

INDANYL-PIPERAZINE COMPOUNDS, A PROCESS FOR THEIR PREPARATION AND
PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

The present invention relates to indanyl-piperazine compounds, to a process for their preparation and to pharmaceutical compositions containing them, and also to their use as serotonin reuptake inhibitors and NK₁ antagonists.

The compounds of the present invention act as serotonin reuptake inhibitors.

5 By virtue of that fact, they are useful in the treatment of depressive states (Goodnick and Goldstein, *J Psychopharmacol* 1998, 12 (Suppl B):S55-S87; Cheer and Goa, *Drugs* 2001, 61:81-110; MacQueen *et al.*, *CNS Drug Rev* 2001, 7:1-24; Wagstaff *et al.*, *Drugs* 2002, 62:655-703), anxiety states such as generalised anxiety, panic attacks and phobias (Feighner, *J Clin Psychiatry* 1999, 60 (Suppl 22):18-22; Bakker *et al.*, *Int clin*
10 *Psychopharmacol* 2000, 15 (Suppl 2):S25-S30; Davidson, *Int Clin Psychopharmacol* 2000, 15 (suppl 1):S13-S17; Schneier, *J Clin Psychiatry* 2001, 62 (Suppl 1):43-48), the harmful effect of stress whether psychological (Marona-Lewicka and Nichols, *Stress* 1997, 2:91-100; Mar *et al.*, *Pharmacol Biochem Behav* 2002, 73:703-712; Will *et al.*, *Mol Psychiatry* 2003, 8:925-932; Ballenger, *J Clin Psychiatry* 2004, 65:1696-1707) or neurotoxic
15 (Malberg and Duman, *Neuropsychopharmacology* 2003, 28:1562-1571; Santarelli *et al.*, *Science* 2003, 301:805-809; Czeh *et al.*, *Neuropsychopharmacology* 2005, 30:67-79; Malberg and Schechter, *Curr Pharm Des* 2005, 11:145-155), impulsive states such as "ODC" or obsessive-compulsive behaviour disorders (Njung'e and Handley, *Br J Pharmacol* 1991, 104:105-112; Ichimaru *et al.*, *Jpn J Pharmacol* 1995, 68:65-70; Pigott
20 and Seay, *J Clin Psychiatry* 1999, 60:101-106; Vythilingum *et al.*, *Int Clin Psychopharmacol* 2000, 15 (Suppl 2):S7-S13), aggressive states (Knutson *et al.*, *Am J Psychiatry* 1998, 155:373-379; Lanctot *et al.*, *Neuropsychopharmacology* 2002, 27:646-654; New *et al.*, *Psychopharmacology* 2004, 176:451-458), obesity and appetite disorders such as bulimia (Proietto *et al.*, *Expert Opin Investig Drugs* 2000, 9:1317-1326; Ljung *et al.*, *J Intern Med* 2001, 250:219-224; Appolinario *et al.*, *CNS Drugs* 2004, 18:629-651;
25 Appolinario and McElroy, *Curr Drug Targets* 2004, 5:301-307), pain states (Aragona *et al.*, *Eur J Pain* 2005, 9:33-38; Millan *et al.*, *Neuropharmacology* 2002, 42:677-684; Duman *et al.*, *J Pharmacol Sci* 2004, 94:161-165; Otsuka *et al.*, *J Anesth* 2004, 15:154-158); and, in relation to those entities, disorders of behaviour and of neuronal degeneration
30 associated with dementia and other disorders of aging (Lyketos *et al.*, *Am J Psychiatry*

2000, 157:1686-1689; Lanctot *et al.*, *J Neuropsychiatry Clin Neurosci* 2001, 13:5-21; Lanctot *et al.*, *Neuropsychopharmacology* 2002, 27:646-654; Pollock *et al.*, *Am J Psychiatry* 2002, 159:460-465).

Furthermore, the compounds of the present invention are also active as neurokinin NK₁ antagonists.

