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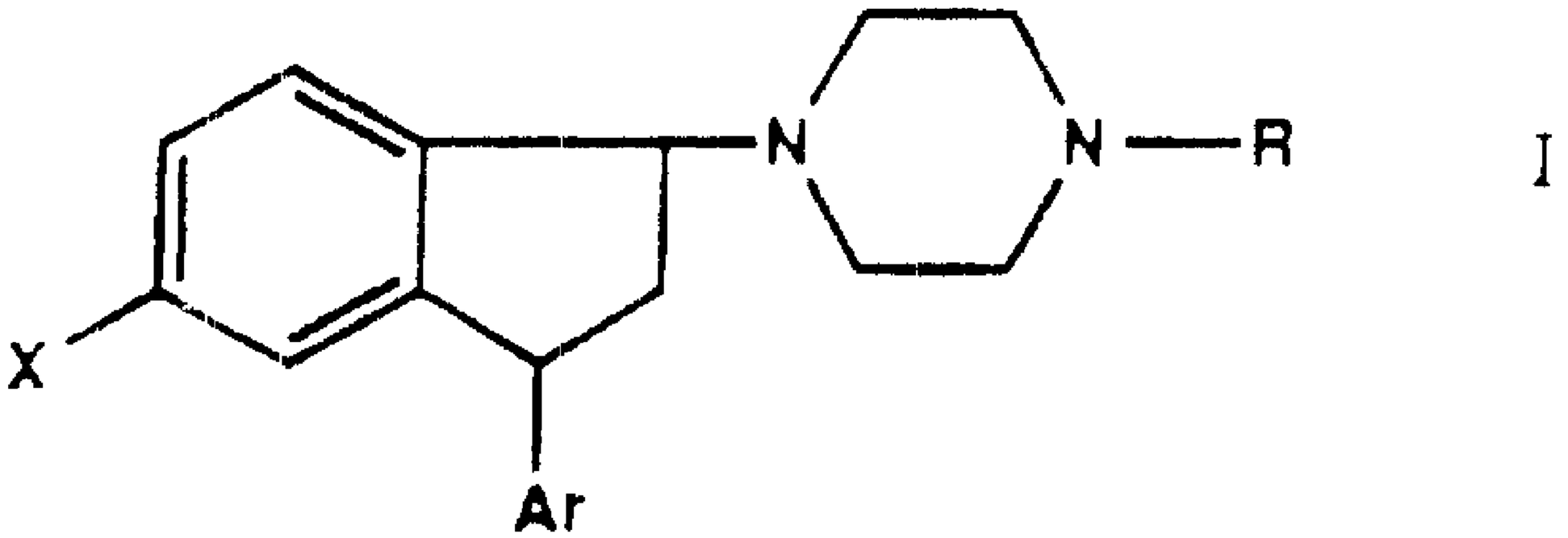

I

(57) Abrégé/Abstract:
5-Substituted trans-1-piperazinoindan derivatives having general formula (I), wherein X is halogen, trifluoromethyl, alkyl, alkylthio, alkyloxy, hydroxy, alkylsulphonyl, alkyl- or dialkylamino, trifluoromethylthio or cyano; R is hydrogen, or alkyl, alkenyl, cycloalkyl, or cycloalkyl lower alkyl, optionally substituted with hydroxy, or R is a substituent (a), wherein n is an integer from 1 to 6; U is CH or N; Y is CH_2, O, S or N-R^1, R^1 being hydrogen or cycloalkyl, cycloalkylmethyl, alkyl or alkenyl optionally substituted with hydroxy or an optionally substituted phenyl group; W is O or S; Z is -$(CH_2)_4$-, (b), (c), where R^2 and R^3 are hydrogen or lower alkyl, -CH=CH-, -CH=CH-CH_2-, optionally substituted 1,2-phenylene, 1,2-$C_6H_4CH_2$- (to form a quinazolidinone or -thione ring system) or 1,2-C_6H_4CO- (to form a quinazolidindion or thioxoquinazolidinon ring system); and Ar is an optionally substituted phenyl, thiophene or furane ring; are selective, centrally acting 5-HT_2 antagonists useful in the treatment of anxiety, depression, sleeping disorders, negative symptoms of schizophrenia and migraine.

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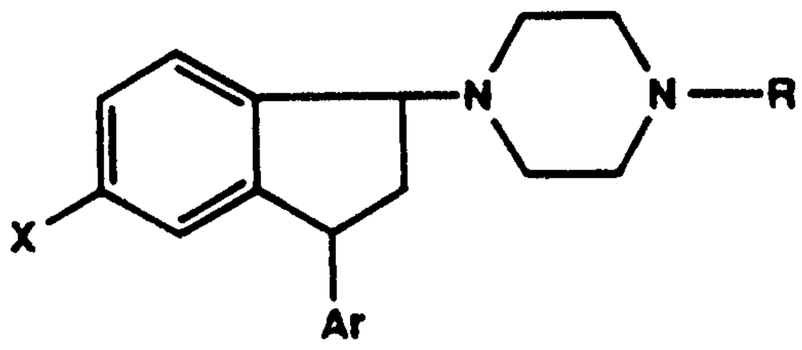
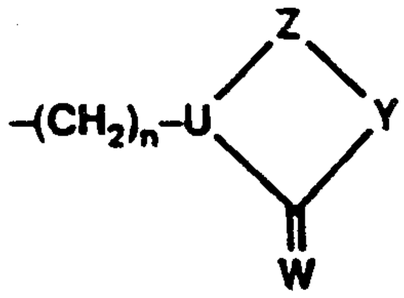
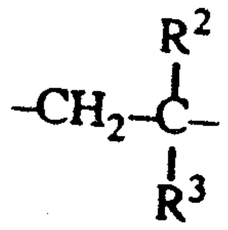


(I)



(a)



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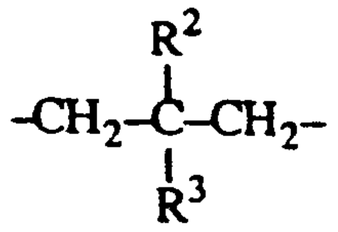

(c)

(57) Abstract

5-Substituted trans-1-piperazinoindan derivatives having general formula (I), wherein X is halogen, trifluoromethyl, alkyl, alkylthio, alkyloxy, hydroxy, alkylsulphonyl, alkyl- or dialkylamino, trifluoromethylthio or cyano; R is hydrogen, or alkyl, alkenyl, cycloalkyl, or cycloalkyl lower alkyl, optionally substituted with hydroxy, or R is a substituent (a), wherein n is an integer from 1 to 6; U is CH or N; Y is CH_2, O, S or N-R^1, R^1 being hydrogen or cycloalkyl, cycloalkylmethyl, alkyl or alkenyl optionally substituted with hydroxy or an optionally substituted phenyl group; W is O or S; Z is -$(CH_2)_4$-, (b), (c), where R^2 and R^3 are hydrogen or lower alkyl, -CH=CH-, -CH=CH-CH_2-, optionally substituted 1,2-phenylene, 1,2-$C_6H_4CH_2$- (to form a quinazolidinone or -thione ring system) or 1,2-C_6H_4CO- (to form a quinazolidindion or thioxoquinazolidinon ring system); and Ar is an optionally substituted phenyl, thiophene or furane ring; are selective, centrally acting 5-HT_2 antagonists useful in the treatment of anxiety, depression, sleeping disorders, negative symptoms of schizophrenia and migraine.

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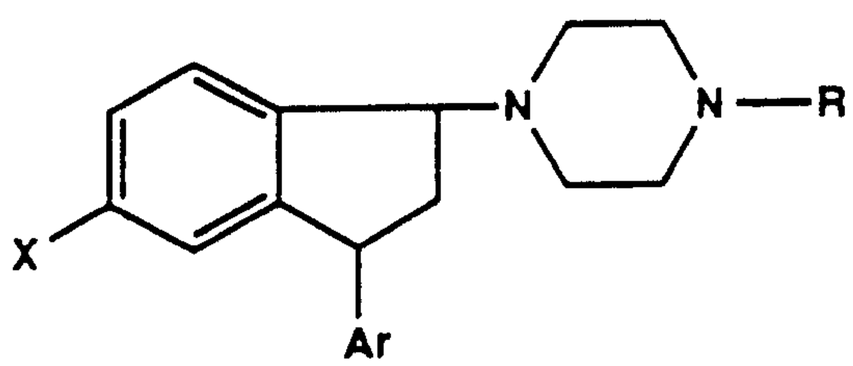
INDAN DERIVATIVES

The present invention relates to 5-substituted 1-piperazinoindan derivatives and acid addition salts thereof with selective antagonistic action on the serotonin-2 (5-hydroxytryptamin-2; 5-HT_2) receptors in the central nervous system, to medicaments comprising such derivatives as active ingredients, to the use of such derivatives in the treatment of diseases in the central nervous system and to methods for the preparation of such compounds.

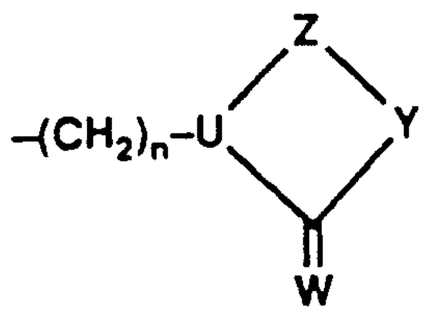
The piperazinylindan derivatives of the invention as broadly disclosed hereinafter are trans-isomers represented by the following formula I:



I

wherein X is halogen, trifluoromethyl, lower alkyl, lower alkylthio, lower alkoxy, hydroxy, lower alkylsulphonyl, lower alkyl- or dialkylamino, trifluoromethylthio or a cyano group;

R is hydrogen, lower alkyl or alkenyl, cycloalkyl, or cycloalkyl lower alkyl, optionally substituted with one or two hydroxy groups, any hydroxy group present being optionally esterified with an aliphatic carboxylic acid having from two to twentyfour carbon atoms inclusive, or R is a substituent



wherein n is an integer from 1 to 6;

U is CH or N;

Y is CH_2, O, S or N-R^1, R^1 being hydrogen or a cycloalkyl or a cycloalkylmethyl or a lower alkyl or alkenyl group optionally substituted with one or two hydroxy groups or a phenyl group optionally substituted with halogen, trifluoromethyl or lower alkyl;

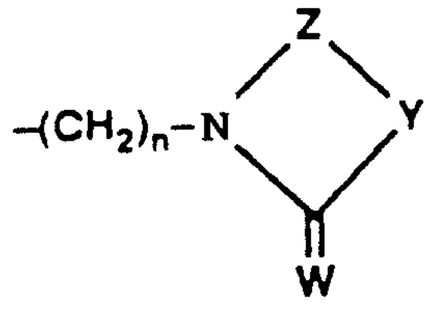
W is O or S;

Z is $-(CH_2)_4-$, $-CH_2-\underset{\underset{R^3}{|}}{\overset{\overset{R^2}{|}}{C}}-$, $-CH_2-\underset{\underset{R^3}{|}}{\overset{\overset{R^2}{|}}{C}}-CH_2-$, wherein R^2 and R^3 are hydrogen or lower alkyl, $-CH=CH-CH_2-$, $-CH=CH-$, 1,2-phenylene, optionally substituted with halogen or trifluoromethyl, or if U is nitrogen and Y is NR^1 Z may also be 1,2-$C_6H_4CH_2$- (to form a quinazolidinone or -thione ring system) or 1,2-C_6H_4CO- (to form a quinazolidindion or thioxoquinazolidinon ring system); and

Ar is a phenyl ring optionally substituted with halogen, trifluoromethyl or lower alkyl or Ar is a thiophene or furane ring optionally substituted with lower alkyl.

