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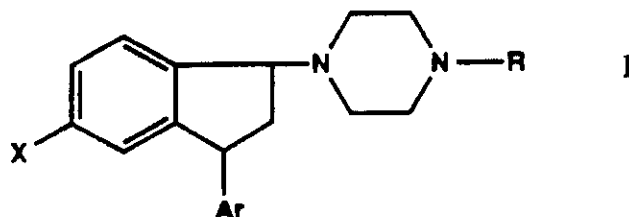
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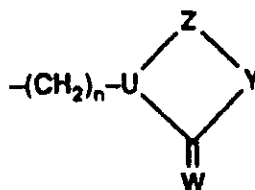
Description

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-HT₂) receptors in the central nervous system, to medicaments comprising such derivatives as active ingredients, to the use of such derivatives for the manufacture of a medicament for the treatment of diseases in the central nervous system and to methods for the preparation of such compounds.

The novel piperazinyindan derivatives of the invention are trans-isomers represented by the following Formula 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



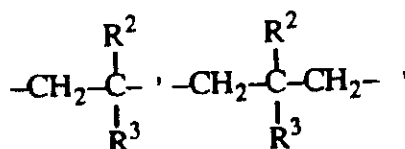
wherein n is an integer from 1 to 6;

U is CH or N;

Y is CH₂, O, S or N-R¹, R¹ 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 -(CH₂)₄-.



wherein R² and R³ are hydrogen or lower alkyl, -CH=CH-CH₂-, -CH=CH-, 1,2-phenylene, optionally substituted with halogen or trifluoromethyl, or if U is nitrogen and Y is NR¹ Z may also be 1,2-C₆H₄CH₂- (to form a quinazolidinone or -thione ring system) or 1,2-C₆H₄CO- (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, with the proviso that when Ar is optionally substituted phenyl, R may not be hydrogen or C₁-C₄ alkyl or C₂-C₄ alkenyl optionally substituted with hydroxy.

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.

5 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 NR¹ wherein R¹ 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
10 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
15 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
20 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.

25 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-HT₂ 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
30 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 *in vivo*, nevertheless many of the compounds still had significant activity for both dopamine D-2 receptors and in particular α_1 adrenoceptors.

The 5-HT₂ 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
35 the sleep quality. Furthermore, selective, centrally acting 5-HT₂ 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-HT₂ 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
40 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-HT₂ 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-HT₂ antagonists without side effects.

45 It has now surprisingly been found that the 5-substituted 1-piperazinoindan derivatives of Formula I, have high affinity for 5-HT₂ 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-HT₂ antagonism. Because of the very low affinity for α_1 adrenoceptors the 5-substituted compounds have, in contrast to the 6-substituted derivatives, substantially
50 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-HT₂ 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
55 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-HT₂ 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 NR¹, R¹ 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 CH₂, 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) QB¹, wherein Q is O or S and B¹ is selected from the substituents defined for B under i) above except hydrogen; and
- iii) NB²B³, wherein B² and B³ independently are selected from the substituents defined for B¹ under ii) above, or B² and B³ 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 CH₂, B is selected from the groups consisting of:

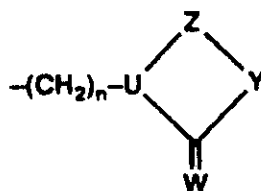
- iv) a group QB¹ as defined in ii);
- v) a group NB²B³ as defined in iii); or
- vi) a group OC(O)B⁴ wherein B⁴ is as defined for B¹.

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 depot formulation in an appropriate 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-HT₂ receptors and very low receptor affinity to D-2 receptors and α₁ adrenoreceptors and consequently they are very selective with respect to the 5-HT₂ receptor. Accordingly, they are useful in the treatment of various 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 -CH₂-CH₂- or -CH₂-CH₂-CH₂-; and

Y is a group NR¹ wherein R¹ 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-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-fluor-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-chlor-3-(4-fluorophenyl)-2,3-dihydro-1H-inden-1-yl]piperazin-1-yl]ethyl]-tetrahydro-2(1H)-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.

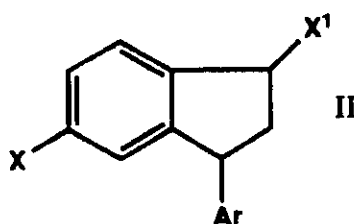
Suitable pharmaceutical preparations may be prepared by methods well known in the art. Conveniently, the compounds of the invention are administered in unit dosage form containing said compound in an amount of about 0.05 - 100 mg, preferably about 1 - 50 mg.

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

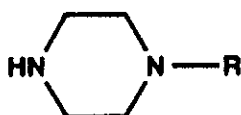
In a further aspect the present invention relates to the use of a compound having the general Formula I as defined above for the manufacture of a medicament for the treatment of a disease in the central nervous system, preferably anxiety, depression, sleeping disorders, negative symptoms of schizophrenia, 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:

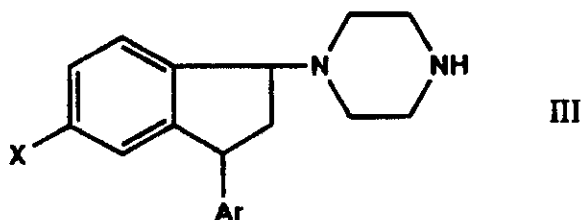


with a piperazine derivative of formula:



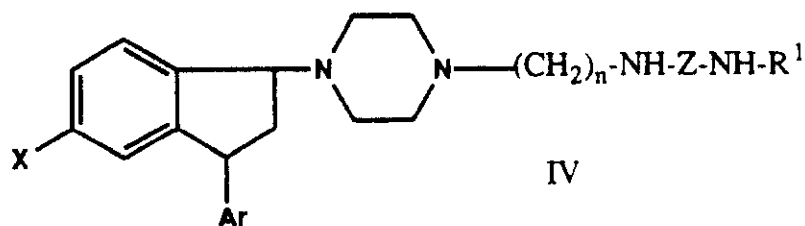
in which formulas X, Ar and R are as defined above, and X' is halogen or -OSO₂R⁴ wherein R⁴ is alkyl such as CH₃ or aryl such as p-toluyyl;

b) treating a compound of the following Formula III:

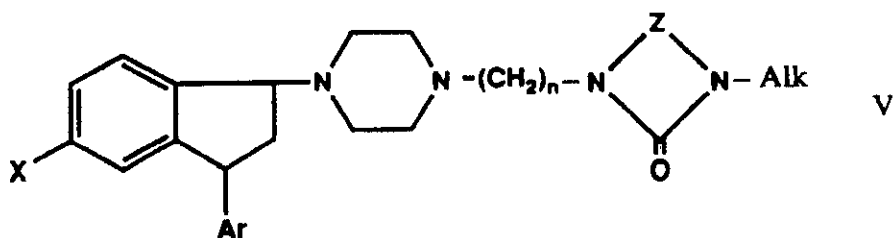


wherein X and Ar are as defined above, with a compound of the formula X'-R wherein R and X' are as defined above except that R cannot be hydrogen;

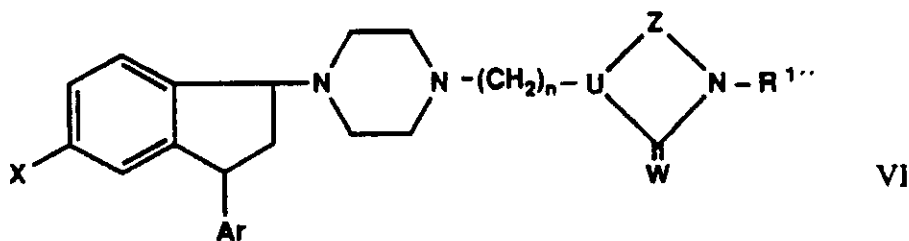
- c) treating a compound of Formula III with a compound $R'-CHO$, wherein R' is such a group that $R'-CH_2-$ is as defined above for R , in the presence of a reducing agent;
 d) treating a compound of the following Formula IV:



- 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:

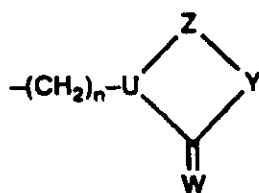


- wherein X , Ar , n , and Z are as defined above and Alk is an alkali metal such as sodium or potassium, with a compound of formula R^5-X^1 wherein R^5 is a lower alkyl group and X^1 is as defined above;
 f) reducing a compound with the following Formula VI:



- 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 and 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 methylisobutylketone 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.

5 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 NaCNBH₃ 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.

10 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, R⁵-X¹, 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.

20 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.

25 The preparation of the compounds of Formula II from the corresponding 2,3-dihydro-inden-1-ones may be carried out analogously 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.

35 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.

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

3-(4-fluorophenyl)-5-(trifluoromethyl)-2,3-dihydro-1H-inden-1-one, mp 105-106 °C

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

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

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

45 5-chloro-3-(3-fluorophenyl)-2,3-dihydro-1H-inden-1-one, mp 118-120 °C.

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

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

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

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

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

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

55 3-(4-fluorophenyl)-5-methyl-2,3-dihydro-1H-inden-1-ol, mp 100-102 °C.

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

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

5-chloro-3-(3-fluorophenyl)-2,3-dihydro-1H-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-1*H*-inden (8.5 g) and 1-[(2-piperazin-1-yl)ethyl]-2-imidazolidinone (20 g) in methylisobutylketone (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 (MgSO₄) 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 methanol (400 ml) and water (400 ml) to give 17 g; mp 221-223 °C. Optical rotation of the base: $[\alpha]_D = -3.2^\circ$ (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: $[\alpha]_D = +3.7^\circ$ (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. $[\alpha] = +5.5^\circ$ (c 0.5, CH₃OH).

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

EXAMPLE 3Optical resolution of Trans-4-[5-fluoro-3-(4-fluorophenyl)-2,3-dihydro-1H-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 converted 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; $[\alpha]_D^{25} = +15.4^\circ$ (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; $[\alpha]_D^{25} = +27.1^\circ$ (c 0.5, CH₃OH). 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; $[\alpha]_D^{25} = -27.1^\circ$ (c 0.5, CH₃OH).

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

(+)-3, dihydrochloride; mp 224-227 °C; $[\alpha]_D^{25} = +13.5^\circ$ (c 0.5, H₂O) and

(-)-3, dihydrochloride; mp 224-227 °C; $[\alpha]_D^{25} = -14.1^\circ$ (c 0.5, H₂O).

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-1H-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-1H-inden-1-yl]-1-piperazineethanol, dimaleate; mp 172-174 °C. Compd. 5.

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

EXAMPLE 4Trans-1-[5-chloro-3-(4-fluorophenyl)-2,3-dihydro-1H-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-1H-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 (MgSO₄) and evaporated to give 140 g of crude 1,5-dichloro-3-(4-fluorophenyl)-2,3-dihydro-1H-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 (MgSO₄) 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; $[\alpha]_D = +30.6^\circ$ (c 0.5, CH₃OH).

(-)-10, maleate salt; mp: 194-196 °C; $[\alpha]_D = -30.2^\circ$ (c 0.5, CH₃OH).

EXAMPLE 6

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 (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, $[\alpha]_D = +17.0^\circ$ (c 0.5, CH₃OH), and

(-)-11, dimaleate, mp 175 °C, $[\alpha]_D = -17.5^\circ$ (c 0.5, CH₃OH).

