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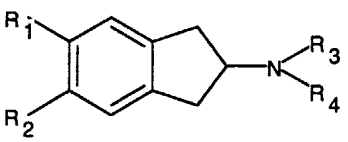
(54) Virsraksts: **2-Aminoindāni kā selektīvi dofamīna D3 ligandi**

(57) Kopsavilkums: Izgudrojums attiecas uz 2-aminoindāna analogiem, kas selektīvi piesaistās dofamīna D_3 receptoram *in vitro*. Aprakstīts savienojums ar formulu (I)



(I),

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R_1 un R_2 ir neatkarīgi izvēlēti no rindas OSO_2CF_3, OSO_2CH_3, SOR_5, CO_2R_5, $CONH_2$, $CONR_5R_6$, COR_5, CN, SO_2NH_2, $SO_2NR_5R_6$, SO_2R_5, -OCO-(C_1-C_6alkilgrupa), -NCO-(C_1-C_6 alkilgrupa), -CH_2O-(C_1-C_6alkilgrupa), -CH_2OH, CO-arilgrupa, -$NHSO_2$-arilgrupa un -$NHSO_2$-(C_1-C_6alkilgrupa);

R_3 un R_4 ir neatkarīgi -(C_1-C_8 alkilgrupa);

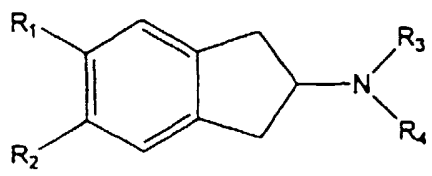
R_5 ir ūdeņraža atoms, -(C_1-C_8 alkilgrupa), -(C_2-C_4 alkenilgrupa) vai -(C_2-C_8 alkinilgrupa), -(C_3-C_8 cikloalkilgrupa); un R_6 ir -(C_1-C_8 alkilgrupa), -(C_2-C_4 alkenilgrupa), -(C_2-C_8 alkinilgrupa), -(C_3-C_8 cikloalkilgrupa) vai arilgrupa, vai savienojuma (I) farmaceitiski pieņemams sāls. Pie tam, arilgrupa satur 6 līdz 12 oglekļa atomus, kas neobligāti ir aizvietoti ar 1 līdz 3 hidroksilgrupām, fluora atomiem, hlora atomiem vai broma atomiem.

Savienojumu (I) var izmantot medikamenta ražošanai centrālās nervu sistēmas traucējumu, kas saistīti ar dofamīna D_3 receptora aktivitāti, tādu kā šizofrēnija, mānija, depresija, geriatriski traucējumi, medikamentu pārmērīga lietošana un pieradums pie pārmērīgas medikamentu lietošanas, Parkinsona slimība, miega traucējumi, diennakts ritma traucējumi, ar trauksmainību saistīti traucējumi un demence, ārstēšanai.

* pieteikums pieņemts ievērojot LR Patentu likuma Pārejas noteikumu 1. punktu (Eiropas pat.publ. Nr. 0712387, reģistrācijas diena 08.12.1999 Eiropas pat. piet. Nr. 94925094.8, iesniegšanas datums 21.07.1994)

IZGUDROJUMA FORMULA

1. Savienojums ar formulu



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R_1 un R_2 ir neatkarīgi izvēlēti no OSO_2CF_3, OSO_2CH_3, SOR_5, CO_2R_5, $CONH_2$, $CONR_5R_6$, COR_5, CN, SO_2NH_2, $SO_2NR_5R_6$, SO_2R_5, -OCO-(C_1-C_6 alkilgrupa), -NCO-(C_1-C_6 alkilgrupa), -CH_2O-(C_1-C_6 alkilgrupa), -CH_2OH, CO-arilgrupas, -$NHSO_2$-arilgrupas un -$NHSO_2$-(C_1-C_6 alkilgrupa);

R_3 un R_4 ir neatkarīgi C_1-C_8 alkilgrupa;

R_5 ir ūdeņraža atoms, C_1-C_8 alkilgrupa, C_2-C_4 alkenilgrupa vai C_3-C_8 cikloalkilgrupa; un

R_6 ir C_1-C_8 alkilgrupa, C_2-C_4 alkenilgrupa, C_2-C_8 alkinilgrupa, C_3-C_8 cikloalkilgrupa vai arilgrupa;

vai tā farmaceitiski pieņemams sāls;

kur arilgrupa ir noteikta kā 6 līdz 12 oglekļa atomus saturoša grupa, kas neobligāti ir aizvietoti ar 1 līdz 3 hidroksilgrupām, fluora atomiem, hlora atomiem vai broma atomiem.