By virtue of that fact, they are also useful in the treatment of depressive states (Rupniak *et al.*, *Behav Pharmacol* 2001, 12:497-508; Rupniak *et al.*, *Neuropharmacology* 2003, 44:516-523; Kramer *et al.*, *Neuropsychopharmacology* 2004, 29:385-392; Dableh *et al.*, *Eur J Pharmacol* 2005, 507:99-105), anxiety states such as generalised anxiety, panic attacks and phobias (Rupniak *et al.*, *Behav Pharmacol* 2001, 12:497-508; Santarelli *et al.*, *Proc Natl Acad Sci USA* 2001, 98:1912-1927; Varty *et al.*, *Neuropsychopharmacology* 2002, 27:371-379; Rupniak and Kramer, *Neuropsychopharmacology* 2002, 13:169-177), the harmful effect of stress whether psychological (Ballard *et al.*, *Eur J Pharmacol* 2001, 412:255-264; Rupniak and Kramer, *Neuropsychopharmacology* 2002, 13:169-177; Spooren *et al.*, *Eur J Pharmacol* 2002, 435:161-170; Steinberg *et al.*, *J Pharmacol Exp Ther* 2002, 303:1180-1188) or neurotoxic (Van der Hart *et al.*, *Mol Psychiatry* 2002, 7:933-941; Morcuende *et al.*, *Eur J Neurosci* 2003, 18:1828-1836; Guest *et al.*, *Brain Res* 2004, 1002:1-10; Czeh *et al.*, *Neuropsychopharmacology* 2005, 30:67-79), impulsive states such as obsessive-compulsive behaviour disorders (Culman *et al.*, *Br J Pharmacol* 1995, 114:1310-1316; Tschöpe *et al.*, *Br J Pharmacol* 1992, 107:750-755; Rupniak *et al.*, *Behav Pharmacol* 2001, 12:497-508; Millan *et al.*, *Neuropharmacology* 2002, 42:677-684), aggressive states (Siegel and Schubert, *Rev Neurosci* 1995, 6:47-61; De Felipe *et al.*, *Nature* 1998, 392:394-397; Rupniak *et al.*, *Behav Pharmacol* 2001, 12:497-508), but also drug abuse (Murtra *et al.*, *Nature* 2000, 405:180-183; Ripley *et al.*, *Neuropharmacology* 2002, 43:1258-1268; Gadd *et al.*, *J Neurosci* 2003, 23:8271-8280), psychotic states (Zachrisson *et al.*, *Eur Neuropsychopharmacol* 2000, 10:355-363) and extrapyramidal motor effects caused by antipsychotics (Anderson *et al.*, *J Pharmacol Exp Ther* 1995, 274:928-936; Steinberg *et al.*, *J Pharmacol Exp Ther* 2002, 303:1180-1188), sexual dysfunctions (Priest *et al.*, *Brain Res Mol Brain Res* 1995, 28:61-71; Daniels *et al.*, *Neurosci Lett* 2003, 338:111-114; Kramer *et al.*, *Science* 1998, 281:1640-1644; Kramer *et al.*, *Neuropsychopharmacology* 2004, 29:385-392), disturbances of chronobiological

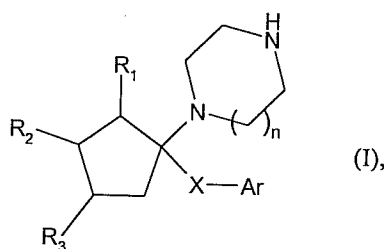
rhythms such as circadian rhythms (Shibata *et al.*, *Brain Res* 1992, 597:257-263; Challet *et al.*, *Brain Res* 1998, 800:32-39; Challet *et al.*, *Neuropharmacology* 2001, 40:408-415; Gannon *et al.*, *Neuropharmacology*, in press), pain (Seguin *et al.*, *Pain* 1995, 61:325-343; De Felipe *et al.*, *Nature* 1998, 392:394-397; Sanger, *Br J Pharmacol* 2004, 141:1303-1312) and/or inflammation (Seabrook *et al.*, *Eur J Pharmacol* 1996, 317:129-135; Holzer, *Digestion* 1998, 59:269-283; Joos and Pauwels, *Curr Opin Pharmacol* 2001, 1:235-241; Sanger, *Br J Pharmacol* 2004, 141:1303-1312), nausea and other gastrointestinal disorders (McAllister and Pratt *Eur J Pharmacol* 1998, 353:141-148; Gardner *et al.*, *Regulatory Peptides* 1996, 65:45-53; Patel and Lindley, *Expert Opin. Pharmacother* 2003, 4:2279-2296; Sanger, *Br J Pharmacol* 2004, 141:1303-1312); and, in relation to those entities, disorders of behaviour and of neuronal degeneration associated with dementia and other disorders of aging (Raffa, *Neurosci Biobehav Rev* 1998, 22:789-813).

