂ is situated on the C9 position of the ring system.

8. The compound of claim 5, wherein the ring fusion is trans.

9. The compound of claim 8, wherein R₄ is benzyl.

10. Trans-3,4,4a,5,6,10b-hexahydro-2-(phenylmethyl)-4-propyl-2H-naphth[1,2-b]-1,4-oxazin-9-ol, or a pharmaceutically acceptable salt thereof.

11. A pharmaceutical composition, comprising, as an active ingredient, one or more of the compounds selected from the group of stereoisomers or mixtures thereof of compounds having dopaminergic activity represented by the formula:

\[
\begin{align*}
&\text{R} _1 \\
&\text{R} _2 \\
&\text{X} \\
&\text{N} \\
&\text{Z} \\
&\text{R} _3 \\
&\text{R} _4
\end{align*}
\]

with positive, negative, or zero optical activity, wherein R₁ and R₂ are selected from the group consisting of H and OA, wherein A is H or is selected from the group consisting of lower alkyl radicals and aromatic radicals, or A is -COR₅, -CONHR₅, or -COOR₅, wherein R₅ is selected from the group consisting of lower alkyl radicals.
and aromatic radicals and wherein R₁, R₂ and R₃ are optionally substituted with one or more halogen atoms; R₃ is a lower alkyl radical; X is selected from the group consisting of CH₂, oxygen, sulfur, NH or NR₃, wherein R₃ is a lower alkyl radical; R₄ is selected from the group consisting of -(CH₂)ₙ-COOR₆ and -(CH₂)ₙ-CH(R₇)-Ar, wherein R₆ is H or R₃, n is 0 or an integer of 1-4, R₇ is selected from the group consisting of R₅, OR₅, OCOR₅ and H, and Ar is selected from the group consisting of radicals represented by the following general formulae:

wherein Y is selected from the group consisting of hydroxy, nitro, cyano, azido, amino, trifluoromethyl, halogen, and hydrocarbyl, wherein said hydrocarbyl radicals comprise from 1-12 carbon atoms, a is 0 or an integer of 1-12 carbon atoms, a is 0 or an integer of from 1 to 2, W is selected from the group consisting of oxygen, sulfur, NH and NR₃, and Z represents two hydrogen radicals, oxygen or sulfur.

12. The composition of claim 11, wherein R₁ is H; R₂ is OA, wherein A is H or is selected from the group consisting of phenyl and alkyl radicals, or A is -COR₅, -CONHR₅ or -COOR₅, wherein R₅ is selected from the group consisting of methyl, t-butyl, phenyl, o-methylphenyl, o-chlorobenzyl, p-isopropylphenyl and o-p-
dichlorophenyl; $R_3$ is selected from the group consisting of methyl, ethyl, and propyl radicals; X is O or S; Z is oxygen or two hydrogen radicals and $R_4$ is selected from the group consisting of benzyl, phenethyl, naphthylmethyl, naphthylethyl, 2-thienylmethyl, 2-thienylethyl, and 2,5-dimethylpyrrolylethyl.

13. The composition of claim 12 wherein X is oxygen.

14. The composition of claim 13, wherein $R_4$ is selected from the group consisting of benzyl, phenethyl, and 2,5-dimethylpyrrolylethyl.

15. The composition of claim 14, wherein $R_3$ is propyl.

16. The composition of claim 15, wherein $R_1$ is H and $R_2$ is OH.

17. The composition of claim 16, wherein $R_2$ is situated on the C9 position of the ring system.

18. The composition of claim 15, wherein the ring fusion is trans.

19. The compound of claim 18, wherein $R_4$ is benzyl.

20. The composition of claim 11, wherein said compound is trans-3,4,4a,5,6,10b-hexahydro-2-(phenylmethyl)-4-propyl-2H-naphth[1,2-b]-1,4-oxazin-9-ol, or a pharmaceutically acceptable salt thereof.