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-1H-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-1H-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-1H-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-1H-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.

5 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.

10 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.

15 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.

20 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

25

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)

30

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).

35 A mixture of 42 g of the hydrochloride salt and ethylenediamine (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 (MgSO₄) 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 ethylenediamine derivative was dissolved in methylene chloride, whereupon carbon disulfide (15 ml) was added. The mixture was
40 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
45 29, dimaleate, mp 172-174 °C.

CHN calculated:	57.04%;	5.25%;	8.32%.
CHN found:	57.30%;	5.43%;	8.17%.

50

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 ethylenediamine with 1,3-propylenediamine. The enantiomers of this compound were prepared in a similar way starting from (+)-2 and (-)-2, respectively:

55 (+)-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, $[\alpha]_D^{25} = +26.7^\circ$ (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, $[\alpha]_D^{25} = -25.6^\circ$ (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-1*H*-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, $[\alpha]_D = +6.6^\circ$ (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, $[\alpha]_D = -6.6^\circ$ (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, $[\alpha]_D = +16.0^\circ$ (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, $[\alpha]_D = -15.0^\circ$ (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, $[\alpha]_D = +16.8^\circ$ (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, $[\alpha]_D = -17.2^\circ$ (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 tetrahydrofuran (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 tetrahydrofuran (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-1H-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 tetrahydrofuran (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-1H-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 hexamethylphosphonic triamide (HMPA, 50 ml) was heated at 100 °C in a N₂-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-HT₂ 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 ³H-KETANSERIN BINDING TO 5-HT₂ RECEPTORS IN RAT CORTEX *IN VITRO*

By this method the inhibition by drugs of the binding of ³H-Ketanserin (0.5 nM) to Serotonin S₂ (5-HT₂) 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 ³H-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 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 TM 15) 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 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 IC₅₀ 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.

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

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

By this method the inhibition by drugs of the binding of ³H-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 with 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 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 ³H-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 TM 15) 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 IC₅₀ 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.

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

55 INHIBITION OF ³H-PRAZOSIN BINDING TO α_1 ADRENOCEPTORS IN RAT BRAIN *IN VITRO*

By this method the inhibition of the binding of ³H-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.

Procedure

5 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 mM 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.

10 Incubation tubes kept on ice in triplicate receive 100 µl of drug solution in water (or water for total binding) and 4000 µl of tissue suspension (final tissue content corresponds to 10 mg original tissue). The binding experiment is initiated by addition of 100 µl of ³H-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
15 counting vials and 4 ml of appropriate scintillation fluid (e.g. Picofluor™ 15) 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
20 S-shaped curve is drawn. The IC₅₀ 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.

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

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TABLE 1
Receptor Binding ; IC₅₀(nM)

Compound No.	5-HT ₂ 3H-Ket	DA D-2 3H-Spi	α_1 3H-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 ; IC₅₀(nM)

Compound No.	5-HT ₂ 3H-Ket	DA D-2 3H-Spi	α_1 3H-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 ; IC₅₀(nM)

Compound No.	5-HT ₂ 3H-Ket	DA D-2 3H-Spi	α ₁ 3H-Praz
Tefludazine	4.6	10	17
Irindalon	3.4	400	16
Ritanserlin	0.40	12	47
39		21	8.3
40	0.71	43	12
41		17	3.1

QUIPAZINE INHIBITION

Quipazine is a 5-HT₂ agonist, which induces head twitches in rats. The test is an *in vivo* test for 5-HT₂-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 ED₅₀ values down to 0.01 mg/kg..

LIGHT/DARK DISCRIMINATION 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 accordance 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-HT₂ receptors and have much lower affinity to D-2 receptors and α₁ 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-HT₂ receptors has a significant affinity to α₁ 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 analogues 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 tableting 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

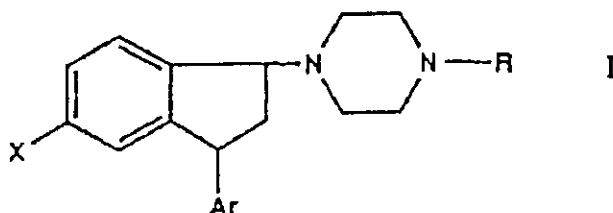
5) Solution for injection containing per milliliter:

Comp. (-)-11	110 mg
Sorbitol	42.9 mg
Acetic acid	0.63 mg
Sodium hydroxide	22 mg
Sterile water	ad 1 ml

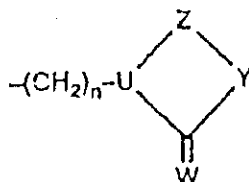
Claims

Claims for the following Contracting States : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE

1. A 5-Substituted trans-1-piperazinoindan derivative having the general formula:



wherein X is halogen, trifluoromethyl, C₁-C₄ alkyl, C₁-C₄ alkylthio, C₁-C₄ alkyloxy, hydroxy, C₁-C₄ alkylsulphonyl, C₁-C₄ alkyl- or di(C₁-C₄)alkylamino, trifluoromethylthio or a cyano group;
R is hydrogen, C₁-C₄ alkyl, C₂-C₄ alkenyl, cycloalkyl, or cycloalkyl(C₁-C₄)alkyl, optionally substituted with one or two hydroxy groups, or R is a substituent



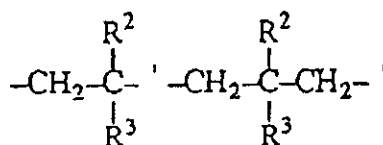
wherein n is an integer from 1 to 6;

U is CH or N;

Y is CH₂, O, S or N-R¹, R¹ being hydrogen or a cycloalkyl, cycloalkylmethyl, C₁-C₄ alkyl or C₂-C₄ alkenyl group, optionally substituted with one or two hydroxy groups, or a phenyl group optionally substituted with halogen, trifluoromethyl or C₁-C₄ alkyl;

W is O or S;

Z is -(CH₂)₄-,

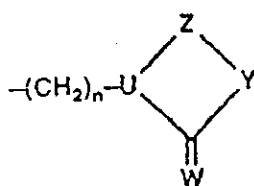


wherein R² and R³ are hydrogen or C₁-C₄ alkyl, -CH=CH-CH₂-, -CH=CH-, 1,2-phenylene, optionally substituted with halogen or trifluoromethyl, or if U is nitrogen and Y is NR¹ Z may also be 1,2-C₆H₄CH₂- (to form a quinazolidinone or -thione ring system) or 1,2-C₆H₄CO- (to form a quinazolidin-dion or thioxoquinazolidinon ring system); and

Ar is a phenyl ring optionally substituted with halogen, trifluoromethyl or C₁-C₄ alkyl, or Ar is a thiophene or furane ring optionally substituted with C₁-C₄ alkyl; any hydroxy group present being optionally esterified with an aliphatic carboxylic acid having from two to twentyfour carbon atoms inclusive;
 5 with the proviso that when Ar is optionally substituted phenyl, R may not be hydrogen or C₁-C₄ alkyl or C₂-C₄ alkenyl optionally substituted with hydroxy;
 or a pharmaceutically acceptable acid addition salt thereof.

2. A 5-Substituted trans-1-piperazinoindan derivative according to Claim 1, **characterized in** that Ar is a phenyl group optionally substituted with halogen or methyl, preferably 4-fluorophenyl, and/or that X is Cl or F.

3. A 5-Substituted trans-1-piperazinoindan derivative according to Claim 1 of 2, **characterized in** that R is a group of the formula:



wherein n is 2, U is N; W is O or S; Z is -CH₂-CH₂- or -CH₂-CH₂-CH₂-; and Y is a group NR¹ wherein R¹ is hydrogen or C₁-C₄ alkyl.

4. A 5-Substituted trans-1-piperazinoindan derivative according to Claim 1, **characterized in** that it is selected from the group 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;

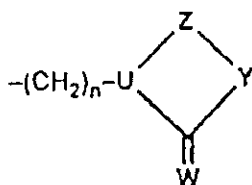
(-)-Trans-1-[2-[4-[5-chloro-3-(4-fluorophenyl)-2,3-dihydro-1H-inden-1-yl]piperazin-1-yl]ethyl]-tetrahydro-2(1H)-pyrimidinethione, dihydrochloride;

(+)-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;

and acid addition salts thereof.

5. A prodrug for a compound of Claim 1 in which R is a group of the formula:



wherein W is O and Y is NR¹, R¹ being hydrogen, and n, Z and U are as defined in Claim 1, **characterized in** that it is 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 is represented by a formula similar to the general Formula I defined in Claim 1 wherein W is O, Y however being a group NR¹¹ wherein R¹¹ designates a group -A-B where A is selected from CO, CS, or CH₂, 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, C₁-C₄ alkyl, C₁-C₄ alkoxy, C₁-C₄ alkylthio, acyloxy, or cyano; or

ii) QB¹, wherein Q is O or S and B¹ is selected from the substituents defined for B under i) above except hydrogen; and

iii) NB²B³, wherein B² and B³ independently are selected from the substituents defined for B¹ under ii) above, or B² and B³ 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 CH₂, B is selected from the groups consisting of:

iv) a group QB¹ as defined in ii);

v) a group NB²B³ as defined in iii); or

vi) a group OC(O)B⁴, wherein B⁴ is as defined for B¹.

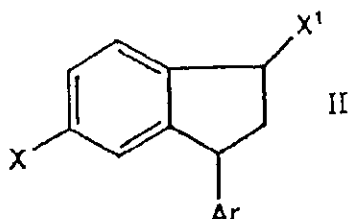
6. Pharmaceutical preparation, **characterized in** that it comprises at least one compound according to Claim 1 or 5 together with a pharmaceutically acceptable carrier or diluent.

7. Pharmaceutical preparation according to Claim 6, **characterized in** that it comprises a prodrug according to Claim 5 in a pharmaceutically acceptable oil.

8. Use of a 5-Substituted trans-1-piperazinoindan derivative having the general Formula I as defined in Claim 1, except that the proviso in Claim 1 does not apply, or a pharmaceutically acceptable acid addition salt thereof for the manufacture of a medicament for the treatment of anxiety, depression, sleeping disorders, negative symptoms of schizophrenia or migraine.