The invention as claimed hereinafter is however restricted to the compound of the above formula I wherein X is chlorine, fluorine, methyl, or trifluoromethyl;

R is a substituent having the formula:



wherein:

n is 2;

Y is O, CH_2, or N-R^1, R^1 being hydrogen, isopropyl, or phenyl;

W is O or S;

Z is $-GH_2CH_2-$, $-CH_2-CH_2-CH_2-$, or 1.2-phenylene; and

Ar is 4-fluorophenyl.

The term "lower alkyl" is intended to mean a straight or branched alkyl group having from one to four carbon atoms, such as methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, etc. Lower alkoxy, lower alkylthio, lower alkylsulfonyl, lower alkylamino and lower dialkylamino similarly designate such groups wherein the alkyl moiety is a lower alkyl group as defined above.

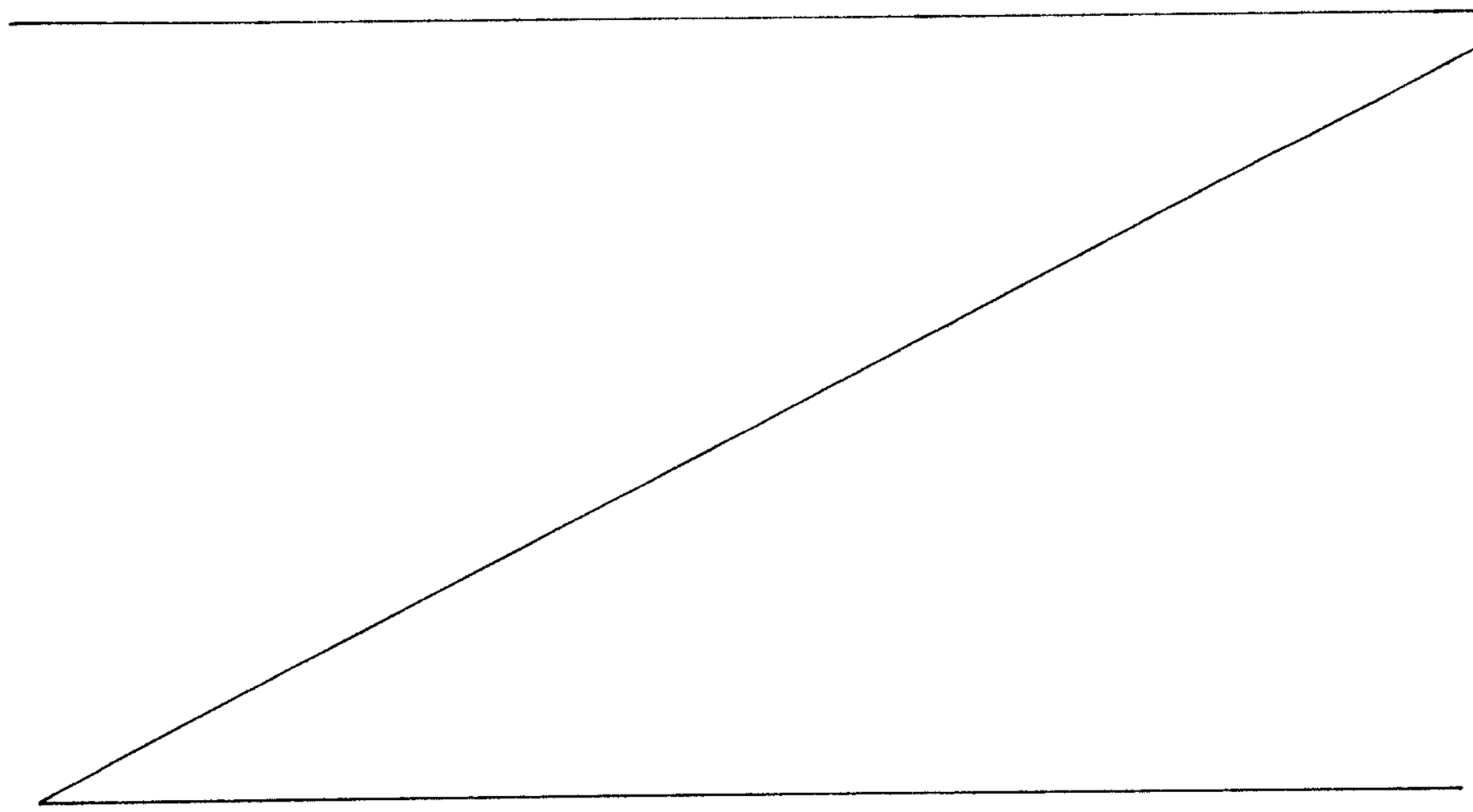
Lower alkenyl is intended to mean an alkenyl group containing from 2 to 4 carbon atoms, for example ethenyl, 1-propenyl, 2-butenyl, etc.

Cycloalkyl is intended to mean cycloalkyl having from 3 to 8 carbon atoms incl. in the ring.

The Z-group may be oriented in both directions in the ring.

Halogen means fluoro, chloro, bromo or iodo.

When Y is NR^1 wherein R^1 is H, the compound may exist in tautomeric form, i.e. wherein W is -OH or -SH, respectively, connected to the ring via a single bond, and having a double bond in the ring, i.e. from the Y to the carbon atom bearing the –OH or –OS group. Such tautomeric forms are intended to be embraced by Formula I.



Compounds similar to the compounds of the present invention are disclosed in our own US patent No. 4,443,448 which relates to 1-piperazino-3-phenylindan derivatives having one substituent in the benzen moiety of the indan ring system and claimed to have neuroleptic or antidepressant activity. The neuroleptic activity of the compounds is based on tests showing dopamine antagonistic activity *in vivo* whereas antidepressant activity is shown by the ability of the compounds to inhibit the reuptake of dopamine. A number of the compounds of the general Formula **I** of the present invention are generically embraced by the general scope of said patent. However, only a few of the 5-substituted derivatives of the general Formula **I** of the present invention are specifically mentioned in said patent. All of said compounds are compounds of the general Formula **I** wherein Ar is 4-fluorophenyl R is lower alkyl optionally substituted with hydroxy. Only some of said compounds were tested and they were all found to be without significant activity as dopamine antagonists in the *in vivo* test used, cf. Table **8** of said patent. Accordingly they were regarded to be without value as neuroleptics. No results as to dopamine reuptake inhibiting effects are given for those compounds.

Our own US patent No. 4,684,650 discloses a series of optionally 6-substituted 1-piperazino-3-phenylindans claimed to have a potent antiserotonergic activity without having any significant neuroleptic activity. It was shown that the compounds had a high affinity to 5-HT_2 receptors whereas they were weak or inactive in an *in vivo* model for antidopaminergic effect, i.e. the methylphenidate antagonism test. Many of the compounds were shown to have potent antihypertensive action. In a later publication about the same series of compounds (K.P. Bøgesø et al., J.Med.Chem., **1988**, 31, 2247) it was shown that in despite of a selective antiserotonergic profile i*n vivo*, nevertheless many of the compounds still had significant activity for both dopamine D-2 receptors and in particular α_1 adrenoceptors.

The 5-HT_2 antagonist ritanserin (Meert, T. F.; Janssen, P. A. J. *Drug. Dev. Res.* **1989**, *18*, 119.) has been shown to be effective in the treatment of anxiety and depression presumably through improvement of the sleep quality. Furthermore, selective, centrally acting 5-HT_2 antagonists have been shown to have an effect towards the negative symptoms of schizophrenia and to reduce extrapyramidal side-effects caused by treatment with classical neuroleptics in schizophrenic patients

(Gelders, Y.G., British J. Psychiatry, **1989**, *155 (suppl.5)*, 33). Finally, selective 5–HT_2 antagonists could be effective in the prophylaxis of migraine since it is known that 5-HT is involved in migraine attacks. The links between 5-HT and migraine attacks are several and they suggest a number of mechanisms whereby 5-HT may be involved (Scrip Report; "Migraine – Current trends in research and treatment"; PJB Publications Ltd.; May 1991). Various 5-HT_2 antagonists are in clinical trials as anti-migraine agents, such as sergolexole (c.f. for example Pharma Projects , May 1991, 1359-1365). Obviously there is a strong demand for selective 5-HT_2 antagonists without side effects.

It has now surprisingly been found that the 5-substituted 1-piperazinoindan derivatives of Formula **I**, have high affinity for 5-HT_2 receptors. As compared to the corresponding 6-substituted derivatives they have very low affinity to both dopamine D-2 receptors and α_1 adrenoceptors. *In vivo* the compounds have potent activity in animal models for central 5-HT_2 antagonism. Because of the very low affinity for α_1 adrenoceptors the 5-substituted compounds have, in contrast to the 6-substituted derivatives, substantially no effect on the blood pressure.

Only trans-isomers of the 5-substituted 1-piperazinoindan derivatives of Formula **I** are active, cis-isomers being without significant 5-HT_2 antagonistic activity.

Accordingly in a first aspect the present invention relates to trans-isomers of the compounds having the general Formula **I** as defined above and pharmaceutically acceptable acid addition salts thereof and prodrugs therefore with the proviso that R may not be hydrogen or lower alkyl or alkenyl optionally substituted with hydroxy when Ar is optionally substituted phenyl.

The trans-isomers of the invention exist as pairs of optically active isomers and such isomers are within the scope of the present invention. Also any other stereoisomer of a compound having the general Formula **I** is embraced by the invention. It has so far been found that the 5-HT_2 antagonistic activity predominantly resides in one of the optical isomers.

Prodrugs of the present invention may be conventional esters when hydroxy groups are available, or in particular if the compound is a compound of the general Formula I wherein W is O and Y is NR^1, R^1 being hydrogen, the prodrug may be a reaction product with an acid or an activated acid, with formaldehyde alone or in the presence of an alcohol or an amine, or with an acyloxymethylene halide, which product accordingly may be represented by a formula similar to the general Formula I defined above wherein W is O, Y however being a group $NR^{1'}$ wherein $R^{1'}$ designates a group **–A–B** where A is selected from CO, CS, or CH_2, and

if A is CO or CS, B is selected from the groups consisting of:

i) hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl or cycloalk(en)ylalk(en)yl, optionally substituted with one or two hydroxy groups, or phenyl optionally substituted with one or more substituents selected from the group consisting of halogen, trifluoromethyl, lower alkyl, lower alkoxy, lower alkylthio, acyloxy, or cyano; or

ii) QB^1, wherein Q is O or S and B^1 is selected from the substituents defined for B under i) above except hydrogen; and

iii) NB^2B^3, wherein B^2 and B^3 independently are selected from the substituents defined for B^1 under ii) above, or B^2 and B^3 are combined to form a four to eight membered heterocyclic ring containing from one to three nitrogen atoms and from zero to three oxygen or sulfur atoms; or

if A is CH_2, B is selected from the groups consisting of:

iv) a group QB^1 as defined in ii);

v) a group NB^2B^3 as defined in iii); or

vi) a group $OC(O)B^4$, wherein B^4 is as defined for B^1.

Although the latter prodrugs are not esters , they would decompose properly in order to release the compound of the invention over a desired period of time when administered parenterally as a depote formulation in an apropriate oil, such as coconut oil, e.g. viscoleo®, peanut oil, sesame oil, cotton seed oil, corn oil, soy bean oil, olive oil, etc. or synthetic esters of fatty acids and glycerol or propylenglycol.