2. Savienojums saskaņā ar 1. punktu, kur R_1 ir OSO_2CF_3.

3. Savienojums saskaņā ar 2. punktu, kur R_2 ir OSO_2CF_3.

4. Savienojums saskaņā ar 1. punktu, kur R_3 ir propilgrupa.

5. Savienojums saskaņā ar 4. punktu, kur R_4 ir propilgrupa.

6. Savienojums saskaņā ar 1. punktu, kurš ir

5,6-di(trifluormetilsulfoniloksi)-2-(di-n-propilamino)indāns.

7. Savienojums saskaņā ar 1. punktu, kurš ir
5,6-di(metoksimetil)-2-(di-n-propilamino)indāns.

8. Savienojuma saskaņā ar jebkuru no 1. līdz 7. punktiem izmantošana medikamenta ražošanai izmantošanai centrālās nervu sistēmas traucējumu, kas saistīti ar dofamīna D_3 receptora aktivitāti, ārstēšanā.

9. Izmantošana saskaņā ar 8. punktu, kur traucējumi ir izvēlēti no šizofrēnijas, mānijas, depresijas, geriatriskiem traucējumiem, medikamentu pārmērīgas lietošanas un pieraduma pie pārmērīgas medikamentu lietošanas, Parkinsona slimības, miega traucējumiem, diennakts ritma traucējumiem, ar trauksmainību saistītiem traucējumiem un demences.

2-AMINOINDANS AS SELECTIVE DOPAMINE D3 LIGANDS

Description

BACKGROUND OF THE INVENTION

[0001] The subject invention is directed toward 2-aminoindan analogs that selectively bind to the dopamine D3 receptor *in vitro*. The dopamine D3 receptor was recently cloned by Sokoloff et al.. (Nature, 347, 146 (1990)). It was hypothesized that this receptor subtype is of importance for the action of anti-psychotics. Interestingly, this receptor shows a high abundance in brain regions associated with emotional and cognitive functions.

[0002] Compounds with this profile may be useful in treating CNS disorders, e.g. schizophrenia, mania, depression, geriatric disorders, drug abuse and addiction, Parkinson's disease, anxiety disorders, sleep disorders, circadian rhythm disorders and dementia.

INFORMATION DISCLOSURE STATEMENT

[0003] Arneric, S.P. et al., Neuropharmacol., 21, 885 (1982) describes indan analogs compared with other dopamine agonists. Compounds with 5,6 substitution were found to be inactive in this model of food intake.

[0004] Arneric, S.P. et al., Arch. Int. Pharmocodyn. Ther., 257, 263 (1982) describes 2-aminotetralin and 2-aminoindan analogs where the 5,6 dimethoxy substituted compound is again disclosed as inactive agents in an assay to evaluate contractions in vascular smooth muscle.

[0005] Bhatnagar, R.K. et al., Pharmacol., Biochem. Behav., 17(Suppl. 1), 11 (1982) discusses SAR studies of various structural entities including aminoindans which interact with dopamine receptors. The 5,6 dimethoxy indans are disclosed as inactive compounds.

[0006] Cannon, J.G. et al., J. Med. Chem., 25, 858 (1982) describes 4,7-dimethoxy-2 aminoindans and their dopaminergic and cardiovascular actions.

[0007] Cannon, J. G. et al., J. Med. Chem., 25, 1442 (1982) discloses the synthesis of the 5,6 di-methoxy and dihydroxy indans and also some biology which shows they are devoid of dopamine receptor activity.

[0008] Cannon, J.G. et al., J. Med. Chem., 27, 186 (1984) describes the synthesis of N-alkylated derivatives of 2-amino-4,6-dihydroxyindans.

[0009] Cannon, J.G. et al., J. Med. Chem., 28, 515 (1985) describes the resolution of the 4-hydroxy aminoindan.

[0010] Cannon, J.G. et al., J. Med. Chem., 29, 2016 (1986) describes the ortho OH/methyl, hydroxymethyl, formyl or carboxy derivatives of 2-aminoindans (4,5 substitution), aminotetralins and benz[f] quinolines.

[0011] Hacksell, U. et al., J. Med. Chem., 24, 429 (1981) describes the synthesis of monophenolic 2-aminoindans as central dopamine receptor stimulants.