Because the compounds are active both on NK₁ receptors and on serotonin (5-HT) reuptake sites, they should have complementary and synergistic mechanisms for controlling impulsive, aggressive, painful and, above all, depressive states. It has moreover been shown that blocking NK₁ receptors potentiates the influence of 5-HT reuptake inhibitors on serotonergic transmission: because of that fact, such compounds should bring about more rapid and more robust antidepressant effects (Guiard *et al.*, *J Neurochem* 2004, 89:54-63; Froger *et al.*, *J Neurosci* 2001, 21:8188-8197). The rapid anxiolytic effects of NK₁ antagonists should, moreover, be complementary to the anxiolytic effects of 5-HT reuptake inhibitors, which are expressed after long-term treatment. With regard to the anxiogenic effects brought about by 5-HT at the start of treatment (Bagdy *et al.*, *Int J Neuropsychopharmacol* 2001, 4:399-408), these should be prevented by the NK₁ antagonist properties (Ballard *et al.*, *Eur J Pharmacol* 2001, 412:255-264; Rupniak *et al.*, *Neuropharmacology* 2003, 44:516-523). As far as the other undesirable effects associated with 5-HT reuptake blocking are concerned, such as emetic effects (Goldstein and Goodnick, *J Psychopharmacol* 1998, 12 (Suppl B):S55-S87; Edwards and Anderson, *Drugs* 1999, 57:507-533; Waugh and Goa, *CNS Drugs* 2003, 17:343-362) and the causation of sexual dysfunctions (Goldstein and Goodnick, *J Psychopharmacol* 1998, 12 (Suppl B):S55-S87; Montgomery *et al.*, *J Affect disord* 2002, 69:119-140; Hirschfeld, *J*

Clin Psychiatry 2003, 64 (Suppl 18):20-24), NK₁ antagonists should also be capable of counteracting those effects.

Consequently, compounds that are both NK₁ antagonists *and* serotonin reuptake inhibitors should have therapeutic advantages over compounds that interact with only one or other of those two targets.

More specifically, the present invention relates to compounds of formula (I) :



wherein :

- R₃ represents a hydrogen atom, and R₁ and R₂ together with the carbon atoms carrying them form a benzene, naphthalene or quinoline ring structure, preferably a benzene ring, each of those ring structures being optionally substituted by one or more identical or different substituents selected from hydrogen, halogen and linear or branched C₁-C₆alkyl optionally substituted by one or more halogen atoms,

or R₁ represents a hydrogen atom, and R₂ and R₃ together with the carbon atoms carrying them form a benzene, naphthalene or quinoline ring structure, preferably a benzene ring, each of those ring structures being optionally substituted by one or more identical or different substituents selected from hydrogen, halogen and linear or branched C₁-C₆alkyl optionally substituted by one or more halogen atoms,

- n represents 1 or 2,

- -X- represents a group selected from $-(CH_2)_m-O-Ak-$, $-(CH_2)_m-NR_4-Ak-$, $-(CO)-NR_4-Ak-$ and $-(CH_2)_m-NR_4-(CO)-$,

m represents an integer between 1 and 6 inclusive, Ak represents a linear or branched C_1-C_6 alkylene chain optionally substituted by a hydroxy group, and R_4 represents a hydrogen atom or a linear or branched C_1-C_6 alkyl group,

- Ar represents an aryl or heteroaryl group,

to their optical isomers, and also to addition salts thereof with a pharmaceutically acceptable acid.

Optical isomers are understood to mean enantiomers and diastereoisomers.

- 10 Among the pharmaceutically acceptable acids there may be mentioned, without implying any limitation, hydrochloric acid, hydrobromic acid, sulphuric acid, phosphonic acid, acetic acid, trifluoroacetic acid, lactic acid, pyruvic acid, malonic acid, succinic acid, glutaric acid, fumaric acid, tartaric acid, maleic acid, citric acid, ascorbic acid, oxalic acid, methanesulphonic acid, benzenesulphonic acid, camphoric acid.
- 15 An aryl group is understood to mean phenyl, biphenyl or naphthyl, each of those groups being optionally substituted by one or more identical or different groups selected from halogen, linear or branched C_1-C_6 alkyl, linear or branched C_1-C_6 alkoxy, hydroxy, cyano and linear or branched C_1-C_6 trihaloalkyl.
- 20 A heteroaryl group is understood to mean an aromatic mono- or bi-cyclic 5- to 12-membered group containing one, two or three hetero atoms selected from oxygen, nitrogen and sulphur, it being understood that the heteroaryl group may be optionally substituted by one or more identical or different groups selected from halogen, linear or branched C_1-C_6 alkyl, linear or branched C_1-C_6 alkoxy, hydroxy and linear or branched C_1-C_6 trihaloalkyl.