21. A method for inducing a dopaminergic response comprising the step of administering to a patient an effective amount of one or more of the compounds selected from the group of stereoisomers or mixtures thereof of compounds having dopaminergic activity represented by the formula:
with positive, negative, or zero optical activity, wherein R₁ and R₂ are selected from
the group consisting of H and OA, wherein A is H or is selected from the group
consisting of lower alkyl radicals and aromatic radicals, or A is -COR₅, -CONHR₅,
or -COOR₅, wherein R₅ is selected from the group consisting of lower alkyl radicals
and aromatic radicals and wherein R₃, R₂ and R₅ are optionally substituted with one
or more halogen atoms; R₃ is a lower alkyl radical; X is selected from the group
consisting of CH₂, oxygen, sulfur, NH or NR₅, wherein R₅ is a lower alkyl radical; R₄
is selected from the group consisting of -(CH₂)ₙ-COOR₆, and -(CH₂)ₙ-CH(R₇)-Ar,
wherein R₆ is H or R₃, n is 0 or an integer of from 1 to about 4, R₇ is selected from
the group consisting of R₃, OR₃, OCOR₃ and H, and Ar is selected from the group
consisting of radicals represented by the following general formulae:
wherein Y is selected from the group consisting of hydroxy, nitro, cyano, azido, amino, trifluoromethyl, halogen, and hydrocarbonyl, wherein said hydrocarbonyl radicals comprise 1-12 carbon atoms, a is 0 or an integer of 1-12 carbon atoms, a is 0 or an integer of from 1 to 2, W is selected from the group consisting of oxygen, sulfur, NH and NR₃, and Z represents two hydrogen radicals, oxygen or sulfur.

22. The method of claim 21, wherein R₁ is H; R₂ is OA, wherein A is H or is selected from the group consisting of phenyl and alkyl radicals, or A is -COR₃, -CONH₂, or -COOR₂, wherein R₃ is selected from the group consisting of methyl, t-butyl, phenyl, o-methylphenyl, o-chlorobenzyl, p-isopropylphenyl and o,p-dichlorophenyl; R₂ is selected from the group consisting of methyl, ethyl, and propyl radicals; X is O or S; Z is oxygen or two hydrogen radicals and R₄ is selected from the group consisting of benzyl, phenethyl, naphthylmethyl, naphthylethyl, 2-thienylmethyl, 2-thienylethyl, and 2,5-dimethylpyrrolylethyl.

23. The method of claim 22 wherein X is oxygen.

24. The method of claim 23, wherein R₄ is selected from the group consisting of benzyl, phenethyl, and 2,5-dimethylpyrrolylethyl.

25. The method of claim 24, wherein R₃ is propyl.

26. The method of claim 25, wherein R₁ is H and R₂ is OH.

27. The method of claim 26, wherein R₂ is situated on the C9 position of the ring system.

28. The method of claim 25, wherein the ring fusion is trans.

29. The method of claim 28, wherein R₄ is benzyl.
30. The method of claim 21, wherein said compound is trans-3,4,4a,5,6,10b-hexahydro-2-(phenylmethyl)-4-propyl-2H-naphth[1,2-b]-1,4-oxazin-9-ol, or a pharmaceutically acceptable salt thereof.

31. A method for alleviating glaucoma, parkinsonism, schizophrenia, or inducing weight loss in mammals, including humans, which comprises the step of administering to said mammals an effective amount of one or more of the compounds selected from the group of stereoisomers or mixtures thereof of compounds represented by the formula:

\[ \text{Diagram: } \text{Chemical Structure} \]

wherein R₁ and R₂ are selected from the group consisting of H and OA, wherein A is H or is selected from the group consisting of lower alkyl radicals and aromatic radicals, or A is -COR₅, -CONHR₅, or -COOR₅, wherein R₅ is selected from the group consisting of lower alkyl radicals and aromatic radicals and wherein R₁, R₂ and R₅ are optionally substituted with one or more halogen atoms; R₃ is a lower alkyl radical; X is selected from the group consisting of CH₂, oxygen, sulfur, NH or NR₃, wherein R₃ is a lower alkyl radical; R₄ is selected from the group consisting of -(CH₂)ₙ-COOR₆, and -(CH₂)ₙ-CH(R₇)-Ar, wherein R₆ is H or R₃, n is 0 or an integer of 1-4, R₇ is selected from the group consisting of R₃, OR₃, OCOR₃ and H, and Ar is selected from the group consisting of radicals represented by the following general formulae:
wherein Y is selected from the group consisting of hydroxy, nitro, cyano, azido, amino, trifluoromethyl, halogen, and hydrocarbyl, wherein said hydrocarbyl radicals comprise 1-12 carbon atoms, a is 0 or an integer of 1-12 carbon atoms, a is 0 or an integer of from 1 to 2, W is selected from the group consisting of oxygen, sulfur, NH and NR₃, and Z represents two hydrogen radicals, oxygen or sulfur.

32. The method of claim 31, wherein R₁ is H; R₂ is OA, wherein A is H or is selected from the group consisting of phenyl and alkyl radicals, or A is -COR₃, -CONHR₃, or -COOR₃, wherein R₃ is selected from the group consisting of methyl, t-butyl, phenyl, o-methylphenyl, o-chlorobenzyl, p-isopropylphenyl and o,p-dichlorophenyl; R₃ is selected from the group consisting of methyl, ethyl, and propyl radicals; X is O or S; Z is oxygen or two hydrogen radicals and R₄ is selected from the group consisting of benzyl, phenethyl, naphthylethyl, naphthylethyl, 2-thienylmethyl, 2-thienylethyl, and 2,5-dimethylpyrroylethyl.