9. Method for the preparation of a 5-Substituted trans-1-piperazinoindan derivative according to Claim 1 **characterised in** that it comprises:

a) treating a compound of the following Formula II:

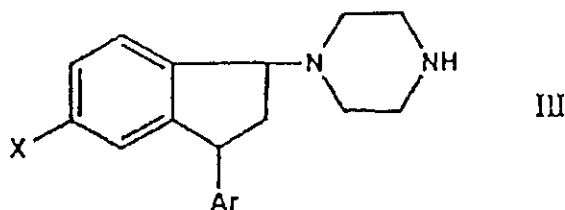


with a piperazine derivative of formula:



in which formulas X, Ar and R are as defined above, and X¹ is halogen or -OSO₂R⁴ wherein R⁴ is alkyl such as CH₃ or aryl such as p-toluy1;

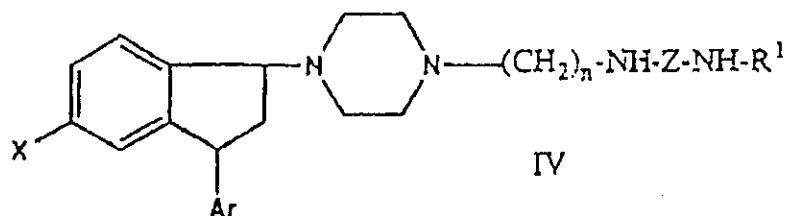
b) treating a compound of the following Formula III:



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;

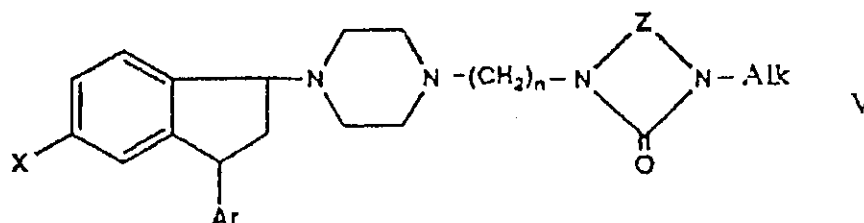
c) treating a compound of Formula III with a compound R^1-CHO , wherein R^1 is such a group that R^1-CH_2- is as defined above for R, in the presence of a reducing agent eg. $NaCNBH_3$ or hydrogen in the presence of a suitable catalyst such as Pt or Pd;

d) treating a compound of the following Formula IV:



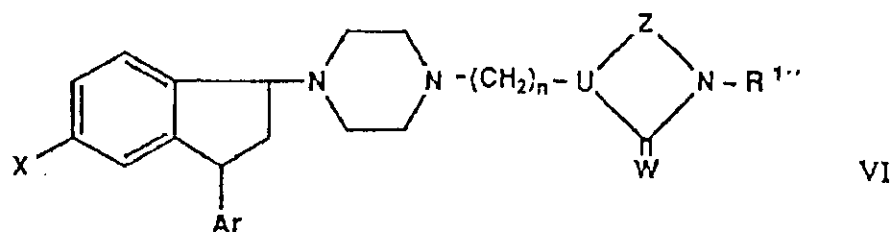
wherein X, Ar, R^1 , Z and n are as defined above, with CS_2 , thiophosgene, urea or phosgene;

e) treating a compound of the following Formula V:



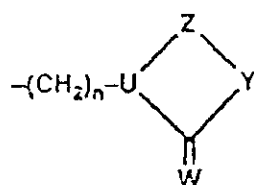
wherein X, Ar, n, and Z are as defined above and Alk is an alkali metal such as sodium or potassium, with a compound of formula R^5-X^1 wherein R^5 is a C_1-C_4 alkyl group and X^1 is as defined above;

f) reducing a compound with the following Formula VI:



wherein X, Ar, n, U, Z and W are as defined above and $R^{1'}$ is a cycloalkyl or C_1-C_4 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 C_1-C_4 alkyl or a cycloalkyl group containing one or more hydroxy groups;

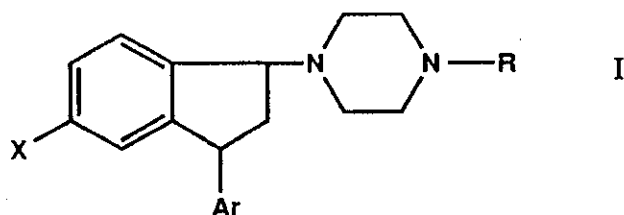
g) reacting a compound of Formula I wherein R is a group of the formula:



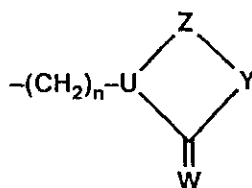
wherein n, U, Z and Y are as defined above and W is O, with P_2S_5 or Lawessons reagent to obtain the corresponding compound wherein W is S; and if desired subsequently transferring the derivative obtained in a corresponding acid addition salt.

5 Claims for the following Contracting States : ES, GR

1. A method for the preparation of a 5-Substituted trans-1-piperazinoindan derivative having the general formula :



wherein X is halogen, trifluoromethyl, C_1 - C_4 alkyl, C_1 - C_4 alkylthio, C_1 - C_4 alkyloxy, hydroxy, C_1 - C_4 alkylsulphonyl, C_1 - C_4 alkyl- or di(C_1 - C_4 alkyl)amino, trifluoromethylthio or a cyano group; R is hydrogen, C_1 - C_4 alkyl, C_2 - C_4 alkenyl, cycloalkyl, or cycloalkyl(C_1 - C_4)alkyl, optionally substituted with one or two hydroxy groups, or R is a substituent



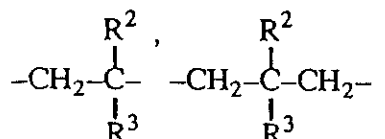
wherein n is an integer from 1 to 6;

U is CH or N;

Y is CH_2 , O, S or $N-R^1$, R^1 being hydrogen or a cycloalkyl, cycloalkylmethyl, C_1 - C_4 alkyl or C_2 - C_4 alkenyl group optionally substituted with one or two hydroxy groups or a phenyl group optionally substituted with halogen, trifluoromethyl or C_1 - C_4 alkyl;

W is O or S;

Z is $-(CH_2)_4-$,

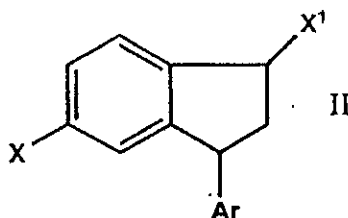


wherein R^2 and R^3 are hydrogen or C_1 - C_4 alkyl, $-CH=CH-CH_2-$, $-CH=CH-$, 1,2-phenylene, optionally substituted with halogen or trifluoromethyl, or if U is nitrogen and Y is NR^1 Z may also be 1,2- $C_6H_4CH_2-$ (to form a quinazolidinone or -thione ring system) or 1,2- C_6H_4CO- (to form a quinazolidin-dion or thioxoquinazolidinon ring system) and

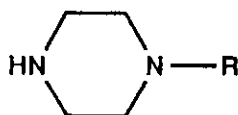
Ar is a phenyl ring optionally substituted with halogen, trifluoromethyl or C_1 - C_4 alkyl or Ar is a thiophene or furane ring optionally substituted with C_1 - C_4 alkyl; any hydroxy group present being optionally esterified with an aliphatic carboxylic acid having from two to twentyfour carbon atoms inclusive;

with the proviso that when Ar is optionally substituted phenyl, R may not be hydrogen or C₁-C₄ alkyl or C₂-C₄ alkenyl optionally substituted with hydroxy; or a pharmaceutically acceptable acid addition salt or prodrug thereof **characterized in that it** comprises:

a) treating a compound of the following Formula II:

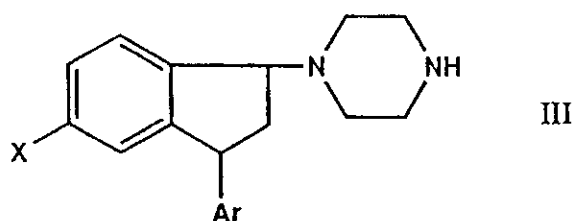


with a piperazine derivative of formula:



in which formulas X, Ar and R are as defined above, and X¹ is halogen or -OSO₂R⁴ wherein R⁴ is alkyl such as CH₃ or aryl such as p-toluyll;

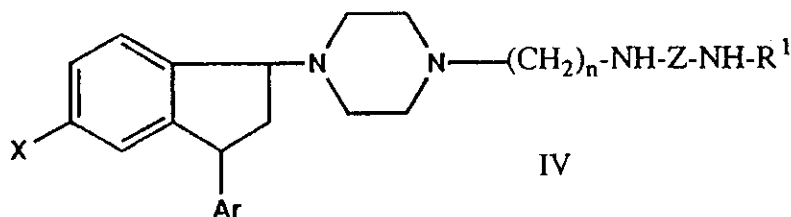
b) treating a compound of the following Formula III:



wherein X and Ar are as defined above, with a compound of the formula X¹-R wherein R and X¹ are as defined above except that R cannot be hydrogen;

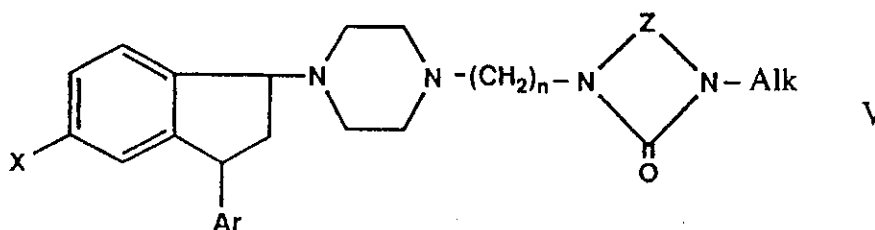
c) treating a compound of Formula III with a compound R'-CHO, wherein R' is such a group that R'-CH₂- is as defined above for R, in the presence of a reducing agent eg. NaCNBH₃ or hydrogen in the presence of a suitable catalyst such as Pt or Pd;

d) treating a compound of the following Formula IV:



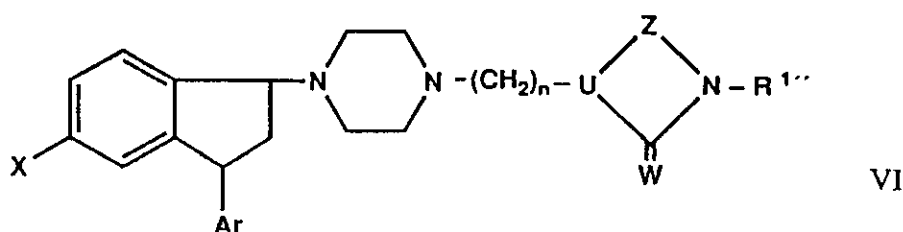
wherein X, Ar, R¹, Z and n are as defined above, with CS₂, thiophosgene, urea or phosgene;

e) treating a compound of the following Formula V:



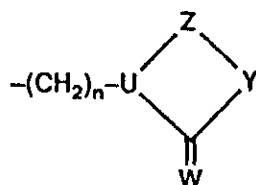
wherein X, Ar, n, and Z are as defined above and Alk is an alkali metal such as sodium or potassium, with a compound of formula R^5-X^1 wherein R^5 is a lower alkyl group and X^1 is as defined above;

f) reducing a compound with the following Formula VI:



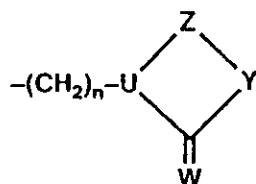
wherein X, Ar, n, U, Z and W are as defined above and $R^{1''}$ is a cycloalkyl or C_1 - C_4 alkyl group containing one or more ester, ketone or aldehyde groups with a suitable reducing agent to a corresponding compound wherein R^1 is a C_1 - C_4 alkyl or a cycloalkyl group containing one or more hydroxy 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 and W is O, with P_2S_5 or Lawessons reagent to obtain the corresponding compound wherein W is S; and if desired subsequently transferring the derivative obtained in a corresponding acid addition salt.