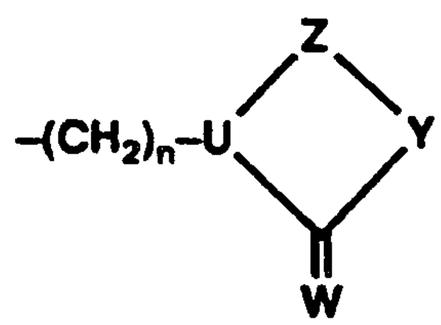
The pharmaceutically acceptable acid addition salts of the compounds used in the invention are salts formed with non-toxic organic or inorganic acids. Exemplary of such organic salts are those with maleic, fumaric, benzoic, ascorbic, embonic,

succinic, oxalic, bis-methylenesalicylic, methanesulfonic, ethanedisulfonic, acetic, propionic, tartaric, salicylic, citric, gluconic, lactic, malic, mandelic, cinnamic, citraconic, aspartic, stearic, palmitic, itaconic, glycolic, p-amino-benzoic, glutamic, benzene sulfonic and theophylline acetic acids, as well as the 8-halotheophyllines, for example 8-bromo-theophylline. Exemplary of such inorganic salts are those with hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric and nitric acids.

The compounds of the invention show high affinity to 5-HT_2 receptors and very low receptor affinity to D-2 receptors and α_1 adrenoceptors and consequently they are very selective with respect to the 5-HT_2 receptor. Accordingly, they are useful in the treatment of varios diseases of the central nervous system, such as anxiety, depression, sleeping disorders, negative symptoms of schizophrenia, extrapyramidal side-effects caused by treatment with classical neuroleptics, and migraine.

Preferred 5-substituted trans-1-piperazinoindan derivatives according to the invention are those wherein:

Ar is a phenyl ring optionally substituted with halogen or methyl, preferably 4-fluorophenyl; X is Cl or F and/or R is a group of the formula:



wherein n is 2,

U is nitrogen; W is O or S; Z is -CH_2–CH_2- or -CH_2–CH_2–CH_2-; and

Y is a group NR^1 wherein R^1 is hydrogen or lower alkyl.

Most preferably the compound of the invention is selected from the group of:

(–)-Trans-1-[2-[4-[5-chloro-3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]piperazin-1-yl]-ethyl]-3-isopropyl-2-imidazolidinone, dimaleate;

(+)-Trans-1-[2-[4-[5-fluoro-3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]piperazin-1-yl]ethyl]-tetrahydro-2(1*H*)-pyrimidinethione,dihydrochloride;

(–)-Trans-1-[2-[4-[5-chloro-3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]piperazin-1-yl]ethyl]-tetrahydro-2(1*H*)-pyrimidinethione,dihydrochloride;

(+)-Trans-1-[2-[4-[5-fluoro-3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]piperazin-1-yl]ethyl]-tetrahydro-2(1*H*)-pyrimidinone,dimaleate; and
(–)-Trans-1-[2-[4-[5-chloro-3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]piperazin-1-yl]ethyl]-tetrahydro-2(1*H*)-pyrimidinone,dimaleate.

In a second aspect the present invention relates to a pharmaceutical preparation comprising at least one derivative of the general Formula **I** as defined above together with a pharmaceutically acceptable carrier or diluent.

The compounds of the Formula **I** and the pharmaceutically acceptable acid addition salts thereof may be administered by any suitable route, for example orally in the form of tablets, capsules, powders, syrups, etc., or parenterally in the form of solutions for injection.

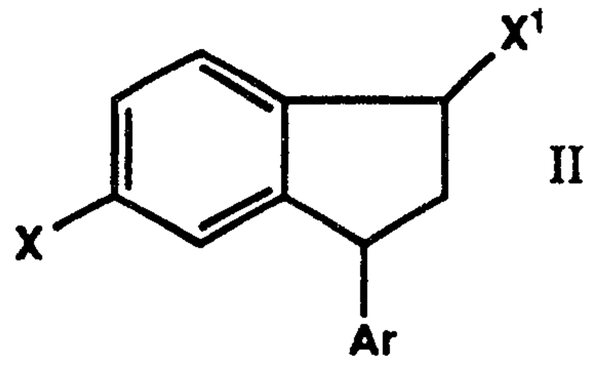
Suitable pharmaceutical preparations may be prepared by methods well known in the art. Conveniently, the compounds of the invention are administered in unit dosage form containing said compound in an amount of about 0.05 - 100 mg, preferably about 1 - 50 mg.

The total daily dose usally ranges from about 0.1 to 500 mg of the active compound of the invention.

In a further aspect the present invention relates to the use of a compound having the general Formula **I** as defined above for the manufacture of a medicament for the treatment of a disease in the central nervous system, preferably anxiety, depression, sleeping disorders, negative symptoms of schizophrenia, extrapyramidal side-effects caused by treatment with classical neuroleptics, and migraine.

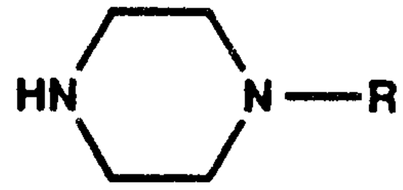
The invention moreover relates to a method for the preparation of the novel 5-substituted derivatives of Formula **I**, which comprises:

a) treating a compound of the following Formula **II**:



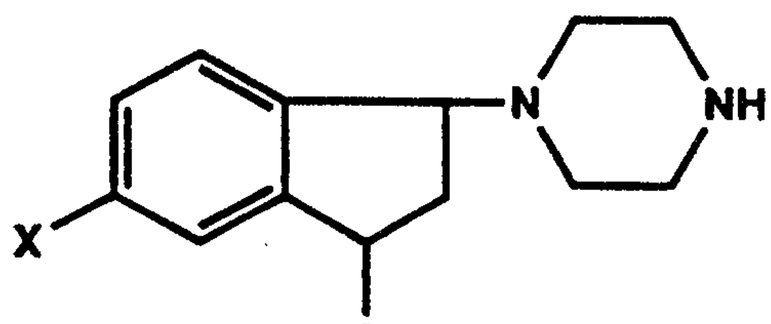
II

with a piperazine derivative of formula:



in which formulas X, Ar and R are as defined above, and X^1 is halogen or $-OSO_2R^4$ wherein R^4 is alkyl such as CH_3 or aryl such as p-toluyl;

b) treating a compound of the following Formula **III**:

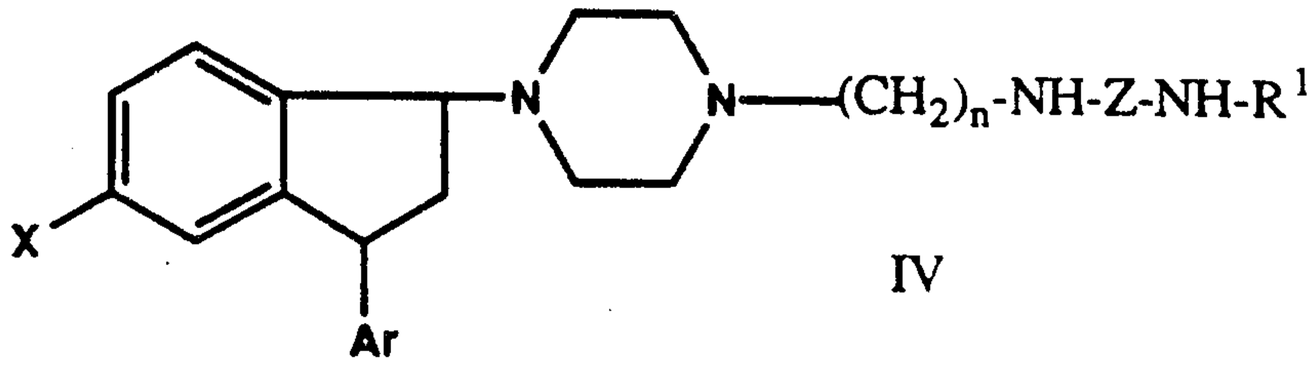


III

wherein X and Ar are as defined above, with a compound of the formula X^1-R wherein R and X^1 are as defined above except that R cannot be hydrogen;

c) treating a compound of Formula **III** with a compound R´-CHO, wherein R´ is such a group that R´-CH_2- is as defined above for R, in the presence of a reducing agent;

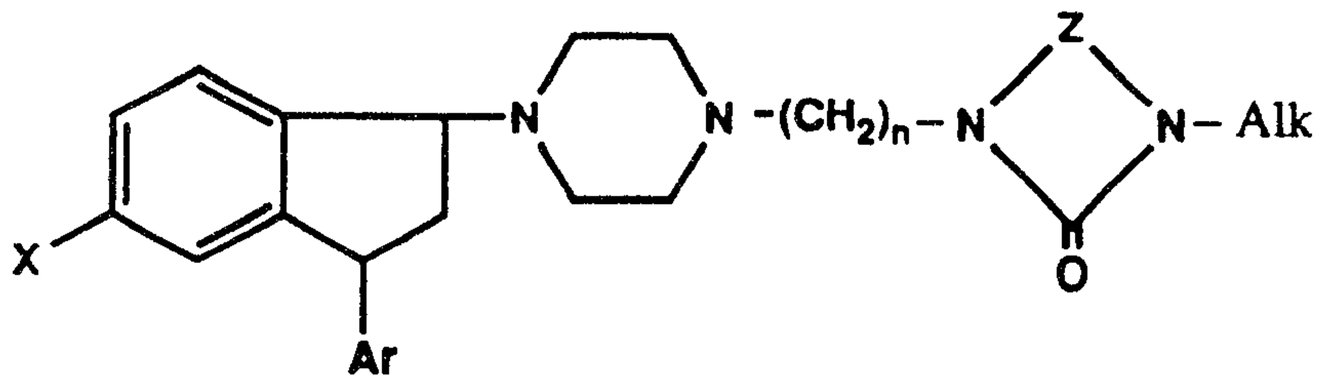
d) treating a compound of the following Formula **IV**:



IV

wherein X, Ar, R^1, Z and n are as defined above, with CS_2, thiophosgene, urea or phosgene;

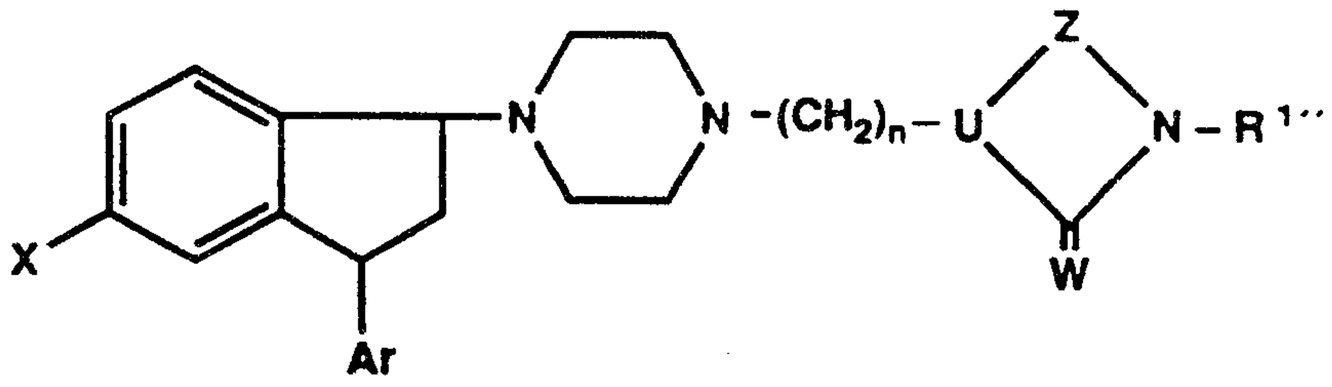
e) treating a compound of the following Formula **V**:



V

wherein X, Ar, n, and Z are as defined above and Alk is an alkali metal such as sodium or potassium, with a compound of formula R^5-X^1 wherein R^5 is a lower alkyl group and X^1 is as defined above;

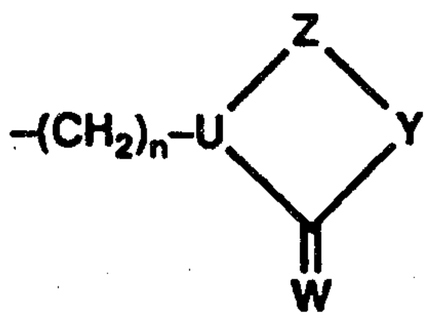
f) reducing a compound with the following Formula **VI**:



VI

wherein X, Ar, n, U, Z and W are as defined above and $R^{1''}$ is a cycloalkyl or lower alkyl group containing one or more ester, ketone or aldehyde groups, with a suitable reducing agent to a corresponding compound wherein R^1 is a lower alkyl or a cycloalkyl group containing one or more hydroxy groups;

g) reacting a compound of Formula **I** wherein R is a group of the formula:



wherein n, U, Z and Y are as defined above an W is O, with P_2S_5 or Lawessons reagent to obtain the corresponding compound wherein W is S.