[0012] Ma *et al*, J. Pharmacol. Exp. Ther. 256:751 (1991), describes dopaminergic structure-activity relationships of 2-aminoindans with mainly di-substitution in the 4,5-positions.

[0013] Nichols *et al*, J. Med. Chem. 33:703 (1990), describes non-neurotoxic tetralin and indan analogues of 3,4-(methylenedioxy)amphetamine.

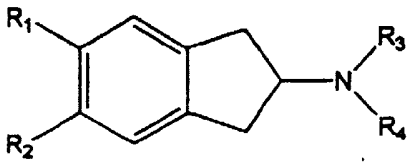
[0014] WO-A-9007490 describes 2-aminotetralins and 2-aminoindans substituted in the aromatic ring with OCH_3 or OH in conjunction with Br.

[0015] EP-A-0334538 (88302599.1) discloses anti-arrhythmic aminoindanes having a bicyclic structure and a methyl group on the amine.

[0016] US-A-4132737 discloses trifluoromethyl-substituted 1-aminoindanes.

SUMMARY OF THE INVENTION

[0017] Novel compounds of the present invention are of formula I



wherein

R_1 and R_2 are independently chosen from OSO_2CF_3, OSO_2CH_3, SOR_5, CO_2R_5, $CONH_2$, $CONR_5R_6$, COR_5, CN, SO_2NH_2, $SO_2NR_5R_6$, SO_2R_5, -OCO-(C_1-C_6 alkyl), -NCO-(C_1-C_6 alkyl), -CH_2O-(C_1-C_6 alkyl), -CH_2OH, CO-aryl, -$NHSO_2$-aryl and -$NHSO_2$-(C_1-C_6 alkyl);

R_3 and R_4 are independently C_1-C_8 alkyl;

R_5 is hydrogen, C_1-C_8 alkyl, C_2-C_4 alkenyl or C_3-C_8 cycloalkyl; and

R_6 is C_1-C_8 alkyl, C_2-C_4 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl or aryl;

or a pharmaceutically-acceptable salt thereof.

[0018] Such compounds are useful for treating central nervous system disorders associated with the dopamine D3 receptor activity in a patient in need of such treatment. Such disorders include schizophrenia, mania, depression, geriatric disorders, drug abuse and addiction, Parkinson's disease, sleep disorders, circadian rhythm disorders, anxiety disorders and dementia. Typically, the compound of formula I is administered in the form of a pharmaceutical composition comprising a pharmaceutically-acceptable carrier or diluent.

[0019] "Alkyl" has one to eight carbon atoms, such as methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl and isomeric forms thereof.

[0020] "Aryl" has six to twelve carbon atoms such as phenyl, α-naphthyl, β-naphthyl, m-methylphenyl, p-trifluoromethylphenyl and the like. The aryl groups can also be substituted with one to three hydroxy, fluoro, chloro, or bromo groups.

[0021] "Cycloalkyl" are three to eight carbon atoms such as cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

[0022] Pharmaceutically acceptable salts include salts of both inorganic and organic acids. The preferred pharmaceutically acceptable salts include salts of the following acids: methanesulfonic, hydrochloric, hydrobromic, sulfuric, phosphoric, nitric, benzoic, citric, tartaric, fumaric or maleic.

[0023] The compounds of Formula I are active orally or parenterally. Orally the Formula I compounds can be given in solid dosage forms such as tablets or capsules, or can be given in liquid dosage forms such as elixirs, syrups or suspensions as is known to those skilled in the art. It is preferred that the Formula I compounds be given in solid dosage form and that it be a tablet.

[0024] Typically, the compounds of Formula I can be given in the amount of about 0.25 mg to about 100 mg/person, one to three times a day. Preferably, about 10 to about 50 mg/day in divided doses.

[0025] The exact dosage and frequency of administration depends on the particular compound of Formula I used, the particular condition being treated, the severity of the condition being treated, the age, weight, general physical condition of the particular patient, other medication the individual may be taking as is well known to those skilled in the art and can be more accurately determined by measuring the blood level or concentration of the active compound in the patient's blood and/or the patient's response to the particular condition being treated.

[0026] Thus, the subject compounds, along with a pharmaceutically-acceptable carrier, diluent or buffer, can be administrated in a therapeutic or pharmacological amount effective to alleviate the central nervous system disorder with respect to the physiological condition diagnosed. The compounds can be administered intravenously, intramuscularly, topically, transdermally such as by skin patches, buccally or orally to man or other vertebrates.