33. The method of claim 32 wherein X is oxygen.

34. The method of claim 33, wherein R₃ is propyl, R₂ is situated on the C9 position of the ring system and R₄ is benzyl.
35. The method of claim 34 wherein said compound is trans-3,4,4a,5,6,10b-hexahydro-2-(phenylmethyl)-4-propyl-2H-naphth[1,2-b]-1,4-oxazin-9-ol, or a pharmaceutically acceptable salt thereof.

36. A method of making a compound selected from the group of compounds represented by the formula:

![Chemical Structure](image)

wherein R₁ and R₂ are selected from the group consisting of H and OA, wherein A is H or is selected from the group consisting of hydrocarbyl radicals having 1-12 carbon atoms, or A is -COR₅, -CONHR₅, or -COOR₅, wherein R₅ is selected from the group consisting of hydrocarbyl radicals having 1-12 carbon atoms and wherein R₁, R₂ and R₅ are optionally substituted with one or more halogen atoms; R₃ is a lower alkyl radical; X is selected from the group consisting of CH₂, oxygen, sulfur, NH or NR₃, wherein R₃ is a lower alkyl radical having 1-4 carbon atoms; R₄ is selected from the group consisting of -(CH₂)ₙ-COOR₆; and -(CH₂)ₙ-CH(R₇)-Ar, wherein R₆ is H or R₇, n is 0 or an integer of 1-4, R₇ is selected from the group consisting of R₃, OR₃, OCOR₃ and H, and Ar is selected from the group consisting of radicals represented by the following general formulae:
wherein Y is selected from the group consisting of hydroxy, nitro, cyano, azido, amino, acylamino, carboxyamido, trifluoromethyl, sulfate, sulfonamido, halogen, hydrocarbyl and heteroatom-substituted hydrocarbyl radicals, wherein said heteroatoms are selected from the group consisting of halogen, nitrogen, oxygen, sulfur, and phosphorous and said hydrocarbyl radicals comprise 1-12 carbon atoms, a is 0 or an integer of from 1 to 2, W is selected from the group consisting of oxygen, sulfur, NH and NR₃, and Z represents two hydrogen radicals, oxygen or sulfur, which comprises reacting a compound of the general formula:
with an $R_4$-substituted (alpha)-halogenated acetic acid derivative represented by the general formula:

\[
R_4\text{-CH-COR}_8
\]

wherein $R_8$ represents OH or halogen.

37. The method of claim 36 further comprising reducing the reaction product of claim 36 to provide a compound represented by the general formula:

38. The method of claim 36 wherein $R_4$ is H and the reaction product is alkylated with an alkylating agent represented by the general formula $R_4X''$, wherein $R_4$ is not H and $X''$ is selected from the group consisting of Cl, Br and I.

39. The method of claim 36 wherein at least one of $R_1$ and $R_2$ is OA, wherein A is a hydrocarbyl radical, and the reaction product of claim 36 is reacted to provide a compound wherein A is H.

40. The method of claim 36 wherein M is oxygen.
**INTERNATIONAL SEARCH REPORT**

**International Application No.** PCT/US 93/05305

**I. CLASSIFICATION OF SUBJECT MATTER**

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07D265/34; C07D279/14; C07D241/38; A61K31/535

**II. FIELDS SEARCHED**

Minimum Documentation Searched

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Documentation Searched other than Minimum Documentation to the extent that such Documents are Included in the Fields Searched

**III. DOCUMENTS CONSIDERED TO BE RELEVANT**

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<td>Y</td>
<td>US,A,4 540 691 (A.S. HORN) 10 September 1985 cited in the application see the whole document</td>
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* Special categories of cited documents:
  - "A" document defining the general state of the art which is not considered to be of particular relevance
  - "E" earlier document but published on or after the international filing date
  - "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another 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
  - "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
  - "A" document member of the same patent family

**IV. CERTIFICATION**

Date of the Actual Completion of the International Search
06 SEPTEMBER 1993

Date of Mailing of this International Search Report
14, 09, 93

International Searching Authority
EUROPEAN PATENT OFFICE

Signature of Authorized Officer
CHOULY J.
### 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. **Claims Nos.**
   - because they relate to subject matter not required to be searched by this Authority, namely:
     - Although claims 21–35 are directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

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

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

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

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

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

2. **As all searchable claims could be searches 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.**
ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. US 9305305 SA 75421

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on EPO/FORM 4009.

The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 06/09/93

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For more details about this annex: see Official Journal of the European Patent Office, No. 12/82