Method a) is preferably carried out in an inert solvent such as acetone or methyl-isobutylketone using either an excess of the piperazine reactant or by using equimolar amounts of reactants in the presence of an alkali metal carbonate such

as potassium carbonate or another alkaline substance at reflux temperatures.

Method b) is preferably carried out in an inert solvent such as ethanol or isobutylketone in the presence of an alkali metal carbonate such as potassium carbonate or another alkaline substance at reflux temperatures.

Method c) is preferably carried out in an inert solvent such as an alcohol (eg methanol) or an ether (eg tetrahydrofuran) by hydrogenation in the presence of a suitable catalyst such as Pt or Pd or by using a borohydride such as $NaCNBH_3$ at a pH of 5-6.

Method d) is preferably carried out by treating a compound of Formula **IV** in an inert solvent, such as n-pentanol or n-butanol, with urea or carbon disulfide succeeded by heating at reflux temperatures.

In Method e), the alkalimetal salt of Formula **V** is preferably formed by treating the corresponding hydrogen derivative with an alkali metal alkoxide such as potassium tert.-butoxide in an inert solvent such as toluene whereupon the salt is reacted directly with the alkylating agent, R^5-X^1, at room or higher temperatures.

Method f) is preferably carried out by reducing the derivative of Formula **VI** with a suitable reducing agent such as lithium or sodium borohydride in an inert solvent such as tetrahydrofurane.

Method g) is preferably carried out in hexamethyl phosphorous triamide (HMPA) or xylene at temperatures between 110 °C and 200 °C.

The acid addition salts of the compounds of the invention are easily prepared by methods well known in the art. The base is reacted with either the calculated amount of organic or inorganic acid in an aqueous miscible solvent, such as acetone or ethanol, with isolation of the salt by concentration and cooling, or with an excess of the acid in an aqueous immiscible solvent, such as ethyl ether or chloroform, with the desired salt separating directly. Of course, these salts may also be prepared by the classical method of double decomposition of appropriate salts.

The preparation of the compounds of Formula **II** from the corresponding 2,3-dihydro-inden-1-ones may be carried out analogueously with the method described in U.S.Patent No. 4,443,448, U.S. Patent No. 4,684,650, and J.Med.Chem. **1983,** *26,* 935. The indanones were either prepared by cyclization of the corresponding diphenylpropionic acids or more conveniently as described for similar compounds in U.S.Patent No. 4,873,344 and in J.Org.Chem. **1990**, 55, 4822 from the proper 3,5-disubstituted 1-amino-3-cyano-1-inden-2-carboxylic acid esters which in turn also may be prepared as described in U.S.Patent No. 4,873,344. Hereby the following novel 3,5-disubstituted 1-amino-3-cyano-1-inden-2-carboxylic acid esters were prepared:

1-Amino-3-cyano-3-(4-fluorophenyl)-5-methyl-1-inden-2-carboxylic acid methyl ester, mp 215-217 °C.

1-Amino-5-chloro-3-cyano-3-phenyl-1-inden-2-carboxylic acid methyl ester, mp 192-194 °C.

1-Amino-5-chloro-3-cyano-3-(2-fluorophenyl)-1-inden-2-carboxylic acid methyl ester, mp 227-228 °C.

1-Amino-5-chloro-3-cyano-3-(3-fluorophenyl)-1-inden-2-carboxylic acid methyl ester, mp 191-193 °C.

1-Amino-5-chloro-3-cyano-3-(2-methyl-4-thienyl)-1-inden-2-carboxylic acid methyl ester, mp 161-163 °C.

1-Amino-5-chloro-3-cyano-3-(4-chlorophenyl)-1-inden-2-carboxylic acid methyl ester, mp 213-215 °C.

1-Amino-5-chloro-3-cyano-3-(4-methylphenyl)-1-inden-2-carboxylic acid methyl ester, mp 228-230 °C.

By the above method the following novel 2,3-dihydro-1*H*-inden-1-ones were prepared:

3-(4-fluorophenyl)-5-(trifluoromethyl)-2,3-dihydro-1*H*-inden-1-one, mp105-106°C

3-(4-fluorophenyl)-5-methyl-2,3-dihydro-1*H*-inden-1-one, mp 69-71 °C.

5-chloro-3-phenyl-2,3-dihydro-1*H*-inden-1-one, mp 127-129 °C.

5-chloro-3-(2-fluorophenyl)-2,3-dihydro-1*H*-inden-1-one, mp 83-85 °C.

5-chloro-3-(3-fluorophenyl)-2,3-dihydro-1*H*-inden-1-one, mp 118-120 °C.

3-(4-fluorophenyl)-5-methylthio-2,3-dihydro-1*H*-inden-1-one, mp 74-76 °C.

5-chloro-3-(2-methyl-4-thienyl)-2,3-dihydro-1*H*-inden-1-one, mp 101-102 °C.

5-chloro-3-(4-chlorophenyl)-2,3-dihydro-1*H*-inden-1-one, mp 140-142 °C.

5-chloro-3-(4-methylphenyl)-2,3-dihydro-1*H*-inden-1-one, mp 112-114 °C.

As previously described (see references cited above) the 2,3-dihydro-1*H*-inden-1-ones may be reduced with sodiumborohydride to the corresponding cis-2,3-dihydro-1*H*-inden-1-ols which serves as the starting materials for preparing the compounds of Formula II. The following new 2,3-dihydro-1*H*-inden-1-ols were obtained:

3-(4-fluorophenyl)-5-(trifluoromethyl)-2,3-dihydro-1*H*-inden-1-ol, mp 81-83 °C.

3-(4-fluorophenyl)-5-methyl-2,3-dihydro-1*H*-inden-1-ol, mp 100-102 °C.

5-chloro-3-phenyl-2,3-dihydro-1*H*-inden-1-ol, mp 110-111 °C.

5-chloro-3-(2-fluorophenyl)-2,3-dihydro-1*H*-inden-1-ol, mp 78-80 °C.

5-chloro-3-(3-fluorophenyl)-2,3-dihydro-1*H*-inden-1-ol, mp 110-112 °C.

3-(4-fluorophenyl)-5-methylthio-2,3-dihydro-1*H*-inden-1-ol, mp 114-116 °C.

5-chloro-3-(2-methyl-4-thienyl)-2,3-dihydro-1*H*-inden-1-ol, mp 119-121 °C.

5-chloro-3-(4-chlorophenyl)-2,3-dihydro-1*H*-inden-1-ol, mp 129-131 °C.

5-chloro-3-(4-methylphenyl)-2,3-dihydro-1*H*-inden-1-ol, mp 107-109 °C.

In the following, the invention is further illustrated by way of examples which must in no way be construed as limiting for the invention.

EXAMPLES

EXAMPLE 1

Trans -1-[2-[4-[3-(4-fluorophenyl)-5-(trifluoromethyl)-2,3-dihydro-1*H*-inden-1-yl]-1-piperazinyl]ethyl]-2-imidazolidinone, dimaleate (Compd. 1)

A mixture of 1-Chloro-3-(4-fluorophenyl)-5-(trifluoromethyl)-2,3-dihydro-1H-inden (8.5 g) and 1-[(2-(piperazin-1-yl)ethyl]-2-imidazolidinone (20 g) in methylisobutyl-ketone (250 ml) was stirred at 80°C for 18 hours.

The reaction mixture was cooled, whereupon ether and water was added. The phases were separated, and the organic phase was washed with water. The ether phase was extracted with 1 N methane sulphonic acid. The base was liberated with 10 N sodium hydroxide and extracted with methylene chloride. The organic phase was dried ($MgSO_4$) and evaporated in vacuo to give 10 g of crude 1. The crude base was dissolved in acetone and transformed to the maleate salt which was recrystallized from ethanol (100 ml) to give 4.9 g of 1, as dimaleate ; mp 169-171°C.

CHN calculated: 55.92%; 5.13%; 7.91%.

CHN found: 55.94%; 5.02%; 7.94%.

EXAMPLE 2

Preparation of (+)-1 (the active enantiomer of 1)

To a solution of trans-1-[3-(4-fluorophenyl)-5-(trifluoromethyl)-2,3-dihydro-1*H*-inden-1-yl]piperazine (38 g) in ethanol (500 ml) was added a solution of L-(+)-tartaric acid (15 g) in water (25 ml). The mixture was left overnight at room temperature. The crystals were filtered and recrystallized from mehanol (400 ml) and water (400 ml) to give 17 g; mp 221-223°C. Optical rotation of the base: $[\alpha]_D$= -3.2° (*c* 0.5, MeOH).

The first filtrate from the L-(+)-tartrate salts was evaporated in vacuo and converted to the base. This base (25 g) was dissolved in methanol (400 ml) and a solution of D-(-)tartaric acid (10 g) in water (50 ml) was added. The mixture was kept for 2 hours at room temperature. The crystals were filtered and recrystallized from methanol (250 ml) and water (250 ml) to give 13 g, mp 222-224°C. Optical rotation of the base: $[\alpha]_D$= +3.7° (*c* 0.5, MeOH).

The D-(-)-tartrate salt was converted to the base (9.5 g) which was added to a mixture of 1-(2-chloroethyl)-2-imidazolidinone (9 g), potassium carbonate (10 g) and potassium iodide (0.5 g) in methylisobutylketone (250 ml). The mixture was refluxed with stirring for 18 hours. The reaction mixture was worked up as described in Example 1, to give a crude base (15 g). The base was converted to the dimaleate salt which was recrystallized three times from ethanol to give **(+)-1, dimaleate salt**, mp 158-159°C. [α]= +5,5° (*c* 0.5, CH_3OH).

CHN calculated: 55.92%; 5.13%; 7.91%.
CHN found: 55.92%; 5.09%; 7.95%.

EXAMPLE 3

Optical resolution of Trans-4-[5-fluoro-3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]-1-piperazine ethanol (Compd.2)

The dihydrochloride salt of Compd.2 (11 g, c.f. U.S.Patent 4,443,448) was conver-

ted to the base (9.5 g). A solution of the base and L-(+)-tartaric acid (4 g) in ethanol (250 ml) was kept at room temperature for 18 hours. The crystals were filtered off and dried (4.5 g), and recrystallized from methanol (600 ml) to give 3.2 g ; mp 216-217°C ; $[\alpha]_D$= +15.4° (*c* 0.5, DMSO). The L-(+)-tartrate salt was converted to the base, which was transferred to the dihydrochloride salt. The dihydrochloride salt was recrystallized from ethanol/ether to give 1 g of **(+)-2**, dihydrochloride; mp 224-226°C; $[\alpha]_D$= +27.1° (*c* 0.5, CH_3OH).