[0027] The compositions of the present invention can be presented for administration to humans and other vertebrates in unit dosage forms, such as tablets, capsules, pills, powders, granules, sterile parenteral solutions or suspensions, oral solutions or suspensions, oil in water and water in oil emulsions containing suitable quantities of the compound, suppositories and in fluid suspensions or solutions.

[0028] For oral administration, either solid or fluid unit dosage forms can be prepared. For preparing solid compositions such as tablets, the compound can be mixed with conventional ingredients such as talc, magnesium stearate, dicalcium phosphate, magnesium aluminum silicate, calcium sulfate, starch, lactose, acacia, methylcellulose, and functionally similar pharmaceutical diluent or carrier materials. Capsules are prepared by mixing the compound with an inert pharmaceutical diluent and filling the mixture into a hard gelatin capsule of appropriate size. Soft gelatin capsules are prepared by machine encapsulation of a slurry of the compound with an acceptable vegetable oil, light liquid petrolatum or other inert oil.

[0029] Fluid unit dosage forms for oral administration such as syrups, elixirs, and suspensions can be prepared. The forms can be dissolved in an aqueous vehicle together with sugar, aromatic flavoring agents and preservatives to form a syrup. Suspensions can be prepared with an aqueous vehicle with the aid of a suspending agent such as acacia, tragacanth, methylcellulose and the like.

[0030] For parenteral administration, fluid unit dosage forms can be prepared utilizing the compound and a sterile vehicle. In preparing solutions, the compound can be dissolved in water for injection and filter sterilized before filling into a suitable vial or ampoule and sealing. Adjuvants such as a local anesthetic, preservative and buffering agents can be dissolved in the vehicle. The composition can be frozen after filling into a vial and the water removed under vacuum. The lyophilized powder can then be sealed in the vial and reconstituted prior to use.

Chemical Synthesis:

Chart A.

[0031] Steps 1 and 2. Conversion of the 1-indanone to the oxime (A-1) followed by hydrogenation to the primary amine (A-2) can be performed by methods known in the art.

[0032] Step 3. The primary amine is reductively aminated to yield di-substitution or coupled with acid to form the amide. This amide can be in turn reduced, with e.g. LiAH. If appropriate, another acylation or alkylation can take place. The primary amine could also be alkylated with an alkyl halide (preferably, alkyl bromide or chloride) under basic conditions to yield N-alkyl derivatives.

[0033] Step 4. If one or more substituents on the aromatic ring is a methoxy group, it may be converted to the corresponding phenol (A-4) using 48% HBr or lithium-diphenyl phosphine in THF.

[0034] Step 5. Conversion of the phenols to the triflates may be accomplished using methods known in the art such as the use of triflic anhydride in base (Example 1) or N-phenyltrifluoromethanesulfonimide.

[0035] Step 6. A di-triflate derivative (A-5, Example 1) can be converted to the dicarbomethoxy derivative via palladium chemistry (A-6, Example 3, *J. Chem. Soc. Chem. Commun.* **1987**, 904). In addition, mono-carbomethoxy, mono-hydroxy derivative is obtained in this transformation (A-6, Example 10). This di-triflate can also be converted to mono-hydroxy, mono-triflate by heating with triethylamine in DMF/MeOH (A-6, Preparation 4). This compound in turn can be converted by acetylation (AC_2O/pyridine) to mono-acetoxy, mono-triflate (A-6, Example 2) and by alkylation (NaH/DMF, MeI) to mono-methoxy, mono-triflate (A-6, 56), via the chemistry known in the art. Following the palladium chemistry described above, the mono-acetoxy, mono-triflate (A-6, Example 2) can be converted to mono-acetoxy, mono-carbomethoxy derivative (A-6, Example 5). The mono-carbomethoxy derivative can be converted to the formyl derivative by DIBAL-H at low temperaure, or to hydroxymethyl derivative by LiAH, both methods known in the art. The mono-carbomethoxy derivative can be converted to mono-carboxamido derivative and in turn to mono-cyano derivative. The di-carbomethoxy derivative (A-6, Example 3) is converted to di-hydroxymethyl derivative via LiAH reduction known in the art and in turn this is converted to di-methoxymethyl derivative (A-6, Example 8).