2. A method according to Claim 1, **characterized in** that Ar is a phenyl group optionally substituted with halogen or methyl, preferably 4-fluorophenyl, and/or that X is Cl or F.
3. A method according to Claim 1 or 2, **characterized in** that R is a group of the formula:



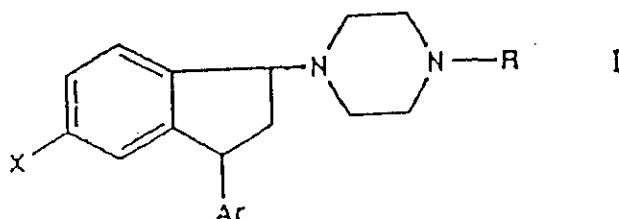
wherein n is 2, U is N; W is O or S; Z is $-\text{CH}_2-\text{CH}_2-$ or $-\text{CH}_2-\text{CH}_2-\text{CH}_2-$; and Y is a group NR^1 wherein R^1 is hydrogen or C_1-C_4 alkyl.

4. A method according to Claim 1, characterized in that the compound prepared is 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;
- and acid addition salts thereof.

Patentansprüche

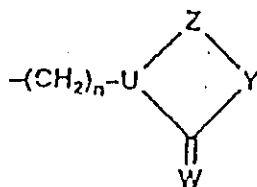
Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE

1. 5-substituiertes Derivat von trans-1-Piperazinoindan mit der allgemeinen Formel:



wobei X ein Halogen, die Trifluormethyl-Gruppe, eine C_1-C_4 -Alkyl-Gruppe, eine C_1-C_4 -Alkylthio-Gruppe, eine C_1-C_4 -Alkyloxy-Gruppe, die Hydroxy-Gruppe, eine C_1-C_4 -Alkylsulfonyl-Gruppe, eine C_1-C_4 -Alkyl- oder eine $\text{Di}(\text{C}_1-\text{C}_4\text{-Alkyl})$ -amino-Gruppe, die Trifluormethylthio-Gruppe oder die Cyanogruppe ist,

wobei R Wasserstoff, eine C_1-C_4 -Alkyl-Gruppe, eine C_2-C_4 -Alkenyl-Gruppe, eine Cycloalkyl-Gruppe oder eine Cycloalkyl(C_1-C_4)-Alkyl-Gruppe, gegebenenfalls substituiert mit einer oder mit zwei Hydroxy-Gruppen, ist, oder wobei R ein Substituent



ist,

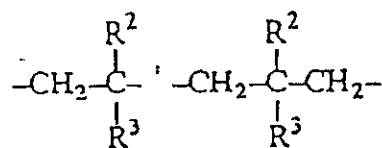
wobei n eine ganze Zahl von 1 - 6 ist;

wobei U CH oder N ist;

wobei Y CH_2 , Sauerstoff, Schwefel oder N-R^1 ist;

wobei R^1 Wasserstoff, eine Cycloalkyl-Gruppe, eine Cycloalkylmethyl-Gruppe, eine C_1-C_4 -Alkyl- oder eine C_2-C_4 -Alkenyl-Gruppe, gegebenenfalls substituiert mit einer oder mit zwei Hydroxy-Gruppen, oder eine Phenyl-Gruppe, gegebenenfalls substituiert mit einem Halogen, der Trifluormethyl-Gruppe oder einer C_1-C_4 -Alkyl-Gruppe, ist; wobei W Sauerstoff oder Schwefel ist;

wobei Z $-(\text{CH}_2)_4-$,



ist,

wobei R^2 und R^3 Wasserstoff, eine C_1 - C_4 -Alkyl-Gruppe, - $\text{CH}=\text{CH}-\text{CH}_2$ -, - $\text{CH}=\text{CH}$ -, 1,2-Phenylen, gegebenenfalls substituiert mit einem Halogen oder der Trifluormethyl-Gruppe, ist;

oder wobei Z auch 1,2- $\text{C}_6\text{H}_4\text{CH}_2$ - (zur Bildung eines Chinazolidinon- oder -thion-Ringsystems) oder 1,2- $\text{C}_6\text{H}_4\text{CO}$ - (zur Bildung eines Chinazolidindion- oder Thioxochinazolidinon-Ringsystems) sein kann, wenn U Stickstoff und Y NR^1 sind;

wobei Ar ein Phenylring, gegebenenfalls substituiert mit einem Halogen, der Trifluormethyl-Gruppe oder einer C_1 - C_4 -Alkyl-Gruppe, oder ein Thiophen- oder Furanring ist, gegebenenfalls substituiert mit einer C_1 - C_4 -Alkyl-Gruppe, ist;

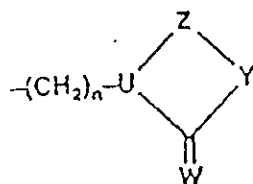
wobei eine eventuell vorhandene Hydroxy-Gruppe gegebenenfalls mit einer aliphatischen Carbonsäure mit 2 bis 24 Kohlenstoffatomen verestert ist;

unter der Voraussetzung, daß R kein Wasserstoff, keine C_1 - C_4 -Alkyl-Gruppe und keine C_2 - C_4 -Alkenyl-Gruppe, gegebenenfalls substituiert mit einer Hydroxy-Gruppe, sein kann, wenn Ar eine gegebenenfalls substituierte Phenyl-Gruppe ist;

und seine pharmazeutisch verträglichen Säure-Additionssalze.

2. Das 5-substituierte Derivat von trans-1-Piperazinoindan nach Anspruch 1, dadurch gekennzeichnet, daß Ar eine Phenyl-Gruppe, gegebenenfalls substituiert mit einem Halogen oder der Methyl-Gruppe, vorzugsweise die 4-Fluorphenyl-Gruppe, ist, und/oder daß X Cl oder F ist.

3. Das 5-substituierte Derivat von trans-1-Piperazinoindan nach Anspruch 1 oder 2, dadurch gekennzeichnet, daß R eine Gruppe der Formel



ist, wobei n 2 ist;

wobei U N ist;

wobei W Sauerstoff oder Schwefel ist;

wobei Z - CH_2-CH_2 - oder - $\text{CH}_2-\text{CH}_2-\text{CH}_2$ - ist; und

wobei Y eine Gruppe NR^1 ist, in der R^1 Wasserstoff oder eine C_1 - C_4 -Alkyl-Gruppe ist.

4. Das 5-substituierte Derivat von trans-1-Piperazinoindan nach Anspruch 1, dadurch gekennzeichnet, daß es ausgewählt ist aus:

(-)-trans-1-[2-[4-[5-Chlor-3-(4-fluorphenyl)-2,3-dihydro-1H-inden-1-yl]piperazin-1-yl]ethyl]-3-isopropyl-2-imidazolidinon-Dimaleat;

(+)-trans-1-[2-[4-[5-Fluor-3-(4-fluorphenyl)-2,3-dihydro-1H-inden-1-yl]piperazin-1-yl]ethyl]-tetrahydro-2-(1H)-pyrimidinthion-Dihydrochlorid;

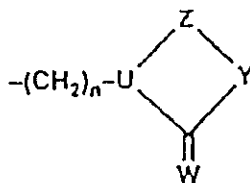
(-)-trans-1-[2-[4-[5-Chlor-3-(4-fluorphenyl)-2,3-dihydro-1H-inden-1-yl]piperazin-1-yl]ethyl]-tetrahydro-2-(1H)-pyrimidinthion-Dihydrochlorid;

(+)-trans-1-[2-[4-[5-Fluor-3-(4-fluorphenyl)-2,3-dihydro-1H-inden-1-yl]piperazin-1-yl]ethyl]-tetrahydro-2-(1H)-pyrimidinon-Dimaleat;

(-)-trans-1-[2-[4-[5-Chlor-3-(4-fluorphenyl)-2,3-dihydro-1H-inden-1-yl]piperazin-1-yl]ethyl]-tetrahydro-2-(1H)-pyrimidinon-Dimaleat;

und deren Säure-Additionssalze.

5. Vorstufe eines Wirkstoffs der Verbindung nach Anspruch 1, wobei R eine Gruppe der Formel



ist,
 in der W Sauerstoff ist, und in der Y NR¹ ist,
 wobei R¹ Wasserstoff ist, und wobei n, Z und U wie in Anspruch 1 definiert sind,
 dadurch gekennzeichnet, daß sie ein Reaktionsprodukt mit einer Säure oder mit einer aktivierten Säure,
 mit Formaldehyd allein oder in Gegenwart eines Alkohols oder Amins, oder mit einem Acyloxymethyl-
 lenhalogenid ist, wobei das Produkt dargestellt wird durch eine Formel ähnlich der allgemeinen Formel
 I gemäß Definition in Anspruch 1,

wobei W Sauerstoff ist, Y jedoch eine Gruppe NR^{1'} ist, in der R^{1'} eine Gruppe -A-B darstellt, in der A
 ausgewählt ist aus CO, CS und CH₂, und in der, wenn A CO oder CS ist, B aus den folgenden
 Gruppen ausgewählt ist:

i) aus Wasserstoff, einer Alkyl-, einer Alkenyl-, einer Cycloalkyl-, einer Cycloalkenyl-, einer Cycloalk-
 (en)ylalk(en)yl-Gruppe, gegebenenfalls substituiert mit einer oder mit zwei Hydroxy-Gruppen, oder
 aus einer Phenyl-Gruppe, gegebenenfalls substituiert mit einem oder mit mehreren Substituenten,
 ausgewählt aus einem Halogen, der Trifluormethyl-Gruppe, einer C₁ - C₄-Alkyl-Gruppe, einer C₁ -
 C₄-Alkoxy-Gruppe, einer C₁ - C₄-Alkylthio-Gruppe, einer Acyloxy- oder der Cyanogruppe;

ii) aus QB¹, wobei Q Sauerstoff oder Schwefel ist, und wobei B¹ ausgewählt ist aus den unter i) für B
 definierten Substituenten mit der Ausnahme von Wasserstoff; und

iii) aus NB²B³, wobei B² und B³ unabhängig voneinander aus den unter ii) für B¹ definierten
 Substituenten ausgewählt sind, oder wobei B² und B³ unter Bildung eines vier- bis achtegliedrigen
 heterocyclischen Rings, der ein bis drei Stickstoffatome und null bis drei Sauerstoff- oder Schwefel-
 atome enthält, miteinander verbunden sind;

oder in der, wenn A CH₂ ist, B aus den folgenden Gruppen ausgewählt ist:

iv) aus einer Gruppe QB¹, definiert wie unter ii);

v) aus einer Gruppe NB²B³, definiert wie unter iii); oder

vi) aus einer Gruppe OC(O)B⁴, in der B⁴ wie B¹ definiert ist.

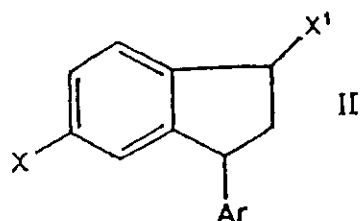
6. Pharmazeutische Zubereitung, dadurch gekennzeichnet, daß sie zumindest eine Verbindung nach
 einem der Ansprüche 1 oder 5 zusammen mit einem pharmazeutisch verträglichen Träger oder
 Verdünner enthält.

7. Die pharmazeutische Zubereitung nach Anspruch 6, dadurch gekennzeichnet, daß sie eine Vorstufe
 eines Wirkstoffes nach Anspruch 5 in einem pharmazeutisch verträglichen Öl enthält.

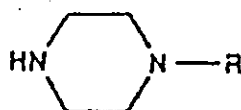
8. Verwendung des 5-substituierten Derivats von trans-1-Piperazinoindan mit der in Anspruch 1 definier-
 ten, allgemeinen Formel, außer daß die einschränkende Voraussetzung in Anspruch 1 nicht zutrifft, oder
 eines seiner pharmazeutisch verträglichen Säure-Additionssalze für die Herstellung eines Medikamen-
 tes zur Behandlung von Angstzuständen, Depressionen, Schlafstörungen, negativen Symptomen der
 Schizophrenie oder der Migräne.