The first filtrate from the L-(+)-tartrate salt was evaporated and converted to the base. The base was converted to the D-(-)-tartaric salt which was recrystallized and converted to the dihydrochloride salt as described for **(+)-2**.

0.6 g of **(-)-2**, dihydrochloride was obtained ; mp 223-226°C ; $[\alpha]_D$= -27.1° (*c* 0.5, CH_3OH).

Trans-4-[5-chloro-3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl)-1-piperazine-ethanol (**3** , c.f. US Patent 4,443,448) was resolved in a similar way to give

(+)-3, dihydrochloride ; mp 224-227°C ; $[\alpha]_D$= +13.5° (*c* 0.5, H_2O) and

(-)-3, dihydrochloride ; mp 224-227°C ; $[\alpha]_D$= -14.1° (*c* 0.5, H_2O).

The method described in Example was used for the preparation of the following compounds:

Trans-1-[2-[4-[5-chloro-3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]piperazine-1-yl]ethyl]-2-imidazolidinone; mp 168-170 °C. Compd. **4**.

Trans-4-[3-(4-fluorophenyl)-5-(trifluoromethyl)-2,3-dihydro-1*H*-inden-1-yl]-1-piperazineethanol, dimaleate; mp 172-174 °C. Compd. **5**.

Trans-4-[5-chloro-3-(2-methyl-4-thienyl)-2,3-dihydro-1*H*-inden-1-yl]-1-piperazineethanol, dimaleate; mp 175-177°C. Compd. **6**.

Trans-1-[2-[4-[5-chloro-3-(2-methyl-4-thienyl)-2,3-dihydro-1*H*-inden-1-yl]piperazine-1-yl]ethyl]-2-imidazolidinone, dimaleate; mp 174-176 °C. Compd. **7**.

Trans-4-[3-(4-fluorophenyl)-5-methyl-2,3-dihydro-1*H*-inden-1-yl]-1-piperazine ethanol, dimaleate; mp 169-171 °C. Compd. **8**.

Trans-1-[2-[4-[3-(4-fluorophenyl)-5-methyl-2,3-dihydro-1*H*-inden-1-yl]piperazine-1-yl]ethyl]-2-imidazolidinone, dimaleate; mp 180-181 °C. Compd. **9**.

EXAMPLE 4

Trans-1-[5-chloro-3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]piperazine, maleate (Compd. **10**)

Thionylchloride (44 ml) was added dropwise with water-cooling to a solution of 5-chloro-3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-ol in ether (2L) with a catalytic amount of DMF (0.5 ml). Then the mixture was stirred for 2 hours at room temperature, poured into ice and neutralized with 9N NaOH. The organic phase was separated, dried ($MgSO_4$) and evaporated to give 140 g of crude 1,5-dichloro-3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden.

A mixture of the chloroderivative (140 g), piperazine (800 g) and acetone (2L) was refluxed with stirring for 18 hours. After cooling piperazine hydrochloride was filtered off and washed with ethyl acetate. The combined filtrate was concentrated in vacuo. The residue was dissolved in ether, washed with water and extracted with 1N methane sulphonic acid. The base was liberated from the acid extract with 9N sodium hydroxide, extracted with ether, dried ($MgSO_4$) and evaporated in vacuo to give crude Compd.**10** (156 g). The residue was dissolved in acetone (600 ml) and ethanol (600 ml), whereupon maleic acid (110 g) was added. After 1 hour at room temperature the maleate salt of Compd.**10** was filtered and dried. Yield: 216 g ; mp 190-191°C.

10 g were recrystallized from ethanol to give pure Compd. **10**, maleate; mp: 194-195°C.

CHN calculated: 61.81%; 5.42%; 6.27%.

CHN found: 61.77%; 5.40%; 6.34%.

EXAMPLE 5

Optical resolution of Compd.**10** (**(+)-10 and (-)-10**)

A solution of Compd.**10** (24 g) and (-)-dibenzoyl-L-tartaric acid hydrate ((-)DBT) (27.3 g) in acetone (250ml) was left for 18 hours at room temperature. The crystals were filtered and dried. The (-)DBT salt was boiled with methanol (1L), cooled, filtered and dried to give 13.5 g of (-)-DBT salt; mp: 213-214°C.

The first filtrate from the (-)-DBT salt was concentrated and converted to the base (13 g), which was treated with (+)-DBT in the same manner as described for the (-)-DBT salt. Yield: 11 g of (+)-DBT salt; mp: 212-213°C.

The DBT salts were converted to the bases and then precipitated as maleate salts. The maleate salts were recrystallized from ethanol (200 ml) and methanol (50 ml) to give

(+)-10 , maleate salt ; mp: 194-196°C ; $[\alpha]_D$= +30.6° (*c* 0.5, CH_3OH).

(-)-10 , maleate salt ; mp: 194-196°C ; $[\alpha]_D$= -30.2° (*c* 0.5, CH_3OH).

EXAMPLE 6

Trans-1-[2-[4-[5-chloro-3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]piperazin-1-yl]-ethyl]-3-isopropyl-2-imidazolidinone, dimaleate (Compd.**11**)

A mixture of Compd.**10** (140 g as the maleate salt , see Example 4), 1-(2-chloroethyl)-3-isopropyl-2-imidazolidinone (75 g), potassium carbonate (260 g) and potassium iodide (5 g) in methylisobutylketone (1L) was refluxed with stirring for 18 hours.

After cooling, water (500 ml) was added. The phases were separated and the organic layer was washed with water and then concentrated in vacuo. The residue was dissolved in ether, washed with water and extracted with 1N methane sulphonic acid. The base was liberated with 9N NaOH, extracted with ether, dried and concentrated in vacuo to give 157 g of crude Compd.**11**. The base was converted to the dimaleate salt in ethanol (2L) to give 193 g of trans-isomer (**11**).

A sample recrystallized from methanol melted at 188-190°C.

CHN calculated: 58.61%; 5.92%; 7.81%.

CHN found: 58.78%; 5.90%; 7.88%.

EXAMPLE 7

Optical resolution of Compd.11 ((+)-11 and (-)-11)

The resolution was performed essentially as described in the Examples 2 and 3 (using L-(+)- and D-(-)-tartaric acid) with the exception that tartrate salts were crystallized and recrystallized from water. From 126 g of **11** (as the base) there was obtained 50 g of D-(-)-tartrate, mp 102-104°C, and 51 g of L-(+)-tartrate, mp 102-104°C.

In a conventional manner the tartrate salts were converted to the maleate salts which were recrystallized from ethanol to give

(+)-11, dimaleate, mp 175°C, $[\alpha]_D$= +17.0° (*c* 0.5, CH_3OH), and

(-)-11, dimaleate, mp 175°C, $[\alpha]_D$= -17.5° (*c* 0.5, CH_3OH).

The method described in Example 6 was used for the preparation of the following compounds:

Trans-1-[2-[4-[3-(4-fluorophenyl)-5-methyl-2,3-dihydro-1*H*-inden-1-yl]piperazin-1-yl]ethyl]-3-isopropyl-2-imidazolidinone,dimaleate; mp 178-180 °C. Compd. **12.**

Trans-1-[2-[4-[3-(4-fluorophenyl)-5-(trifluoromethyl)-2,3-dihydro-1H-inden-1-yl]piperazin-1-yl]ethyl]-3-isopropyl-2-imidazolidinone, dimaleate; mp 174-176 °C. Compd. **13.**

Trans-3-[2-[4-[5-chloro-3-(4-fluorophenyl)-2,3-dihydro-1-*H*-inden-1-yl]piperazin-1-yl]ethyl]-2-oxazolidinone,diHCl; mp 244-246 °C. Compd. **14**.

Trans-1-[2-[4-[5-chloro-3-(4-fluorophenyl)-2,3-dihydro-1-*H*-inden-1-yl]piperazin-1-yl]ethyl]-2-pyrrolidinone,diHCl; mp 250-252 °C. Compd. **15**.

Trans-1-[3-[4-[5-chloro-3-(4-fluorophenyl)-2,3-dihydro-1-*H*-inden-1-yl]piperazin-1-yl]propan-1-yl]-2-imidazolidinone,dimaleate; mp 159-160 °C. Compd. **16**.

Trans-1-[2-[4-[5-chloro-3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]piperazin-1-yl]ethyl]-3-phenyl-2-imidazolidinone,dimaleate; mp 174-176 °C. Compd.**17**.

Trans-1-[2-[4-[5-chloro-3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]piperazin-1-yl]ethyl]-3-methyl-2-imidazolidinone,dimaleate; mp 164-166 °C. Compd.**18**.

Trans-1-[2-[4-[5-chloro-3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]piperazin-1-yl]ethyl]-3-ethyl-2-imidazolidinone,dimaleate; mp 178-180 °C. Compd.**19**.

Trans-1-[2-[4-[5-chloro-3-phenyl-2,3-dihydro-1*H*-inden-1-yl]piperazin-1-yl]ethyl]-3-isopropyl-2-imidazolidinone,dimaleate; mp 189-190 °C. Compd.**20**.

Trans-1-[2-[4-[5-chloro-3-(2-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]piperazin-1-yl]ethyl]-3-isopropyl-2-imidazolidinone,dimaleate; mp 190-192°C. Compd.**21**.

Trans-1-[2-[4-[3-(4-fluorophenyl)-5-(methylthio)-2,3-dihydro-1*H*-inden-1-yl]piperazin-1- yl]ethyl]-2-imidazolidinone,dimaleate; mp 182-184 °C. Compd. **22**.

Trans-1-[2-[4-[3-(4-fluorophenyl)-5-(methylthio)-2,3-dihydro-1*H*-inden-1-yl]piperazin-1-yl]ethyl]-3-isopropyl-2-imidazolidinone,dimaleate; mp 186-188 °C. Compd. **23**.

Trans-1-[2-[4-[5-bromo-3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]piperazin-1-yl]ethyl]-3-isopropyl-2-imidazolidinone,dimaleate; mp 180-182 °C. Compd. **24**.

Trans-1-[2-[4-[5-chloro-3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]piperazin-1-yl]ethyl]-benzimidazolin-2-one,dimaleate; mp 192-194 °C. Compd. **25**.

Trans-1-[2-[4-[5-chloro-3-(4-methylphenyl)-2,3-dihydro-1*H*-inden-1-yl]piperazin-1-yl]ethyl]-3-isopropyl-2-imidazolidinone,dimaleate; mp 184-186 °C. Compd. **26** .

Trans-1-[2-[4-[5-chloro-3-(4-chlorophenyl)-2,3-dihydro-1*H*-inden-1-yl]piperazin-1-yl]ethyl]-3-isopropyl-2-imidazolidinone,dimaleate; mp 170-172 °C. Compd. **27** .

Trans-1-[2-[4-[5-chloro-3-(3-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]piperazin-1-yl]ethyl]-3-isopropyl-2-imidazolidinone,dimaleate; mp 180-182 °C. Compd. **28**

EXAMPLE 8

Trans-1-[2-[4-[5-fluoro-3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]piperazin-1-yl]-ethyl]-2-imidazolidinthione, dimaleate (Compd. **29**)

A mixture of Compound **2** (140 g, base, c.f. US Patent 4,443,448), thionyl chloride (100 ml) and DMF (10 ml) in chloroform (2L) was refluxed for 2 hours. After cooling, the hydrochloride salt of the chloroethyl derivative of **2** was filtered, washed with ethyl acetate and dried (Yield: 84 g).