Among the heteroaryl groups there may be mentioned, without implying any limitation, the groups thienyl and pyridyl.

n preferably represents 1.

m preferably represents 1.

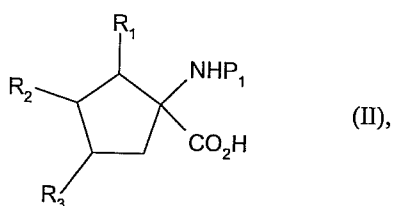
5 Ar preferably represents an aryl group.

Preferred compounds according to the invention are :

- 1-[(1RS)-1-(3,5-dibromobenzyloxymethyl)indan-1-yl]piperazine, its optical isomers, and also addition salts thereof with a pharmaceutically acceptable acid,
- 1-[(1RS)-1-(3,5-dimethylbenzyloxymethyl)indan-1-yl]piperazine, its optical isomers, and also addition salts thereof with a pharmaceutically acceptable acid,
- 1-[2-(3,5-dimethylbenzyloxymethyl)indan-2-yl]piperazine, and also addition salts thereof with a pharmaceutically acceptable acid,
- N-[(3,5-bis(trifluoromethyl)benzyl)-2-(1-piperazinyl)-2-indancarboxamide, and also addition salts thereof with a pharmaceutically acceptable acid,
- 15 - (1RS)-N-benzyl-N-methyl-1-(1-piperazinyl)-1-indancarboxamide, its optical isomers, and also addition salts thereof with a pharmaceutically acceptable acid,
- (1RS)-N-[3,5-bis(trifluoromethyl)benzyl]-N-methyl-1-(1-piperazinyl)-1-indancarboxamide, its optical isomers, and also addition salts thereof with a pharmaceutically acceptable acid,
- 20 - (1RS)-N-(3,5-dimethylbenzyl)-1-(1-piperazinyl)-1-indancarboxamide, its optical isomers, and also addition salts thereof with a pharmaceutically acceptable acid,
- N-(3,5-difluorobenzyl)-2-(1-piperazinyl)-2-indancarboxamide, its optical isomers, and also addition salts thereof with a pharmaceutically acceptable acid,
- N-(3,5-dichlorobenzyl)-N-methyl-2-(1-piperazinyl)-2-indancarboxamide, and also addition salts thereof with a pharmaceutically acceptable acid,
- 25 - (1RS)-N-(3,5-difluorobenzyl)-N-methyl-1-(1-piperazinyl)-1-indancarboxamide, its optical isomers, and also addition salts thereof with a pharmaceutically acceptable acid,

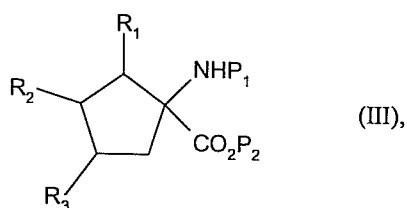
- (1RS)-N-[3-fluoro-5-(trifluoromethyl)benzyl]-N-methyl-1-(1-piperazinyl)-1-indan-carboxamide, its optical isomers, and also addition salts thereof with a pharmaceutically acceptable acid,
- (1RS)-1-[1-(3,5-difluorobenzyloxymethyl)indan-1-yl]piperazine, its optical isomers, and also addition salts thereof with a pharmaceutically acceptable acid,
- N-(3-chloro-5-fluorobenzyl)-N-methyl-2-(1-piperazinyl)-2-indancarboxamide, and also addition salts thereof with a pharmaceutically acceptable acid,
- 1-[(1RS)-1-(3,5-difluorobenzyloxymethyl)indan-1-yl]piperazine, its optical isomers, and also addition salts thereof with a pharmaceutically acceptable acid,
- (1RS)-N-(3,5-difluorobenzyl)-N-methyl-1-(1-piperazinyl)-1-indancarboxamide, its optical isomers, and also addition salts thereof with a pharmaceutically acceptable acid,
- 1-[(1RS)-1-(3,5-difluorobenzyloxymethyl)-5,6-difluoroindan-1-yl]piperazine, its optical isomers, and also addition salts thereof with a pharmaceutically acceptable acid,
- and 1-[(1RS)-1-(3-bromo-5-fluorobenzyloxymethyl)indan-1-yl]piperazine, its optical isomers, and also addition salts thereof with a pharmaceutically acceptable acid.