Preparation 1 5,6-Dimethoxy-2-aminoindan (A-2, Chart A)

[0036] This preparation was carried out following the procedure outlined in Cannon *et al,* J. Med. Chem. 25:1442 (1982). Briefly, to a solution of 5,6-dimethoxy-2-oximo-1-indanone (Cannon *et al, supra)* in acetic acid (70 mL) and sulfuric acid (4.9 mL) was added 10% Pd/C; the mixture was hydrogenated at 345 kPa (50 psi) for 6 hours. The reaction mixture was filtered over Celite and concentrated. This material was used as is in the following reaction.

Preparation 2 5,6-Dimethoxy-2-(di-n-propylamino)indan (A-3, Chart A)

[0037] To a solution of 5,6-dimethoxy-2-aminoindan (Preparation 1, 30 mmol) in 1,2-dichloroethane (100 mL) and THF (30 mL) was added TEA to pH 4-5. Propionaldehyde (8.7 mL, 120 mmol) was added followed by sodium triacetoxyborohydride (19.07 g, 90 mmol) in portions. The reaction was concentrated to remove solvents, followed by addition of 10% HCl. The solution was basified using 1 N NaOH to pH>10 and extracted with ethyl acetate. The combined organic layers were washed with brine, dried, filtered and evaporated to yield a white solid; mp 210-213°C.

Preparation 3 5,6-Dimethoxy-2-(di-n-propylamino)indan hydrobromide (A-3, Chart A)

[0038] A solution of 5,6-dimethoxy-2-(di-n-propylamino)indan (Preparation 2) in 48% HBr (10 mL) was refluxed at 100°C overnight. The solution was concentrated to dryness and recrystallised from methanol/ether to yield a light grey solid; mp 275-280°C.

Example 1 5,6-Di(trifluoromethylsulfonyloxy)-2-(di-n-propylamino)indan (A-4, Chart A)

[0039] To a solution of 5,6-dihydroxy-2-(di-n-propylamino)indan (Preparation 3, 4.5 mmol) in dimethylformamide/acetonitrile (1:6, 49 mL) was added sodium carbonate (1.43 g, 13.5 mmol) and was heated (100°C) overnight. The mixture was diluted with ethyl acetate, filtered and the filtrate concentrated. The oily residue was chromatographed (400 g silica gel) eluting with methylene chloride/methanol (9:1) to yield a yellow oil. The oil was converted into the HCl salt and recrystallised from ether/ethyl acetate, to yield a white solid (129 mg, 90%); mp 157-163°C.

Preparation 4 5-(Trifluoromethylsulfonyloxy)-6-hydroxy-2-(di-n-propylamino)indan (A-6, Chart A)

[0040] A mixture of 5,6-(ditrifluoromethylsulfonyloxy)-2-(di-n-propylamino)indan (Example 1, 4 mmol) and triethylamine (4.4 mmol, 0.6 mL) in DMF/methanol (3:1, 20 mL) was heated at 70°C for 3 h. The reaction was quenched with water and extracted with methylene chloride. The combined organic layers were washed with water, brine, dried ($MgSO_4$, filtered and concentrated to give a dark brown oil. Chromatography using 400 g silica, eluting with hexane /acetone (3:1) yielded a light yellow oil (1.18 g, 78%). The HCl salt was formed and crystallized from ethyl acetate/methanol to give the title compound as a white solid; mp 235-237°C.

Example 2. 5-(Trifluoromethylsulfonyloxy)-6-acetoxy-2-(di-n-propylamino)indan (A-5, Chart A).

[0041] 5-(Trifluoromethylsulfonyloxy)-6-hydroxy-2-(di-n-propylamino)indan (Preparation 4, 1.18 g, 3.1 mmol) was stirred in a mixture of acetic anhydride (1 mL), pyridine (2 mL) and methylene chloride (10 mL) at rt for 24 h. The reaction was quenched with methanol (2 mL), stirred for 1 h followed by extraction using methylene choride. The organic layers were washed with water, satd. sodium bicarbonate, brine, dried ($MgSO_4$, filtered and concentrated. The oil was chromatographed on 400 mg silica gel, eluting with hexane/acetone (3:1) to give a light yellow oil. The HCl salt was formed and crystallized from methanol/ethyl acetate/ hexane to yield the title compound as a white solid: mp 190-191°C.