A mixture of 42 g of the hydrochloride salt and ethylendiamine (100 ml) in ethanol (500 ml) was refluxed with stirring for 3 hours. The mixture was concentrated in vacuo; the residue was dissolved in a mixture of methylene chloride and water, the organic layer was separated, washed with saturated NaCl solution, dried ($MgSO_4$) and evaporated in vacuo to give 40 g of crude trans-1-[5-fluoro-3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]-4-[2-[(2-aminoethyl)amino]ethyl] piperazine as an oil. Said ethylendiamine derivative was dissolved in methylene chloride, whereupon carbon disulfide (15 ml) was added. The mixture was kept for 1 hour at room temperature, and was then evaporated in vacuo. The crude dithiocarbamate salt was dissolved in n-pentanol and refluxed for 1 hour (evolution of hydrogen sulfide). The reaction mixture was concentrated in vacuo. The residue was dissolved in ether, extracted with 1N methanesulfonic acid, whereupon the base was liberated with 9N NaOH and extracted with ether. The ether solution was filtered through silica gel, and concentrated to yield 24 g of an oil, which was transformed to the dimaleate to give **29** , dimaleate, mp 172-174°C.

CHN calculated: 57.04%; 5.25%; 8.32%.

CHN found: 57.30%; 5.43%; 8.17%.

Trans-1-[2-[4-[5-fluoro-3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]piperazin- 1-yl]ethyl]-tetrahydro-2(1*H*)-pyrimidinethione,dimaleate. mp 174-176 °C., Compd. **30** was prepared in a similar way, by replacing ethylendiamine with 1,3-

propylendiamine. The enantiomers of this compound were prepared in a similar way starting from **(+)-2** and **(-)-2**, respectively:

(+)-Trans-1-[2-[4-[5-fluoro-3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]piperazin-1-yl]ethyl]-tetrahydro-2(1*H*)-pyrimidinethione,dihydrochloride; mp 205-206 °C, $[\alpha]_D$= +26.7° (*c* 0.5, water). Compd. **(+)-30.**

(-)-Trans-1-[2-[4-[5-fluoro-3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]piperazin-1-yl]ethyl]-tetrahydro-2(1*H*)-pyrimidinethione,dihydrochloride; mp 205-206 °C, $[\alpha]_D$= –25.6° (*c* 0.5, water). Compd. **(-)-30.**

The following compounds was prepared in a corresponding manner:

Trans-1-[2-[4-[5-chloro-3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]piperazin-1-yl]ethyl]-2-imidazolidinthione,dimaleate; mp 183-184 °C. Compd.**31.**

Trans-1-[2-[4-[5-chloro-3-(4-fluorophenyl)-2,3-dihydro-1H-inden-1-yl]piperazin-1-yl]ethyl]-tetrahydro-2(1*H*)-pyrimidinethione,dimaleate; mp 184-185 °C. Compd.**32** .

(+)-Trans-1-[2-[4-[5-chloro-3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]piperazin-1-yl]ethyl]-tetrahydro-2(1*H*)-pyrimidinethione,dihydrochloride; mp 212-213 °C, $[\alpha]_D$= +6.6° (*c* 0.5, water). Compd. **(+)-32.**

(-)-Trans-1-[2-[4-[5-chloro-3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]piperazin-1-yl]ethyl]-tetrahydro-2(1*H*)-pyrimidinethione,dihydrochloride; mp 212-213 °C, $[\alpha]_D$= –6.6° (*c* 0.5, water). Compd. **(-)-32.**

The following compounds were also prepared as described in Example 8, except that the diamines were treated with urea instead of carbondisulfide. A mixture of the diamine and urea in NMP was heated for 4 h at 140-160 °C, whereupon the reaction mixture was worked-up in a conventional manner.

(+)-Trans-1-[2-[4-[5-fluoro-3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]piperazin- 1-

yl]ethyl]-tetrahydro-2(1*H*)-pyrimidinone,dimaleate; mp 170-171 °C, $[\alpha]_D$= + 16.0° (*c* 0.5, water). Compd. **(+)-33** .

(-)-Trans-1-[2-[4-[5-fluoro-3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]piperazin- 1-yl]ethyl]-tetrahydro-2(1*H*)-pyrimidinone,dimaleate; mp 170-171 °C, $[\alpha]_D$= - 15.0° (*c* 0.5, water). Compd. **(–)-33** .

(+)-Trans-1-[2-[4-[5-chloro-3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]piperazin- 1-yl]ethyl]-tetrahydro-2(1*H*)-pyrimidinone,dimaleate; mp 179-180 °C, $[\alpha]_D$= + 16.8° (*c* 0.5, water). Compd. **(+)-34.**

(-)-Trans-1-[2-[4-[5-chloro-3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]piperazin- 1-yl]ethyl]-tetrahydro-2(1*H*)-pyrimidinone,dimaleate; mp 179-180 °C, $[\alpha]_D$= - 17.2° (*c* 0.5, water). Compd. **(-)-34.**

(±)-Trans-1-[2-[4-[5-chloro-3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]piperazin- 1-yl]ethyl]-5,5-dimethyl-tetrahydro-2(1*H*)-pyrimidinone,dimaleate; mp 166-168 °C, Compd. **35.**

EXAMPLE 9

Trans-1-[2-[4-[5-chloro-3-(4-fluorophenyl)-2,3-dihydro-1-*H*-inden-1-yl]piperazin-1-yl]ethyl]-3-isopropyl-2-imidazolidinthione, dimaleate (Compd.36)

A mixture of **10** (15 g as the base), chloroacetonitrile (4.6 g) and potassium carbonate (10 g) in methyl ethylketone (400 ml) was refluxed overnight with stirring. After cooling and evaporation in vacuo the residue was treated with water and ether. The ether phase was dried and evaporated to give an oil which was chromatographed using 100 g of silica gel and ethyl acetate - methanol - triethylamine (80:10:10) as the mobile phase. Yield: 15 g, which was used without further purification.

The acetonitrile derivative (15 g) in dry tetrahydrofurane (150 ml) was treated under cooling with 3 g of pelleted lithium aluminium hydride. The reaction mixture was refluxed for 4 hours and worked-up in a conventional manner to give 15 g of the crude N-(2-aminoethyl) derivative of **10**.

Chloroacetylchloride (4.5 g) was added at 10-15°C to a stirred mixture of the aminoethyl derivative (15 g) and triethylamine (15 g) in trichloroethane. The mixture was stirred for 1 hour, whereupon isopropylamine (25 ml) was added. The reaction mixture was refluxed for 5 hours and was then treated with water. The organic phase was evaporated , and the resulting oil was dissolved in dry tetrahydrofurane (250 ml) and was then treated with 4 g of pelleted lithium aluminium hydride. After 2 hours' reflux the reaction mixture was worked-up in a conventional manner to give 11 g of crude trans-1-[5-chloro-3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]-4-[2-[(2-isopropylaminoethyl)amino]ethyl]piperazine, which was used without further purification in the final step:

Thiophosgene (2.8 g = 1.9 ml) was added dropwise at 5°C to a mixture of the crude product mentioned above (11 g) and triethylamine (2.8 g) in trichloroethane. The resulting mixture was stirred at room temperature for 15 min. and was then refluxed for 2 hours. After evaporation in vacuo the product was purified by extraction with 1N methanesulfonic acid followed by liberation of the base with 9N sodium hydroxide as described in Example 8 . The resulting oil was purified by column chromatography using silica gel and acetone-toluene -isopropylamine - ammonium hydroxide (60:40:2:2) as a mobile phase. There was obtained 1.1 g of a base, which was transformed to the dimaleate salt. This salt was recrystallized twice from acetone/ether to give 0.4 g of **36**, dimaleate, mp: 156-159°C.

CHN calculated: 57.32%; 5.78%; 7.64%.
CHN found: 57.33%; 5.76%; 7.17%.

EXAMPLE 10

Trans-1-[2-[4-[5-chloro-3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]piperazin-1-yl]-ethyl]-3-(2-hydroxyethyl)-2-imidazolidinone, dimaleate, (Compd. **37**)

Compound **4** (4,4 g as the base) was added to a suspension of potassium tert-butoxide (1.7 g) in dry toluene (200 ml). The mixture was kept at room temperature for 1 hour with stirring, whereupon ethylbromoacetate (2.5 g) was added. The mixture was stirred for 1 hour at room temperature and was then poured into ice. The organic phase was separated, washed with water, dried and evaporated in vacuo. The resulting oil was dissolved in dry tetrahydrofurane (150 ml) whereupon lithium borohydride (1 g) was added. The mixture was stirred for 1 hour at room temperature and was then evaporated in vacuo. The residue was treated with ether and 1N methanesulfonic acid. The acid phase was basified with 9N sodium hydroxide and extracted with methylene chloride. After drying and evaporation in vacuo there was obtained 2.5 g of **37**, which was converted to the maleate salt (in acetone). The salt was recrystallized from ethanol-methanol to give 1.4 pure **37**, mp: 168-170°C.

CHN calculated: 56.78%; 5.61%; 7.79%.
CHN found: 56.45%; 5.62%; 7.83%

EXAMPLE 11

Trans-1-[2-[4-[5-chloro-3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]piperazin-1-yl]-ethyl]-2-pyrrolidinthione, dimaleate, (Compd. **38**)

A mixture of Compound **15** (15 g) and Lawesson's reagent (5 g) in hexamethyl-phosphonic triamide (HMPA, 50 ml) was heated at 100°C in a N_2-atmosphere for 1.5 hours. The reaction mixture was poured into water, treated with 9N sodium hydroxide (25 ml) and extracted with ether. The etherphase was extracted with 1N methane sulphonic acid, whereupon the base was liberated with 9N sodium hydroxide and again extracted with ether. The organic phase was evaporated to give 3.5 g of an oil, which was transformed to the dimaleate salt. This salt was recrystallized from ethanol (200 ml) to give **38** , mp: 192-193°C.

CHN calculated: 57.42%; 5.41%; 6.09%.
CHN found: 57.50%; 5.49%; 6.17%.

PHARMACOLOGICAL TESTS

The compounds of the invention were tested in well recognized and reliable methods. The tests were as follows, and the results are given in the following Table I. The well-known 5-HT_2 antagonists, ritanserin tefludazine and irindalone, and the corresponding analogues of Compounds **1**, **9** and **4**, respectively, substituted in the 6-position of the indane ring system in stead of the 5–position, i.e. compounds Nos. **39** , **40** and **41**, were included in the tests for comparison purposes. The results of the tests are shown in the Table **1**.

INHIBITION OF ^{3}H-KETANSERIN BINDING TO 5-HT_2 RECEPTORS IN RAT CORTEX *IN VITRO*

By this method the inhibition by drugs of the binding of ^{3}H-Ketanserin (0,5 nM) to Serotonin S_2 (5-HT_2) receptors in membranes from rat is determined *in vitro*. Method in Hyttel, *Pharmacology & Toxicology*, ***61***, 126-129, 1987.

Procedure

Male Wistar (Mol:Wist) rats (125-250 g) are sacrificed and cortical tissue is dissected and weighed. The tissue is homogenized (Ultra Turrax,* 10 sec.) in 10 ml of ice-cold 50 mM tris buffer pH 7.7 (at 25°C). The centrifuge glassware used in this step has been rinsed by sonication for 10 min. in ethanol. The homogenate is centrifuged twice at 20,000 g for 10 min. at 4°C with rehomogenization of the pellet in 10 ml ice-cold buffer. The final pellet is homogenized in 500 vol (w/v) ice-cold buffer.