The invention relates also to a process for the preparation of compounds of formula (I), starting from the compound of formula (II) :



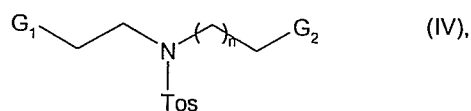
wherein R₁, R₂ and R₃ are as defined for formula (I) and P₁ represents a protecting group for the amine function,

the acid function of which is protected to yield the compound of formula (III) :



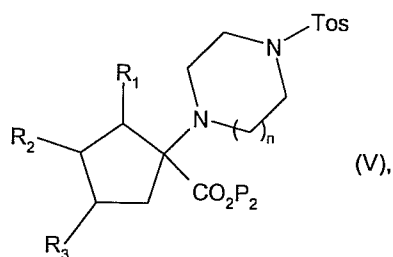
wherein R_1 , R_2 , R_3 and P_1 are as defined hereinbefore and P_2 represents a protecting group for the acid function which is different from P_1 ,

the amine function of which is deprotected before reaction with the compound of
5 formula (IV) :



wherein G_1 and G_2 each represent a halogen atom or a p-toluenesulphonyloxy group, Tos represents a para-toluenesulphonyl group, and n is as defined for formula (I),

to yield the compound of formula (V) :

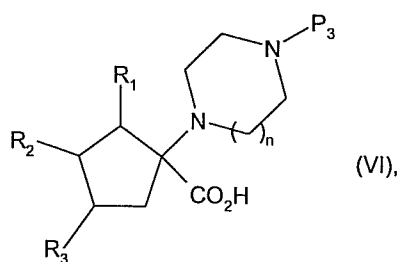


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wherein R_1 , R_2 , R_3 , P_2 , n and Tos are as defined hereinbefore,

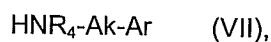
from which the para-toluenesulphonyl group is cleaved,

the acid function is deprotected and then the amine function is protected to yield the compound of formula (VI) :



wherein R_1 , R_2 , R_3 and n are as defined hereinbefore and P_3 represents a protecting group for the amine function,

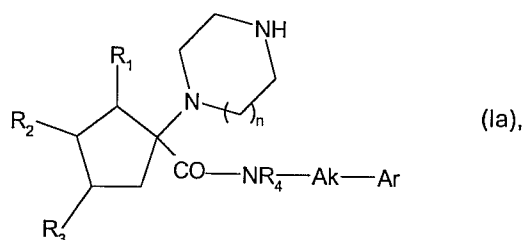
- which compound of formula (VI) is reacted, when it is desired to obtain compounds of formula (I) wherein X represents $-(CO)-NR_4-Ak-$ or $-CH_2-NR_4-Ak-$, with a compound of formula (VII) :



wherein R_4 , Ak and Ar are as defined for formula (I),

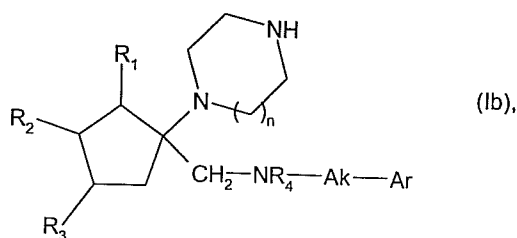
in the presence of one or more coupling agents,

to yield, after deprotection of the ring amine function, compounds of formula (Ia), a particular case of the compounds of formula (I) wherein X represents a group $-(CO)-NR_4-Ak-$:



wherein R_1 , R_2 , R_3 , n , R_4 and Ak are as defined hereinbefore and Ar is as defined for formula (I),

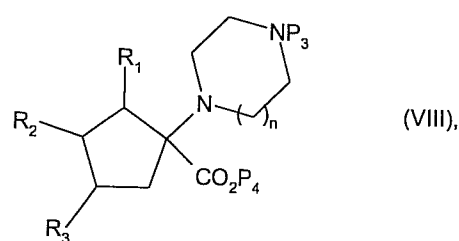
which is reacted, when it is desired to obtain compounds of formula (Ib), a particular case of the compounds of formula (I) wherein X represents a group $-\text{CH}_2\text{-NR}_4\text{-Ak}$, with a reducing agent to yield compounds of formula (Ib) :