9. Verfahren zur Herstellung des 5-substituierten Derivats von trans-1-Piperazinoindan nach Anspruch 1,
 das die folgenden Schritte umfaßt:

a) eine Verbindung der folgenden Formel II:



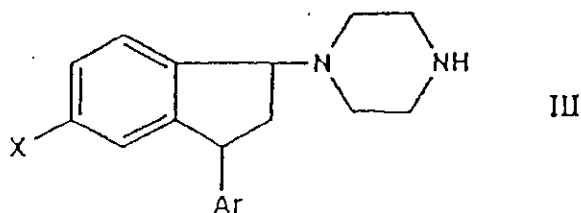
mit einem Piperazin-Derivat der Formel



umzusetzen,

wobei in den beiden Formeln X, Ar und R wie oben definiert sind, und wobei X¹ ein Halogen oder eine -OSO₂R⁴-Gruppe ist, in der R⁴ eine Alkyl-Gruppe wie die Methyl-Gruppe oder eine Aryl-Gruppe wie die p-ToluyI-Gruppe ist;

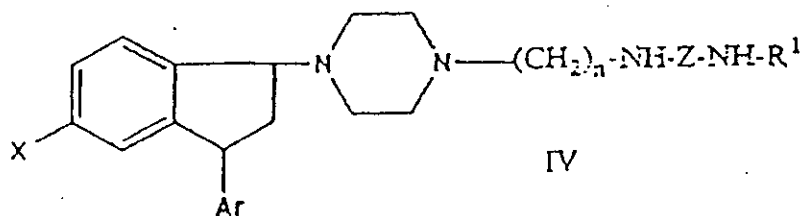
b) eine Verbindung der folgenden Formel III:



wobei X und Ar wie oben definiert sind, mit einer Verbindung der Formel X¹-R, in der R und X¹ wie oben definiert sind, außer daß R kein Wasserstoff sein kann, zu behandeln;

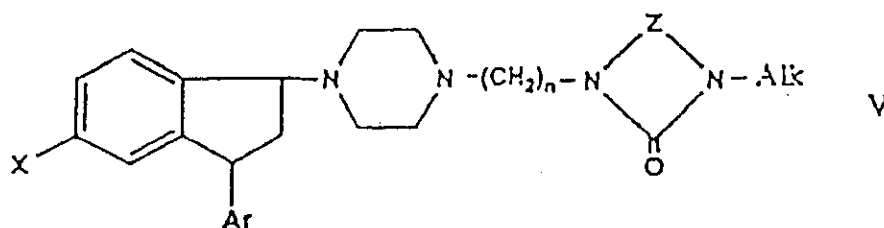
c) eine Verbindung der Formel III in Gegenwart eines Reduktionsmittels wie z.B. NaCNBH₃ oder Wasserstoff und eines geeigneten Katalysators wie Pt oder Pd mit einer Verbindung R'-CHO, in der R' eine Gruppe derart ist, daß R'-CH₂- wie oben für R definiert ist, zu behandeln;

d) eine Verbindung der folgenden Formel IV:



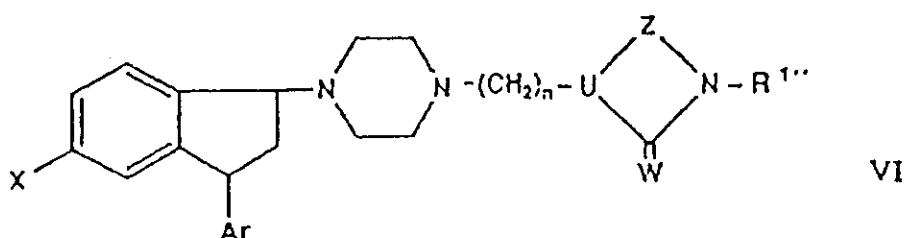
wobei X, Ar, R¹, Z und n wie oben definiert sind, mit CS₂, Thiophosgen, Harnstoff oder Phosgen zu behandeln;

e) eine Verbindung der folgenden Formel V:



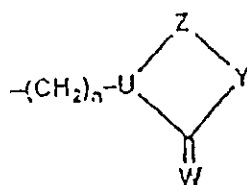
wobei X, Ar, n und Z wie oben definiert sind, und wobei Alk ein Alkalimetall wie Natrium oder Kalium ist, mit einer Verbindung der Formel R^5-X^1 , wobei R^5 eine $C_1 - C_4$ -Alkyl-Gruppe ist, und wobei X^1 wie oben definiert ist, zu behandeln;

f) eine Verbindung der folgenden Formel VI:



wobei X, Ar, n, U, Z und W wie oben definiert sind, und wobei $R^{1''}$ eine Cycloalkyl-Gruppe oder eine $C_1 - C_4$ -Alkyl-Gruppe ist, die eine oder mehrere Ester-, Keto- oder Aldehyd-Gruppen enthält, mit einem geeigneten Reduktionsmittel zu einer entsprechenden Verbindung zu reduzieren, in der R^1 eine $C_1 - C_4$ -Alkyl- oder eine Cycloalkyl-Gruppe ist, die eine oder mehrere Hydroxy-Gruppen enthält;

g) eine Verbindung der Formel I, in der R eine Gruppe der Formel:



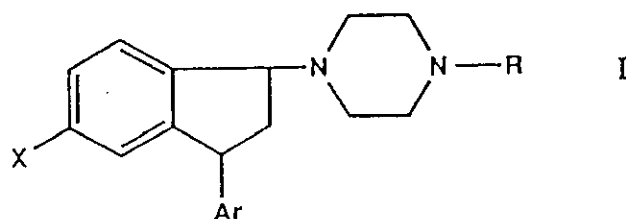
ist,

wobei n, U, Z und Y wie oben definiert sind, und wobei W Sauerstoff ist, unter Bildung der entsprechenden Verbindung, in der W Schwefel ist, mit P_2S_5 oder dem Lawessonschen Reagens umzusetzen;

und das erhaltene Derivat, sofern erwünscht, im Anschluß daran in ein entsprechendes Säure-Additionssalz zu überführen.

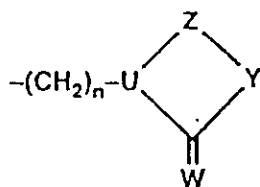
Patentansprüche für folgende Vertragsstaaten : ES, GR

1. Verfahren zur Herstellung eines 5-substituierten Derivats von trans-1-Piperazinoindan mit der allgemeinen Formel I:



wobei X ein Halogen, die Trifluormethyl-Gruppe, eine C₁ - C₄-Alkyl-Gruppe, eine C₁ - C₄-Alkylthio-Gruppe, eine C₁ - C₄-Alkyloxy-Gruppe, die Hydroxy-Gruppe, eine C₁ - C₄-Alkylsulfonyl-Gruppe, eine C₁ - C₄-Alkyl- oder eine Di(C₁ - C₄-Alkyl)amino-Gruppe, die Trifluormethylthio-Gruppe oder die Cyanogruppe ist,

wobei R Wasserstoff, eine C₁ - C₄-Alkyl-Gruppe, eine C₂ - C₄-Alkenyl-Gruppe, eine Cycloalkyl-Gruppe oder eine Cycloalkyl(C₁ - C₄)-Alkyl-Gruppe, gegebenenfalls substituiert mit einer oder mit zwei Hydroxy-Gruppen, ist, oder wobei R ein Substituent



ist,

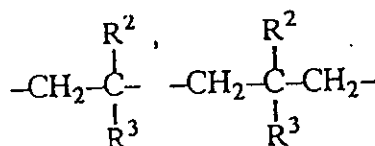
wobei n eine ganze Zahl von 1 - 6 ist;

wobei U CH oder N ist;

wobei Y CH₂, Sauerstoff, Schwefel oder N-R¹ ist;

wobei R¹ Wasserstoff, eine Cycloalkyl-Gruppe, eine Cycloalkylmethyl-Gruppe, eine C₁ - C₄-Alkyl- oder eine C₂ - C₄-Alkenyl-Gruppe, gegebenenfalls substituiert mit einer oder mit zwei Hydroxy-Gruppen, oder eine Phenyl-Gruppe, gegebenenfalls substituiert mit einem Halogen, der Trifluormethyl-Gruppe oder einer C₁ - C₄-Alkyl-Gruppe, ist; wobei W Sauerstoff oder Schwefel ist;

wobei Z -(CH₂)₄-,



ist,

wobei R² und R³ Wasserstoff, eine C₁ - C₄-Alkyl-Gruppe, -CH=CH-CH₂-, -CH=CH-, 1,2-Phylen, gegebenenfalls substituiert mit einem Halogen oder der Trifluormethyl-Gruppe, ist;

oder wobei Z auch 1,2-C₆H₄CH₂- (zur Bildung eines Chinazolidinon- oder -thion-Ringsystems) oder 1,2-C₆H₄CO- (zur Bildung eines Chinazolidindion- oder Thioxochinazolidinon-Ringsystems) sein kann, wenn U Stickstoff und Y NR¹ sind;

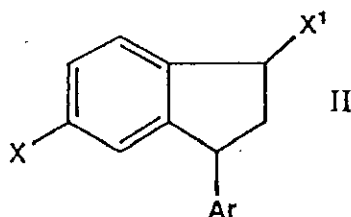
wobei Ar ein Phenylring, gegebenenfalls substituiert mit einem Halogen, der Trifluormethyl-Gruppe oder einer C₁ - C₄-Alkyl-Gruppe, oder ein Thiophen- oder Furanring, gegebenenfalls substituiert mit einer C₁ - C₄-Alkyl-Gruppe, ist;

wobei eine eventuell vorhandene Hydroxy-Gruppe gegebenenfalls mit einer aliphatischen Carbonsäure mit 2 bis 24 Kohlenstoffatomen verestert ist;

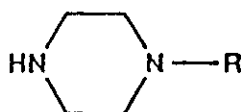
unter der Voraussetzung, daß R kein Wasserstoff, keine C₁ - C₄-Alkyl-Gruppe und keine C₂ - C₄-Alkenyl-Gruppe, gegebenenfalls substituiert mit einer Hydroxy-Gruppe, sein kann, wenn Ar eine gegebenenfalls substituierte Phenyl-Gruppe ist;

und eines seiner pharmazeutisch verträglichen Säure-Additionssalze oder einer Vorstufe seines Wirkstoffs, dadurch gekennzeichnet, daß das Verfahren die folgenden Schritte umfaßt:

a) eine Verbindung der folgenden Formel II:



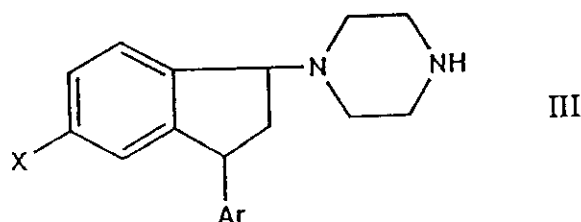
mit einem Piperazin-Derivat der Formel



umzusetzen,

wobei in den beiden Formeln X, Ar und R wie oben definiert sind, und wobei X¹ ein Halogen oder eine -OSO₂R⁴-Gruppe ist, in der R⁴ eine Alkyl-Gruppe wie die Methyl-Gruppe oder eine Aryl-Gruppe wie die p-Toluy-Gruppe ist;