Example 3 5,6-Dicarbomethoxy-2-(di-n-propylamino)indan (A-5, Chart A)

[0042] To a solution of 5,6-di(trifluoromethylsulfonyloxy)-2-(di-n-propylamino)indan (Example 1, 15 mmol, 7.7 g) and triethylamine (66 mmol) in methanol/DMF (1:3) which had been degassed with nitrogen followed by CO (gas) was added a solution of palladium acetate (3 mmol) and dppp (1,3-bis(diphenylphosphino)-propane) in DMF/methanol (3:1) which had also been degassed with nitrogen. The bubbling of CO gas continued for 6 hours at 60°C. The mixture was cooled to room temperature, acidified with 6N HCl and basified with saturated sodium bicarbonate. This mixture was extracted with ethyl acetate/hexane (3:1, 2 x 800 mL). The organic layer was washed with water, brine, dried ($MgSO_4$), filtered and concentrated to give a brown oil. The oil was chromatographed on 800 g silica gel, eluting with hexane/acetone (3:1), to give 5-carbomethoxy-6-hydroxy-2-(di-n-propylamino)indan as the least polar product (0.37 g). This was converted to the HCl salt and crystallised from ethyl acetate/methanol to give white solid: mp 178-179°C. Also, 5,6-dicarbomethoxy)-2-(di-n-propylamino)indan was obtained (0.4 g). The HCl salt was formed and crystallised from ethyl acetate/methanol to give a white solid: mp 202-203°C. The major product was 5-(trifluoromethylsulfonyloxy)-6-hydroxy-2-(di-n-propylamino)indan (3.3 g) (see Preparation 4).

Example 4 5,6-Di(toluenesulfonyloxy)-2-(di-n-propylamino)indan (A-5, Chart A)

[0043] To a solution of 5,6-dihydroxy-2-(di-n-propylamino)indan (Preparation 3, 357 mg, 1.08 mmol) in methylene chloride (30 mL) was added dimethylaminopyridine (cat, 10 mg), triethylamine (0.9 mL, 6.48 mmol) and p-tosyl chloride (1.12 g, 3.24 mmol) in methylene chloride. After 12 h, additional tosyl chloride (1 g) and triethylamine (1 mL) were added. After 48 h, the reaction was quenched with water and extracted with methylene chloride (3 x 70 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and evaporated to yield a brown oil (1.08 g). The oil was chromatographed using 300 g silica gel, eluting with methylene chloride/methanol (19:1), to yield the title compound as an oil (520 mg, 86%). High resolution FAB MS: theory $C_{29}H_{35}NS_2O_6$ +1H: 558.1984; observed: 558.2000.

Example 5 5 -Carbomethoxy-6-acetoxy-2-(di-n-propylamino)indan (A-6, Chart A)

[0044] Following the general procedure of Example 3 and making non-critical variations but starting with 5-trifluoromethanesulfonyloxy-6-acetoxy-2-(di-n-propylamino)indan (Example 2), the title compound is obtained.

Example 6 5-Carbomethoxy-6-trifluoromethanesulfonyloxy-2-(di-n-propylamino)indan (A-6, Chart A)

[0045] Following the general procedure of Example 1 and making non-critical variations but starting with 5-carbomethoxy-6-hydroxy-2-(di-n-propylamino)indan (Example 3), the title compound is obtained.

Example 7 5,6-Di(hydroxymethyl)-2-(di-n-propylamino)indan (A-6, Chart A)

[0046] A solution of 5,6-dicarbomethoxy-2-(di-n-propylamino)indan (Example 3), in THF at 0°C under nitrogen is treated with excess lithium aluminium hydride. After work-up and purification, the title compound is obtained.

Example 8 5,6-Di(hydroxymethyl)-2-(di-n-propylamino)indan (A-6, Chart A)