Incubation tubes kept on ice in triplicate receive 100 µl of drug solution in water (or water for total binding) and 2000 µl of tissue suspension (final tissue content corresponds to 4 mg original tissue). The binding experiment is initiated by addition of 100 µl of ^{3}H-Ketanserin (final concentration 0.5 nM) and by placing the tubes in a 37°C water bath. After incubation for 30 min. the samples are filtered under vacuum (0-50 mBar) through Whatman*GF/F filters (25 mm). The tubes are rinsed with 5 ml ice-cold buffer which are then poured on the filters. Thereafter, the filters are

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washed with 2 x 5 ml of buffer. The filters are placed in counting vials and 4 ml of appropriate scintillation fluid (e.g. Picofluor TM15) are added. After shaking for 1 h and storage 2 hrs in the dark the content of radioactivity is determined by liquid scintillation counting. Specific binding is obtained by subtracting the nonspecific binding in the presence of 1 µM mianserin.

For determination of the inhibiiton of binding five concentrations of drugs covering 3 decades are used.

The measured cpm are plotted against drug concentration on semilogarithmic paper and the best fitting S-shaped curve is drawn. The IC_{50} value is determined as the concentration at which the binding is 50% of the total binding in control samples minus the nonspecific binding in the presence of 1 µM mianserin.

^{3}H-Ketanserin = [ethylene-^{3}H]-ketanserin hydrochloride from New England Nuclear, specific activity 60-80 Ci/mmol).

INHIBITION OF ^{3}H-SPIPERONE BINDING TO DOPAMINE D-2 RECEPTORS IN RAT CORPUS STRIATUM *IN VITRO*

By this method the inhibition by drugs of the binding of ^{3}H-spiperone (0.5 nM) to dopamine D-2 receptors in membranes from rat corpus striatum is determined *in vitro*. Method and results in Hyttel & Larsen, *J. Neurochem*, ***44***, 1615-1622, 1985).

Procedure

Male Wistar (Mol:Wistar) rats (125-250 g) are sacrificed and striatal tissue is dissected and weighed. The tissue is homogenized (Ultra Turrax*, 10 sec.) in 10 ml of ice-cold 50 mM K-phosphate buffer pH 7.4 (at 25°C). The homogenate is centrifuged twice at 20,000 g for 10 min. at 4°C wtih rehomogenization of the pellet in 10 ml ice-cold buffer. The final pellet is homogenized in 1300 vol (w/v) ice-cold buffer.

Incubation tubes kept on ice in triplicate receive 100 µl of drug solution in water (or

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water for total binding) and 4000 µl of tissue suspension (final tissue content corresponds to 3.08 mg original tissue). The binding experimental is initiated by addition of 100 µl of ^{3}H-spiperone (final concentration 0.5 nM) and by placing the tubes in a 37°C water bath. After incubation for 10 min. the samples are filtered under vacuum (0-50 mBar) through Whatman*GF/F filters (25 mm). The tubes are rinsed with 5 ml ice-cold buffer which are then poured on the filters. Thereafter, the filters are washed with 2 x 5 ml of buffer. The filters are placed in counting vials and 4 ml of appropriate scintillation fluid (e.g. Picofluor TM15) are added. After shaking for 1 h and storage 2 hrs in the dark the content of radioactivity is determined by liquid scintillation counting. Specific binding is obtained by subtracting the nonspecific binding in the presence of 10 µM of 6,7-ADTN.

For determination of the inhibition of binding five concentrations of drugs covering 3 decades are used.

The measured cpm are plotted against drug concentration on semilogarithmic paper and the best fitting S-shaped curve is drawn. The IC_{50} value is determined as the concentration at which the binding is 50% of the total binding in control samples minus the nonspecific binding in the presence of 10 µM of 6,7-ADTN.

^{3}H-Spiperone = [phenyl-4-^{3}H]-spiperone from Amersham International plc. England, specific activity 15-25 Ci/mmol.

INHIBITION OF ^{3}H-PRAZOSIN BINDING TO α_1 ADRENOCEPTORS IN RAT BRAIN *IN VITRO*

By this method the inhibition of the binding of ^{3}H-Prazosin (0.25 nM) to α_1 adrenoceptors in membranes from rat brain is determined *in vitro*. Method and results in Hyttel & Larsen, *J. Neurochem*, ***44***, 1615-1622, 1985; Skarsfeldt & Hyttel, *Eur. J. Pharmacol.* ***125***, 323-340, 1986.

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Procedure

Male Wistar (Mol:Wist) rats (125-200 g) are sacrificed and brain tissue is dissected and weighed. The tissue is homogenized (Ultra Turrax*, 10 sec.) in 10 ml of ice-cold 50 nM Tris buffer pH 7.7 (at 25°C). The homogenate is centrifuged twice at 20,000 g for 10 min. at 4°C with rehomogenization of the pellet in 10 ml ice-cold buffer. The final pellet is homogenized in 400 vol (w/v) ice-cold buffer.

Incubation tubes kept on ice in triplicate receive 100 µl of drug solution in water (or water for total binding) and 4000µl of tissue suspension (final tissue content corresponds to 10 mg original tissue). The binding experiment is initiated by addition of 100 µl of ^{3}H-Prazosin (final concentration 0.25 nM) and by placing the tubes in a 25°C water bath. After incubation for 20 min. the samples are filtered under vacuum (0-50 mBar) through Whatman*GF/F filters (25 mm). The tubes are rinsed with 5 ml ice-cold buffer which then are poured on the filters. Thereafter, the filters are washed with 5 ml of buffer. The filters are placed in counting vials and 4 ml of appropriate scintillation fluid (e.g. PicofluorTM15) are added. After shaking for 1 h and storage 2 hrs in the dark the content of radioactivity is determined by liquid scintillation counting. Specific binding is obtained by subtracting the nonspecific binding in the presence of 1 µM of Prazosin.

For determination of the inhibition of binding five concentrations of drugs covering 3 decades are used.

The measured cpm are plotted against drug concentration on semilogarithmic paper and the best fitting S-shaped curve is drawn. The IC_{50} value is determined as the concentration at which the binding is 50% of the total binding in control samples minus the nonspecific binding in the presence of 1 µM of Prazosin.

^{3}H-Prazosin = [furoyl-5-^{3}H]-Prazosin from New England Nuclear, specific activity approximately 20 Ci/mmol.

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TABLE 1

Receptor Binding ; IC_{50}(nM)

Compound No.	5-HT_2 ^{3}H-Ket	DA D-2 ^{3}H-Spi	α_1 ^{3}H-Praz
1	2.9	760	320
(+)-1	2.0	290	330
2	21	1100	150
(+)-2	12	330	72
(-)-2	500	22000	1100
3	25	2200	230
(-)-3	11	370	210
(+)-3	230	6300	2500
4	2.9	360	200
5	8.9	1300	380
6	56	2600	1000
7	7.9	2800	240
8	12	1000	270
9	3.7	370	220
10	11	2500	840
(-)-10	15	730	390
(+)-10	3300	28000	
11	3.9	280	260
(+)-11	75	1300	340
(-)-11	1.1	200	210
12	3.0	450	120
13	3.7	510	350
14	23	550	140
15	10	500	370
16	10	160	73
17	44	300	310
18	2.8	190	600
19	2.6	260	240

TABLE 1 (cont'd)

Receptor Binding ; IC_{50}(nM)

Compound No.	5-HT_2 ^{3}H-Ket	DA D-2 ^{3}H-Spi	α_1 ^{3}H-Praz
20	9.9	750	510
21	3.5	920	670
22	3.5	1100	240
23	4.0	720	250
24	6.4	240	270
25	5.6	110	66
26	11	450	60
27	15	280	180
28	26	490	970
29	1.5	230	110
30	1.7	220	110
(+)-30	0.95	140	43
(–)-30	42	2900	
31	1.5	67	52
32	1.5	93	170
(+)-32	21	490	350
(–)-32	0.75	33	67
(+)-33	1.1	280	41
(–)-33	57	4600	
(+)-34	120	1700	
(–)-34	1.3	94	62
35	4.8	150	120
36	3.6	260	69
37	6.1	320	710
38	5.3	290	260

TABLE 1 (cont'd)

Receptor Binding ; IC_{50}(nM)

Compound No.	5-HT_2 ^{3}H-Ket	DA D-2 ^{3}H-Spi	α_1 ^{3}H-Praz
Tefludazine	4.6	10	17
Irindalon	3.4	400	16
Ritanserin	0.40	12	47
39		21	8.3
40	0.71	43	12
41		17	3.1

QUIPAZINE INHIBITION

Quipazine is a 5-HT_2 agonist, which induces head twitches in rats. The test is an *in vivo* test for 5-HT_2-antagonistic effect testing the ability to inhibit head twitches. The method and test results for some reference substances are published by Arnt et al. (*Drug Development Research, **16***, 59-70, 1989).

In this test the compounds showed effects with ED_{50} values down to 0.01 mg/kg..

LIGHT/DARK DISCRIMATION TEST IN MICE

This test was carried out in accordance with the method described in Costall et al. Br. J. Pharmacol. 90 275P (1987).

The test was conducted using a two compartment activity box in which the actions of anxiolytic compounds to reduce aversion against a brightly-lit environment may be readily detected. The box is designed as an open-top experimental box (45*27*27cm) one third of which was partitioned from the rest, painted black and illuminated with red light. The remainder of the box was painted white and brightly illuminated (1000 W). The floor of each area was lined into squares. Behavioural changes were determined for each area from video recordings for periods of 40 min.

Data obtained from dose groups of 5 animals (male albino BKW mice, 25 - 30 g) were analysed using single factor analysis of variance, and Dunnett´s t-test. Test compounds were given intraperitoneally 45 min before testing. In this test model Compounds **(+)-30**, **(-)-32** and **(+)-33** showed significant anxiolytic activity ($p<0.05$) in doses from 0.01 to 1 mg/kg.

LIGHT/DARK DISCRIMINATION TEST IN RATS.

The test was carried out similarly to the test in mice described above, however modified in accodance with F.C.Colpaert et al., Psychopharmacology (1985) 86: 45-54. The test used Wistar WU rats. In this test model Compounds **(-)-32** and **(+)-33** showed significant anxiolytic activity ($p<0.05$) in doses from 0.1 to 1 mg/kg.

All the compounds except the weak or inactive stereoisomers of Compd. **2**, **3** , **10**, **11**, **30** , **32**, **33**, and **34** show high affinity to 5-HT_2 receptors and have much lower affinity to D-2 receptors and α_1 adrenoceptors than the prior art compounds included in the tests for comparison purposes. Tefludazine, a 6-substituted 1-piperazino-3-phenylindan derivative representative for US Patent 4,443,448, shows high affinity to all three receptor types whereas irindalone, a 1-piperazino-3-(fluorophenyl)indan derivative representative for US patent 4,684,650, in addition to a high affinity to 5-HT_2 receptors has a significant affinity to α_1 adrenoceptors. The dramatic effect of the change from 6- to 5-substitution is illustrated by comparison of the receptor profiles of the 6-substituted derivatives **39**, **40** and **41** with their otherwise identical 5-substituted analouges **1**, **9** and **4**.

FORMULATION EXAMPLES

The pharmaceutical formulations of the invention may be prepared by conventional methods in the art. For example: Tablets may be prepared by mixing the active ingredient with ordinary adjuvants and/or diluents and subsequently compressing the mixture in a conventional tabletting machine. Examples of adjuvants or diluents comprise: corn starch, potato starch, talcum, magnesium stearate, gelatine, lactose, gums, and the like. Any other adjuvants or additives usually used for such purposes

such as colourings, flavourings, preservatives etc. may be used provided that they are compatible with the active ingredients.