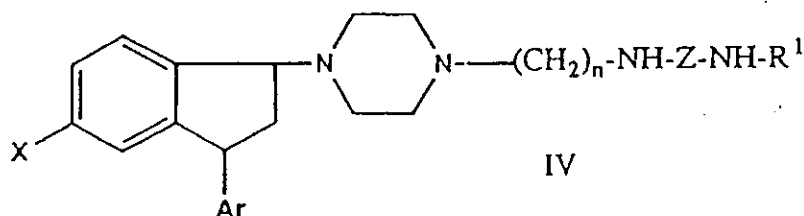
b) eine Verbindung der folgenden Formel III:



wobei X und Ar wie oben definiert sind, mit einer Verbindung der Formel X¹-R, in der R und X¹ wie oben definiert sind, außer daß R kein Wasserstoff sein kann, zu behandeln;

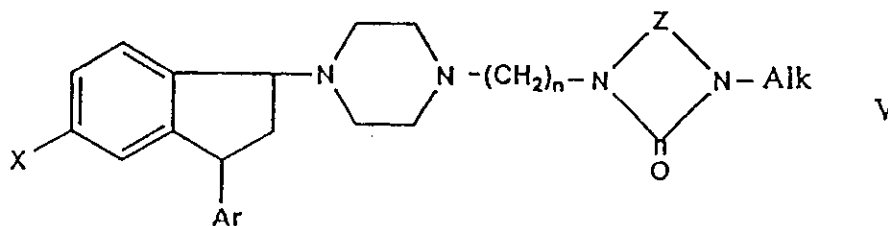
c) eine Verbindung der Formel III in Gegenwart eines Reduktionsmittels wie z.B. NaCNBH₃ oder Wasserstoff und eines geeigneten Katalysators wie Pt oder Pd mit einer Verbindung R'-CHO, in der R' eine Gruppe derart ist, daß R'-CH₂- wie oben für R definiert ist, zu behandeln;

d) eine Verbindung der folgenden Formel IV:



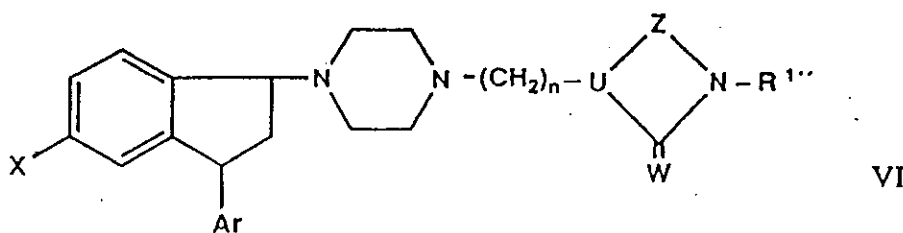
wobei X, Ar, R¹, Z und n wie oben definiert sind, mit CS₂, Thiophosgen, Harnstoff oder Phosgen zu behandeln;

e) eine Verbindung der folgenden Formel V:



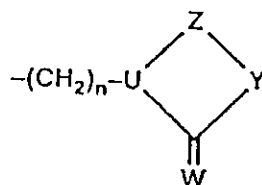
wobei X, Ar, n und Z wie oben definiert sind, und wobei Alk ein Alkalimetall wie Natrium oder Kalium ist, mit einer Verbindung der Formel R^5-X^1 , wobei R^5 eine niedere Alkyl-Gruppe ist, und wobei X^1 wie oben definiert ist, zu behandeln;

f) eine Verbindung der folgenden Formel VI:



wobei X, Ar, n, U, Z und W wie oben definiert sind, und wobei R''' eine Cycloalkyl-Gruppe oder eine $C_1 - C_4$ -Alkyl-Gruppe ist, die eine oder mehrere Ester-, Keto- oder Aldehyd-Gruppen enthält, mit einem geeigneten Reduktionsmittel zu einer entsprechenden Verbindung zu reduzieren, in der R^1 eine $C_1 - C_4$ -Alkyl- oder eine Cycloalkyl-Gruppe ist, die eine oder mehrere Hydroxy-Gruppen enthält;

g) eine Verbindung der Formel I, in der R eine Gruppe der Formel:



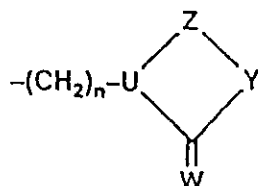
ist,

wobei n, U, Z und Y wie oben definiert sind, und wobei W Sauerstoff ist, unter Bildung der entsprechenden Verbindung, in der W Schwefel ist, mit P_2S_5 oder dem Lawessonschen Reagens umzusetzen;

und das erhaltene Derivat, sofern erwünscht, im Anschluß daran in ein entsprechendes Säure-Additionssalz zu überführen.

- Das Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß Ar eine Phenyl-Gruppe, gegebenenfalls substituiert mit einem Halogen oder der Methyl-Gruppe, vorzugsweise die 4-Fluorphenyl-Gruppe, ist, und/oder daß X Cl oder F ist.

3. Das Verfahren nach Anspruch 1 oder 2, dadurch gekennzeichnet, daß R eine Gruppe der Formel



ist, wobei n 2 ist; U N ist; W Sauerstoff oder Schwefel ist; Z -CH₂-CH₂- oder -CH₂-CH₂-CH₂- ist; und Y eine Gruppe NR¹ ist, in der R¹ Wasserstoff oder eine C₁ - C₄-Alkyl-Gruppe ist.

4. Das Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß die hergestellte Verbindung ausgewählt ist aus:

(-)-trans-1-[2-[4-[5-Chlor-3-(4-fluorphenyl)-2,3-dihydro-1H-inden-1-yl]piperazin-1-yl]ethyl]-3-isopropyl-2-imidazolidinon-Dimaleat;

(+)-trans-1-[2-[4-[5-Fluor-3-(4-fluorphenyl)-2,3-dihydro-1H-inden-1-yl]piperazin-1-yl]ethyl]-tetrahydro-2-(1H)-pyrimidinthion-Dihydrochlorid;

(-)-trans-1-[2-[4-[5-Chlor-3-(4-fluorphenyl)-2,3-dihydro-1H-inden-1-yl]piperazin-1-yl]ethyl]-tetrahydro-2-(1H)-pyrimidinthion-Dihydrochlorid;

(+)-trans-1-[2-[4-[5-Fluor-3-(4-fluorphenyl)-2,3-dihydro-1H-inden-1-yl]piperazin-1-yl]ethyl]-tetrahydro-2-(1H)-pyrimidinon-Dimaleat;

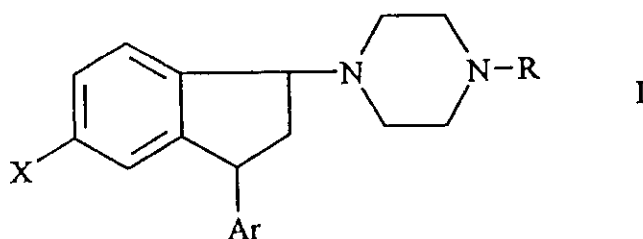
(-)-trans-1-[2-[4-[5-Chlor-3-(4-fluorphenyl)-2,3-dihydro-1H-inden-1-yl]piperazin-1-yl]ethyl]-tetrahydro-2-(1H)-pyrimidinon-Dimaleat;

und deren Säure-Additionssalze.

Revendications

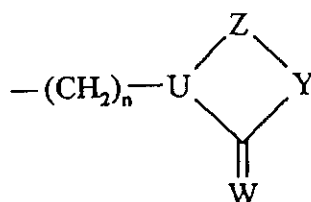
Revendications pour les Etats contractants suivants : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE

1. Dérivé de trans-1-pipérazinoindane substitué en 5, ayant la formule générale:



dans laquelle X est un halogène ou un groupe trifluorométhyle, alkyle en C₁-C₄, alkylthio en C₁-C₄, alkyloxy en C₁-C₄, hydroxy, alkylsulfonyl en C₁-C₄, (alkyl en C₁-C₄)- ou di(alkyl en C₁-C₄)amino, trifluorométhylthio ou cyano;

R est un hydrogène ou un groupe alkyle en C₁-C₄, alcényle en C₂-C₄, cycloalkyle ou cycloalkyl(alkyle en C₁-C₄), éventuellement substitué par un ou deux groupes hydroxy, ou R est un substituant

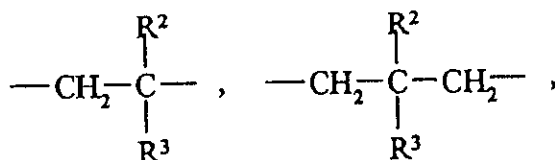


dans lequel n est un entier de 1 à 6;

U est CH ou N;

Y est CH₂, O, S ou N-R¹, R¹ étant un hydrogène ou un groupe cycloalkyle, cycloalkylméthyle, alkyle en C₁-C₄ ou alcényle en C₂-C₄, éventuellement substitué par un ou deux groupes hydroxy, ou un groupe phényle éventuellement substitué par halogène, trifluorométhyle ou alkyle en C₁-C₄;

W est O ou S; Z est -(CH₂)₄-;



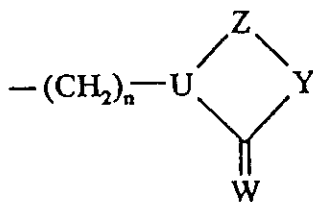
où R² et R³ sont un hydrogène ou un alkyle en C₁-C₄, -CH=CH-CH₂-, -CH=CH-, 1,2-phénylène, éventuellement substitué par halogène ou trifluorométhyle, ou, si U est un azote et Y est NR¹, Z peut aussi être un 1,2-C₆H₄CH₂- (pour former un système cyclique quinazolidinone ou -thione) ou 1,2-C₆H₄CO- (pour former un système cyclique quinazolidinedione ou thioxoquinazolidinedione); et

Ar est un noyau phényle éventuellement substitué par halogène, trifluorométhyle ou alkyle en C₁-C₄, ou Ar est un noyau thiophène ou furane éventuellement substitué par alkyle en C₁-C₄;

tout groupe hydroxy présent étant éventuellement estérifié avec un acide carboxylique aliphatique ayant 2 à 24 atomes de carbone inclus;

sous réserve que, lorsque Ar est un phényle éventuellement substitué, R ne puisse pas être un hydrogène ou un groupe alkyle en C₁-C₄ ou alcényle en C₂-C₄ éventuellement substitué par hydroxy; ou un de ses sels d'addition d'acides pharmaceutiquement acceptables.

2. Dérivé de trans-1-pipérazinoindane substitué en 5 selon la revendication 1, caractérisé en ce que Ar est un groupe phényle éventuellement substitué par halogène ou méthyle, de préférence un groupe 4-fluorophényle, et/ou en ce que X est Cl ou F.
3. Dérivé de trans-1-pipérazinoindane substitué en 5 selon la revendication 1 ou 2, caractérisé en ce que R est un groupe de formule

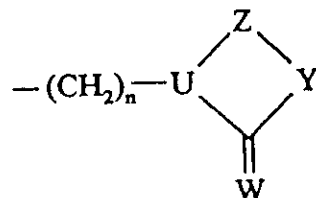


dans laquelle n est 2; U est N; W est O ou S; Z est -CH₂-CH₂- ou -CH₂-CH₂-CH₂- et Y est un groupe NR¹ dans lequel R¹ est un hydrogène ou un alkyle en C₁-C₄.