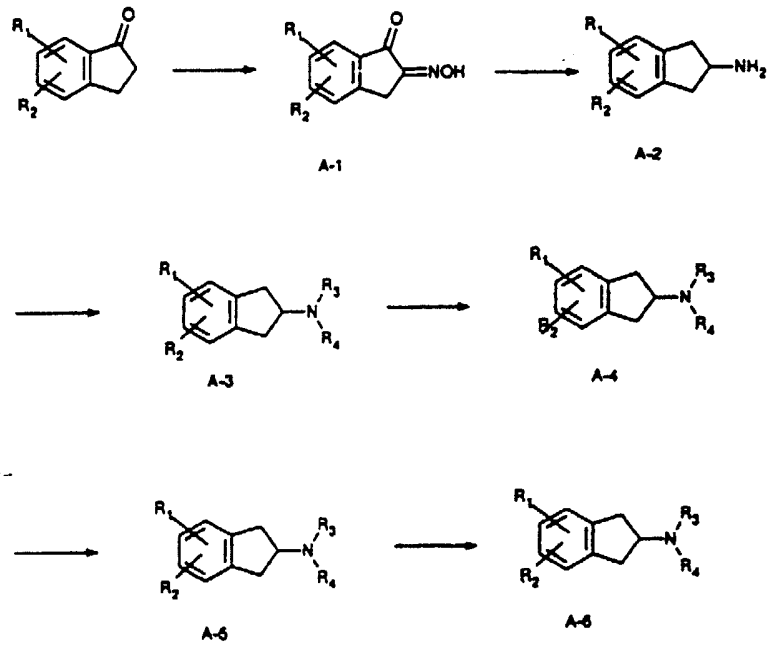
[0047] A solution of 5,6-di(hydroxymethyl)-2-(di-n-propylamino)indan (Example 7) in DMF is added to a suspension of sodium hydride in DMF under nitrogen. The mixture is alkylated with methyl iodide to yield the title compound.

Binding Data

[0048] Competition binding experiments employed eleven dilutions oftest competing with [^{3}H]-5-(dipropylamino)-5,6-dihydro-4H-imidazo(4,5,1-ij)quinolin-2(1H)-one (R-enantiomer) (62 Ci/mmol, 2 nM) and [^{3}H]-spiperone (107 Ci/mmol, 0.5 nM) for D2 and D3 binding sites, respectively; see Lahti, Eur. J. Pharmacol. 202:289 (1991). In each experiment, cloned mammalian receptors expressed in CHO-K1 cells were used; see Chio, Nature 343:266 (1990); and Huff, Mol. Pharmacol. (1993), in press. IC50 values were estimated by fitting the data to a one-site model by non-linear least squares minimisation. Ki values were calculated with the Chen-Prushoff equation.

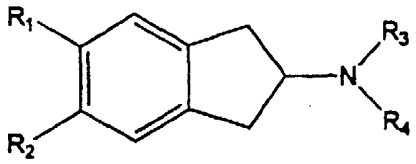
Example	D2 (Ki, nM)	D3 (Ki, nM)
1	367	16
4	291	45

Chart A:



Claims

1. A compound of the formula



wherein

R_1 and R_2 are independently chosen from OSO_2CF_3, OSO_2CH_3, SOR_5, CO_2R_5, $CONH_2$, $CONR_5R_6$, COR_5, CN, SO_2NH_2, $SO_2NR_5R_6$, SO_2R_5, -OCO-(C_1-C_6 alkyl), -NCO-(C_1-C_6 alkyl), -CH_2O-(C_1-C_6 alkyl), -CH_2OH, CO-aryl, -$NHSO_2$-aryl and -$NHSO_2$-(C_1-C_6 alkyl);
R_3 and R_4 are independently C_1-C_8 alkyl;
R_5 is hydrogen, C_1-C_8 alkyl, C_2-C_4 alkenyl or C_3-C_8 cycloalkyl; and
R_6 is C_1-C_8 alkyl, C_2-C_4 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl or aryl;

or a pharmaceutically-acceptable salt thereof;
wherein aryl is defined as having 6 to 12 carbon atoms optionally substituted with 1 to 3 hydroxy, fluoro, chloro or bromo groups.

2. A compound of claim 1, wherein R_1 is OSO_2CF_3.

3. A compound of claim 2, wherein R_2 is OSO_2CF_3.

4. A compound of claim 1, wherein R_3 is propyl.

5. A compound of claim 4, wherein R_4 is propyl.

6. A compound of claim 1, which is
5,6-di(trifluoromethylsulfonyloxy)-2-(di-n-propylamino)indan.

7. A compound of claim 1, which is
5,6-di(methoxymethyl)-2-(di-n-propylamino)indan.

8. Use of a compound of any of claims 1 to 7, for the manufacture of a medicament for use in treating a central nervous system disorder associated with dopamine D3 receptor activity.

9. The use of claim 8, wherein the disorder is selected from schizophrenia, mania, depression, geriatric disorders, drug abuse and addiction, Parkinson's disease, sleep disorders, circadian rhythm disorders, anxiety disorders and dementia.