Solutions for injections may be prepared by dissolving the active ingredient and possible additives in a part of the solvent for injection, preferably sterile water, adjusting the solution to desired volume, sterilization of the solution and filling in suitable ampules or vials. Any suitable additive conventionally used in the art may be added, such as tonicity agents, preservatives, antioxidants, etc.

Typical examples of recipes for the formulation of the invention are as follows:

1) Tablets containing 5 milligrams of Compound 4c calculated as the free base:

Comp. **(+)-33**	5 mg
Lactose	18 mg
Potato starch	27 mg
Sucrose	58 mg
Sorbitol	3 mg
Talcum	5 mg
Gelatine	2 mg
Povidone	1 mg
Magnesium stearate	0.5 mg

2) Tablets containing 50 milligrams of Compound 4b calculated as the free base:

Comp. **(+)-30**	50 mg
Lactose	16 mg
Potato starch	45 mg
Sucrose	106 mg
Sorbitol	6 mg
Talcum	9 mg
Gelatine	4 mg
Povidone	3 mg
Magnesium stearate	0.6 mg

3) Syrup containing per milliliter:

Comp. **(–)-32**	10 mg
Sorbitol	500 mg
Tragacanth	7 mg
Glycerol	50 mg
Methyl-paraben	1 mg
Propyl-paraben	0.1 mg
Ethanol	0.005 ml
Water	ad 1 ml

4) Solution for injection containing per milliliter:

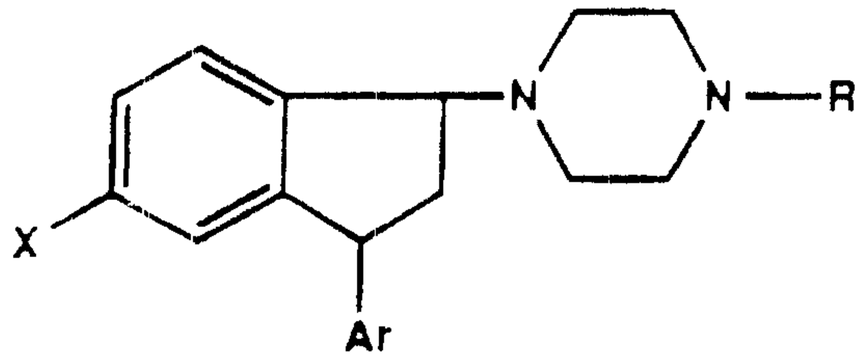
Comp. **(–)-34**	50 mg
Acetic acid	17.9 mg
Sterile water	ad 1 ml

5) Solution for injection containing per milliliter:

Comp. **(–)-11**	10 mg
Sorbitol	42.9 mg
Acetic acid	0.63 mg
Sodium hydroxide	22 mg
Sterile water	ad 1 ml

CLAIMS

1. A 5-substituted trans-1-piperazinolindan compound having the formula:



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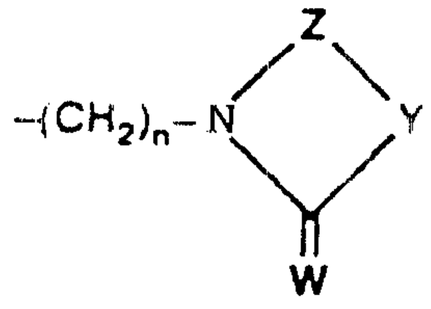
wherein X is chlorine, fluorine, methyl, or trifluoromethyl;

R is a substituent having the formula:



wherein:

n is 2;

Y is O, CH_2, or N-R^1, R^1 being hydrogen, isopropyl, or phenyl;

W is O or S;

Z is $-CH_2CH_2-$, $-CH_2-CH_2-CH_2-$, or 1.2-phenylene; and

Ar is 4-fluorophenyl,

or a pharmaceutically acceptable acid addition salt thereof.

2. A 5-substituted trans-1-piparazinoindan compound according to claim 1, wherein in the definition of substituent R

n is 2;

Y is N-R^1, R^1 being defined as in claim 1;

W is O or S; and

Z is $-CH_2CH_2-$ or $-CH_2-CH_2-CH_2$.

3. A substituted trans-1-piperazinoindan compound according to claim 1, wherein X is chlorine or fluorine.

4. A 5-substituted trans-1-piperazinoindan compound selected from the group consisting of:
(-)-Trans-1-[2-[4-[5-chloro-3-(4-fluorophenyl)-2,3-dihydro-1H-inden-1-yl]piperazin-1-yl]-ethyl]-3-isopropyl-2-imidazolidinone;
(+)-Trans-1-[2-[4-[5-fluoro-3-(4-fluorophenyl)-2,3-dihydro-1H-inden-1-yl]piperazin-1-yl]ethyl]-tetrahydro-2(1H)-pyrimidinethione;
(-)-Trans-1-[2-[4-[5-chloro-3-(4-fluorophenyl)-2,3-dihydro-1H-inden-1-yl]piperazin-1-yl]-ethyl]-tetrahydro-2(1H)-pyrimidinethione;
(+)-Trans-1-[2-[4-[5-fluoro-3-(4-fluorophenyl)-2,3-dihydro-1H-inden-1-yl]piperazin-1-yl]ethyl]-tetrahydro-2(1H)-pyrimidinone; and
(-)-Trans-1-[2-[4-[5-chloro-3-(4-fluorophenyl)-2,3-dihydro-1H-inden-1-yl]piperazine-1-yl]ethyl]-tetrahydro-2(1H)-pyrimidinone;
or an acid addition salt thereof.

5. A 5-substituted trans-1-piperazinoindan derivative selected from the group consisting of:
(-)-Trans-1-[2-[4-[5-chloro-3-(4-fluorophenyl)-2,3-dihydro-1H-inden-1-yl]piperazin-1-yl]-ethyl]-3-isopropyl-2-imidazolidinone, dimaleate;
(+)-Trans-1-[2-[4-[5-fluoro-3-(4-fluorophenyl)-2,3-dihydro-1H-inden-1-yl]piperazin-1-yl]ethyl]-tetrahydro-2(1H)-pyrimidinethione, dihydrochloride;

(-)-Trans-1-[2-[4-[5-chloro-3-(4-fluorophenyl)-2,3-dihydro-1H-inden-1-yl]piperazin-1-yl]-ethyl]-tetrahydro-2(1H)-pyrimidinethione, dihydrochloride;

(+)-Trans-1-[2-[4-[5-fluoro-3-(4-fluorophenyl)-2,3-dihydro-1H-inden-1-yl]piperazin-1-yl]ethyl]-tetrahydro-2(1H)-pyrimidinone, dimaleate; and

(-)-Trans-1-[2-[4-[5-chloro-3-(4-fluorophenyl)-2,3-dihydro-1H-inden-1-yl]piperazin-1-yl]ethyl]-tetrahydro-2(1H)-pyrimidinone, dimaleate.

6. A pharmaceutical preparation comprising at least one compound according to any one of claims 1 to 5 together with a pharmaceutically acceptable carrier or diluent.

7. Use of a compound as defined in any one of claims 1 to 5 for the manufacture of a medicament for the treatment of anxiety, depression, sleeping disorders, negative symptoms of schizophrenia or migraine.

8. A prodrug for a compound according to claim 1, said prodrug being the reaction product with an acid or an activated acid, with formaldehyde alone or in the presence of an alcohol or an amine, or with an acyloxymethylene halide, said reaction product being of the formula (I) as defined in claim 1, wherein W is O, Y is a group $NR^{1'}$ wherein $R^{1'}$ designates a group -A-B where A is selected from CO, CS, or CH_2, and

if A is CO or CS, B is selected from the groups consisting of:

i) hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl or cycloalk(en)ylalk(en)yl, optionally substituted with one or two hydroxy groups, or phenyl optionally

substituted with one or more substitutents selected from the group consisting of halogen, trifluoromethyl, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 alkylthio, acyloxy, or cyano; or

ii) QB^1, wherein Q is O or S and B^1 is selected from the substituents defined for B under i) above except hydrogen; and

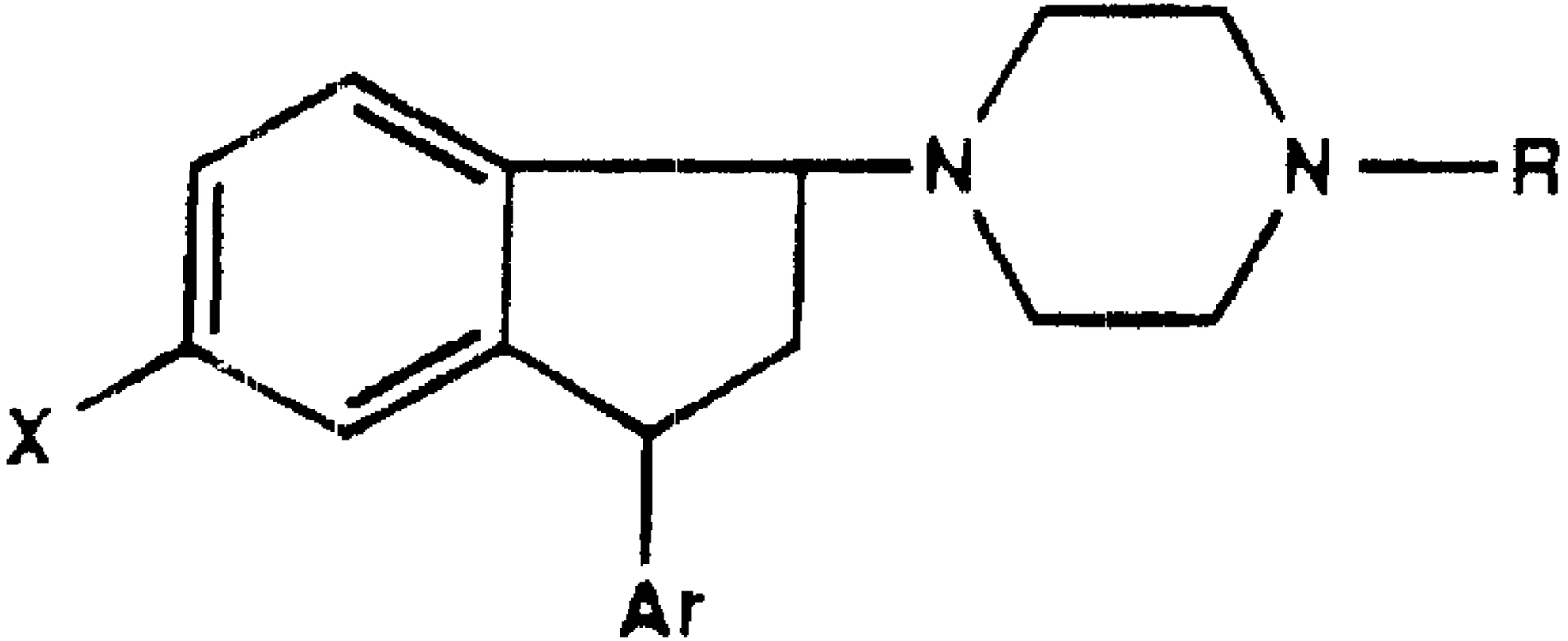
iii) NB^2B^3, wherein B^2 and B^3 independently are selected from the substituents defined for B^1 under ii) above, or B^2 and B^3 are combined to form a four to eight membered heterocyclic ring containing from one to three nitrogen atoms and from zero to three oxygen or sulfur atoms; or

if A is CH_2, B is selected from the groups consisting of:

iv) a group QB^1 as defined in ii);

v) a group NB^2B^3 as defined in iii); or

vi) a group $OC(O)B^4$, wherein B^4 is as defined for B^1.



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