4. Dérivé de trans-1-pipérazinoindane substitué en 5 selon la revendication 1, caractérisé en ce qu'il est choisi dans le groupe constitué par:
le dimaléate de (-)-trans-1-[2-[4-[5-chloro-3-(4-fluorophényl)-2,3-dihydro-1H-indène-1-yl]pipérazine-1-yl]-éthyl]-3-isopropyl-2-imidazolidinone;
le dichlorhydrate de (+)-trans-1-[2-[4-[5-fluoro-3-(4-fluorophényl)-2,3-dihydro-1H-indène-1-yl]pipérazine-1-yl]éthyl]-tétrahydro-2(1H)-pyrimidinethione;
le dichlorhydrate de (-)-trans-1-[2-[4-[5-chloro-3-(4-fluorophényl)-2,3-dihydro-1H-indène-1-yl]pipérazine-1-yl]éthyl]-tétrahydro-2(1H)-pyrimidinethione;
le dimaléate de (+)-trans-1-[2-[4-[5-fluoro-3-(4-fluorophényl)-2,3-dihydro-1H-indène-1-yl]piperazine-1-yl]éthyl]-tétrahydro-2-(1H)-pyrimidione; et
le dimaléate de (-)-trans-1-[2-[4-[5-chloro-3-(4-fluorophényl)-2,3-dihydro-1H-indène-1-yl]pipérazine-1-yl]-éthyl]-tétrahydro-2-(1H)-pyrimidinone;

et leurs sels d'addition d'acides.

5. Promédicament pour un composé selon la revendication 1 dans lequel R est un groupe de formule:



dans laquelle W est O et Y est NR¹, R¹ étant un hydrogène, et n, Z et U sont tels que définis dans la revendication 1, caractérisé en ce qu'il est un produit de réaction avec un acide ou un acide activé, avec du formaldéhyde seul ou en présence d'un alcool ou d'une amine, ou avec un halogénure d'acyloxyméthylène, ce produit étant en conséquence représenté par une formule similaire à la formule générale I définie dans la revendication 1 dans laquelle W est O, Y étant toutefois un groupe NR¹ où R¹ représente un groupe -A-B dans lequel A est choisi parmi CO, CS et CH₂, et, quand A est CO ou CS, B est choisi parmi les groupes constitués par

i) l'hydrogène, les groupes alkyle, alcényle, cycloalkyle, cycloalcényle ou cycloalkyl(ou alcényl)-alkyle(ou alcényle), éventuellement substitués par un ou deux groupes hydroxy, ou phényle éventuellement substitué par un ou plusieurs substituants choisis dans le groupe constitué par les restes halogène, trifluorométhyle, alkyle en C₁-C₄, alcoxy en C₁-C₄, alkylthio en C₁-C₄, acyloxy ou cyano; ou

ii) QB¹, où Q est O ou S et B¹ est choisi parmi les substituants définis pour B sous i) à l'exception de l'hydrogène; et

iii) NB²B³, où B² et B³ sont choisis indépendamment parmi les substituants définis pour B¹ sous ii) ci-dessus, ou B² et B³ sont combinés pour former un noyau hétérocyclique de 4 à 8 chaînons contenant 1 à 3 atomes d'azote et 0 à 3 atomes d'oxygène ou de soufre; ou quand A est CH₂, B est choisi dans les groupes constitués par

iv) un groupe QB¹ tel que défini dans ii);

v) un groupe NB²B³ tel que défini dans iii); ou

vi) un groupe OC(O)B⁴ dans lequel B⁴ a la définition donnée pour B¹.

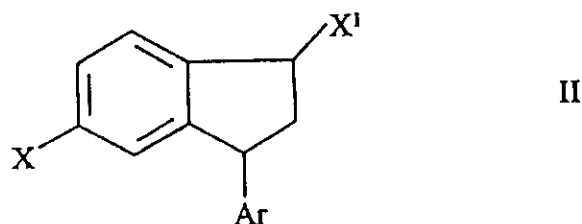
6. Préparation pharmaceutique, caractérisée en ce qu'elle comprend au moins un composé selon la revendication 1 ou 5 avec un support ou diluant pharmaceutiquement acceptable.

7. Préparation pharmaceutique selon la revendication 6, caractérisée en ce qu'elle comprend un promédicament selon la revendication 5 dans une huile pharmaceutiquement acceptable.

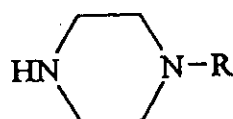
8. Utilisation d'un dérivé de trans-1-pipérazinoindane substitué en 5 ayant la formule générale I définie dans la revendication 1, si ce n'est que la réserve de la revendication 1 ne s'applique pas, ou un de ses sels d'addition d'acides pharmaceutiquement acceptables, pour la préparation d'un médicament pour le traitement de l'anxiété, de la dépression, des troubles du sommeil, des symptômes négatifs de la schizophrénie ou de la migraine.

9. Méthode de préparation d'un dérivé de trans-1-pipérazinoindane substitué en 5 selon la revendication 1, caractérisée en ce qu'elle comprend

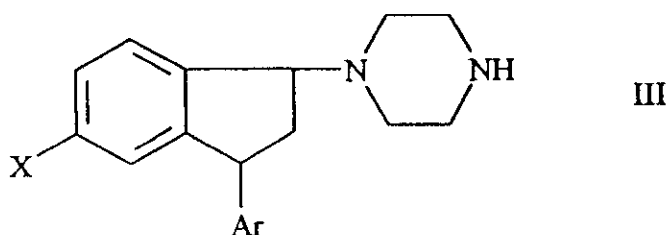
a) le traitement d'un composé de la formule II ci-dessous:



avec un dérivé de pipérazine de formule:

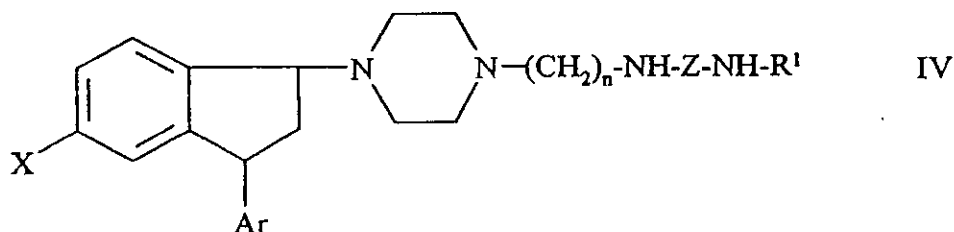


X, Ar et R ayant dans ces formules les significations données ci-dessus, et X' est un halogène ou -OSO₂R⁴ où R⁴ est un alkyle comme CH₃ ou un aryle comme le reste p-toluyle;
b) le traitement d'un composé ayant la formule III ci-dessous:



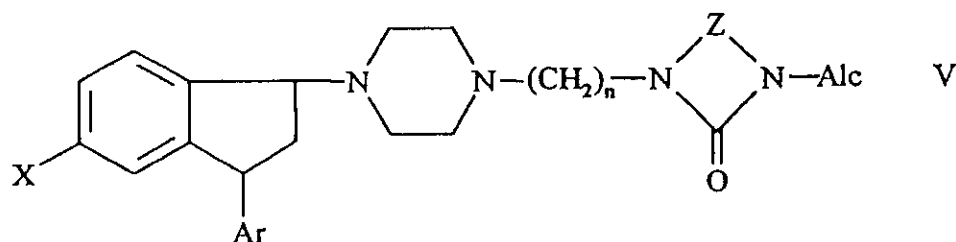
dans laquelle X et Ar sont tels que définis ci-dessus, avec un composé de formule X'-R dans lequel R et X' sont tels que définis ci-dessus, si ce n'est que R ne peut être l'hydrogène;

c) le traitement d'un composé de formule III avec un composé R'-CHO, où R' est un groupe tel que R'-CH₂- a la définition donnée ci-dessus pour R, en présence d'un agent réducteur, par exemple NaCNBH₃ ou l'hydrogène, en présence d'un catalyseur convenable, comme Pt ou Pd;
d) le traitement d'un composé ayant la formule IV ci-dessous:



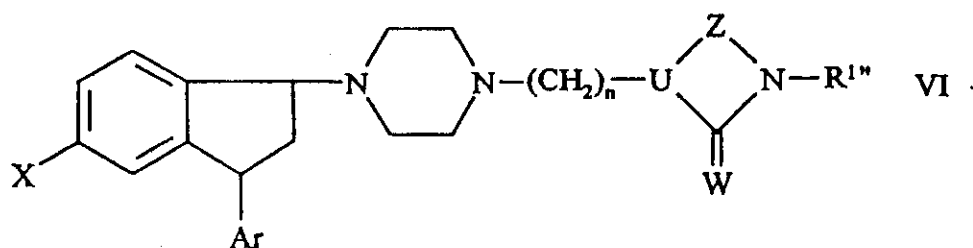
dans laquelle X, Ar, R', Z et n sont tels que définis ci-dessus, avec CS₂, le thiophosgène, l'urée ou le phosgène;

e) le traitement d'un composé ayant la formule V ci-dessous:



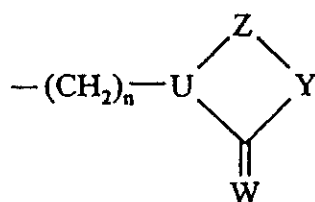
15 dans laquelle X, Ar, n et Z sont tels que définis ci-dessus, et Alc est un métal alcalin comme le sodium ou le potassium, avec un composé de formule R^5-X^1 dans laquelle R^5 est un groupe alkyle en C_1-C_4 et X^1 est tel que défini ci-dessus;

f) la réduction d'un composé ayant la formule VI ci-dessous:



30 dans laquelle X, Ar, n, U, Z et W sont tels que définis ci-dessus et $R^{1''}$ est un groupe cycloalkyle ou alkyle en C_1-C_4 contenant un ou plusieurs groupes ester, cétone ou aldéhyde, avec un agent réducteur convenable, pour former un composé correspondant dans lequel R^1 est un groupe alkyle en C_1-C_4 ou cycloalkyle contenant un ou plusieurs groupes hydroxy;

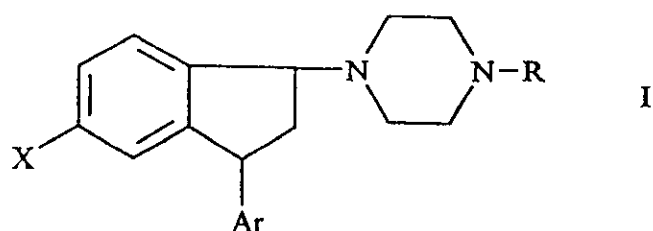
g) la réaction d'un composé de formule I dans lequel R est un groupe de formule:



45 dans laquelle n, U, Z et Y sont tels que définis ci-dessus et W est O, avec P_2S_5 ou le réactif de Lawesson pour donner le composé correspondant dans lequel W est S; et si désiré la transformation ultérieure du dérivé obtenu en un sel d'addition d'acide correspondant.

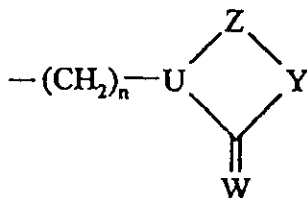
Revendications pour les Etats contractants suivants : ES, GR

- 50 1. Méthode de préparation d'un dérivé de trans-1-pipérazinoindane substitué en 5, ayant la formule générale:



dans laquelle X est un halogène ou un groupe trifluorométhyle, alkyle en C₁-C₄, alkylthio en C₁-C₄, alkyloxy en C₁-C₄, hydroxy, alkylsulfonyl en C₁-C₄, (alkyl en C₁-C₄)- ou di(alkyl en C₁-C₄)amino, trifluorométhylthio ou cyano;

R est un hydrogène ou un groupe alkyle en C₁-C₄, alcényle en C₂-C₄, cycloalkyle ou cycloalkyl(alkyle en C₁-C₄), éventuellement substitué par un ou deux groupes hydroxy, ou R est un substituant



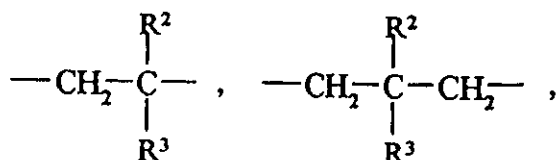
dans lequel n est un entier de 1 à 6;

U est CH ou N;

Y est CH₂, O, S ou N-R', R' étant un hydrogène ou un groupe cycloalkyle, cycloalkylméthyle, alkyle en C₁-C₄ ou alcényle en C₂-C₄, éventuellement substitué par un ou deux groupes hydroxy, ou un groupe phényle éventuellement substitué par halogène, trifluorométhyle ou alkyle en C₁-C₄;

W est O ou S;

Z est -(CH₂)₄-;



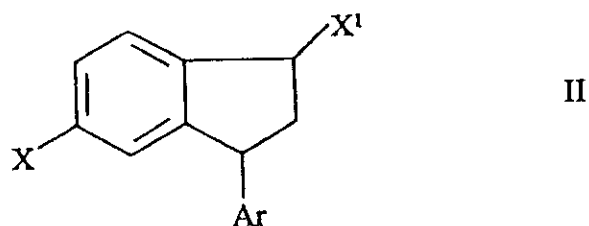
où R² et R³ sont un hydrogène ou un alkyle en C₁-C₄, -CH=CH-CH₂-, -CH=CH-, un groupe 1,2-phénylène, éventuellement substitué par halogène ou trifluorométhyle, ou, si U est un azote et Y est NR', Z peut aussi être un groupe 1,2-C₆H₄CH₂- (pour former un système cyclique quinazolidinone ou -thione) ou 1,2-C₆H₄CO- (pour former un système cyclique quinazolidinedione ou thioxoquinazolidinone); et

Ar est un noyau phényle éventuellement substitué par halogène, trifluorométhyle ou alkyle en C₁-C₄, ou Ar est un noyau thiophène ou furane éventuellement substitué par alkyle en C₁-C₄;

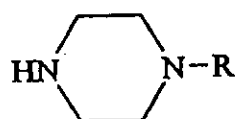
tout groupe hydroxy présent étant éventuellement estérifié avec un acide carboxylique aliphatique ayant 2 à 24 atomes de carbone inclus;

sous réserve que, lorsque Ar est un phényle éventuellement substitué, R ne puisse pas être un hydrogène ou un groupe alkyle en C₁-C₄ ou alcényle en C₂-C₄ éventuellement substitué par hydroxy; ou un de ses sels d'addition d'acides pharmaceutiquement acceptables ou un de ses promédicaments, caractérisée en ce qu'elle comprend

a) le traitement d'un composé de la formule II ci-dessous:

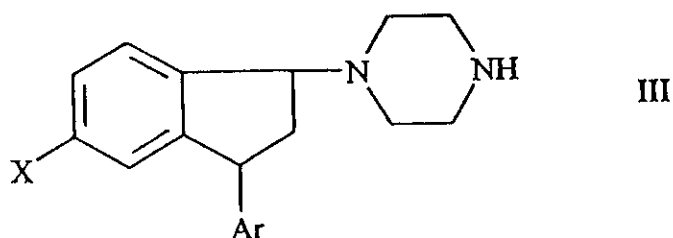


avec un dérivé de pipérazine de formule:



X, Ar et R ayant dans ces formules les significations données ci-dessus, et X¹ est un halogène ou -OSO₂R⁴ où R⁴ est un alkyle comme CH₃ ou un aryle comme le reste p-toluyle;

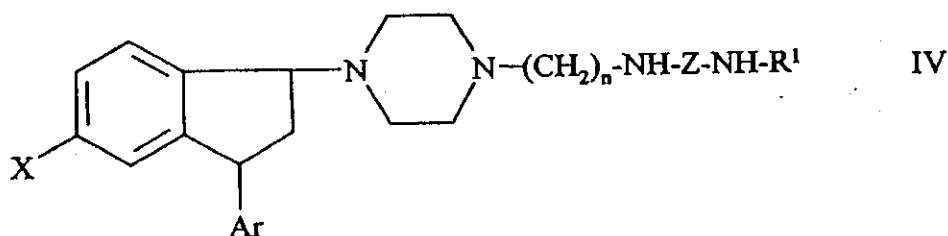
b) le traitement d'un composé ayant la formule III ci-dessous:



dans laquelle X et Ar sont tels que définis ci-dessus, avec un composé de formule X¹-R dans lequel R et X¹ sont tels que définis ci-dessus, si ce n'est que R ne peut être l'hydrogène;

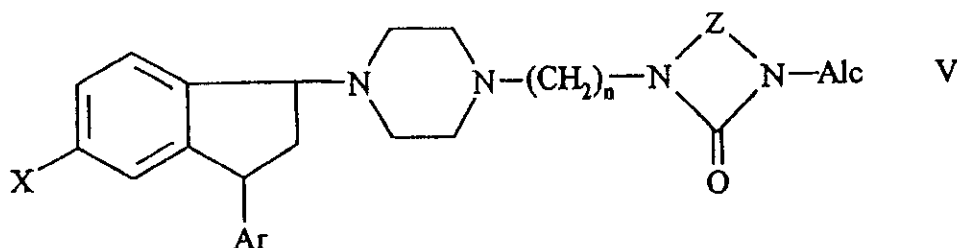
c) le traitement d'un composé de formule III avec un composé R'-CHO, où R' est un groupe tel que R'-CH₂- à la définition donnée ci-dessus pour R, en présence d'un agent réducteur, par exemple NaCNBH₃ ou l'hydrogène, en présence d'un catalyseur convenable, comme Pt ou Pd;

d) le traitement d'un composé ayant la formule IV ci-dessous:



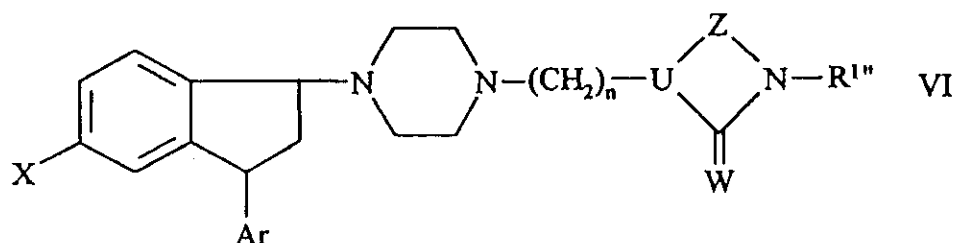
dans laquelle X, Ar, R¹, Z et n sont tels que définis ci-dessus, avec CS₂, le thiophosgène, l'urée ou le phosgène;

e) le traitement d'un composé ayant la formule V ci-dessous:



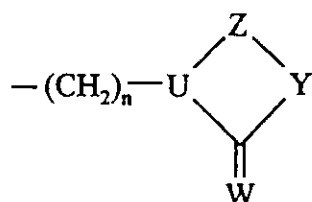
15 dans laquelle X, Ar, n et Z sont tels que définis ci-dessus, et Alc est un métal alcalin comme le sodium ou le potassium, avec un composé de formule R^5-X^1 dans laquelle R^5 est un groupe alkyle inférieur et X^1 est tel que défini ci-dessus;

f) la réduction d'un composé ayant la formule VI ci-dessous:



30 dans laquelle X, Ar, n, U, Z et W sont tels que définis ci-dessus et $R^{1''}$ est un groupe cycloalkyle ou alkyle en C_1-C_4 contenant un ou plusieurs groupes ester, cétone ou aldéhyde, avec un agent réducteur convenable pour former un composé correspondant dans lequel R^1 est un groupe alkyle en C_1-C_4 ou cycloalkyle contenant un ou plusieurs groupes hydroxy;

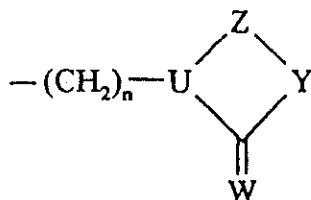
g) la réaction d'un composé de formule I dans lequel R est un groupe de formule:



45 dans laquelle n, U, Z et Y sont tels que définis ci-dessus et W est O, avec P_2S_5 ou le réactif de Lawesson pour donner le composé correspondant dans lequel W est S; et si désiré la transformation ultérieure du dérivé obtenu en un sel d'addition d'acide correspondant.

- 50 2. Méthode selon la revendication 1, caractérisée en ce que Ar est un groupe phényle éventuellement substitué par halogène ou méthyle, de préférence un groupe 4-fluorophényle, et/ou en ce que X est Cl ou F.

3. Méthode selon la revendication 1 ou 2, caractérisée en ce que R est un groupe de formule



dans laquelle n est 2; U est N; W est O ou S; Z est $-\text{CH}_2-\text{CH}_2-$ ou $-\text{CH}_2-\text{CH}_2-\text{CH}_2-$ et Y est un groupe NR' dans lequel R' est un hydrogène ou un alkyle en C_1-C_4 .

4. Méthode selon la revendication 1, caractérisée en ce que le composé préparé est choisi dans le groupe constitué par:

le dimaléate de (-)-trans-1-[2-[4-[5-chloro-3-(4-fluorophényl)-2,3-dihydro-1H-indène-1-yl]pipérazine-1-yl]éthyl]-3-isopropyl-2-imidazolidinone; le dichlorhydrate de (+)-trans-1-[2-[4-[5-fluoro-3-(4-fluorophényl)-2,3-dihydro-1H-indène-1-yl]pipérazine-1-yl]éthyl]-tétrahydro-2(1H)-pyrimidine-thione;

le dichlorhydrate de (-)-trans-1-[2-[4-[5-chloro-3-(4-fluorophényl)-2,3-dihydro-1H-indène-1-yl]pipérazine-1-yl]éthyl]-tétrahydro-2(1H)-pyrimidine-thione;

le dimaléate de (+)-trans-1-[2-[4-[5-fluoro-3-(4-fluorophényl)-2,3-dihydro-1H-indène-1-yl]pipérazine-1-yl]éthyl]-tétrahydro-2(1H)-pyrimidinone; et le dimaléate de (-)-trans-1-[2-[4-[5-chloro-3-(4-fluorophényl)-2,3-dihydro-1H-indène-1-yl]pipérazine-1-yl]éthyl]-tétrahydro-2(1H)-pyrimidinone; et leurs sels d'addition d'acides.

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