5 wherein R_1 , R_2 , R_3 , n , R_4 , Ak and Ar are as defined hereinbefore,

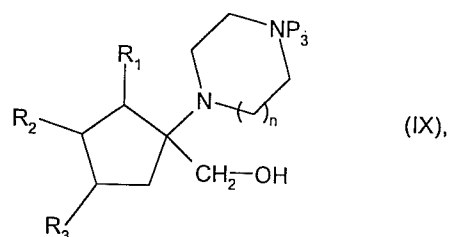
- or which compound of formula (VI) is esterified, when it is desired to obtain compounds of formula (I) wherein X represents a group $-\text{CH}_2\text{-OAK-}$ or $-\text{CH}_2\text{-NR}_4\text{-(CO)-}$,

to yield the compound of formula (VIII) :



10 wherein R_1 , R_2 , R_3 , n and P_3 are as defined hereinbefore and P_4 represents a benzyl or linear or branched $\text{C}_1\text{-C}_6$ alkyl group,

which is placed in the presence of a reducing agent to yield the alcohol of formula (IX) :



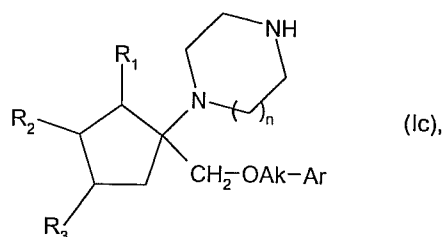
wherein R_1 , R_2 , R_3 , n and P_3 are as defined hereinbefore,

which alcohol of formula (IX) is reacted, when it is desired to obtain compounds of formula (Ic), a particular case of the compounds of formula (I) wherein X represents the group $-\text{CH}_2-\text{O}-\text{Ak}-$, with a compound of formula (X) :



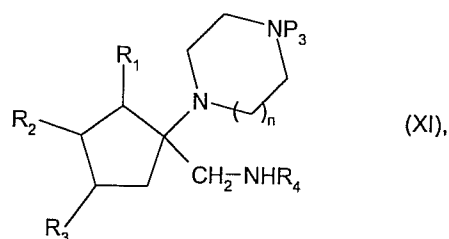
wherein Ak and Ar are as defined for formula (I) and Hal represents a halogen atom,

to yield, after deprotection of the ring amine function, compounds of formula (Ic) :



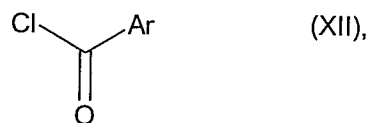
wherein R_1 , R_2 , R_3 , n , Ak and Ar are as defined hereinbefore,

10 or which alcohol of formula (IX) is converted by conventional reactions of organic chemistry into an amine of formula (XI) :



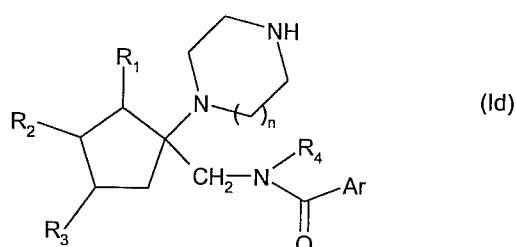
wherein R_1 , R_2 , R_3 , n , R_4 and P_3 are as defined hereinbefore,

which is reacted with a compound of formula (XII) :



wherein Ar is as defined for formula (I),

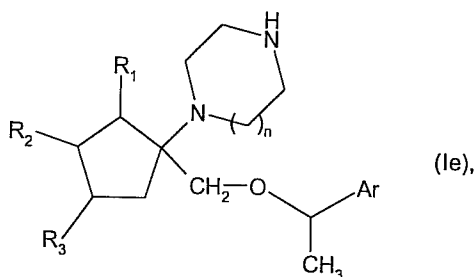
to yield, after deprotection of the ring amine function, compounds of formula (Id), a particular case of the compounds of formula (I) wherein X represents a group
 5 -CH₂-NR₄-(CO)- :



wherein R₁, R₂, R₃, n, R₄ and Ar are as defined hereinbefore,

which compounds of formulae (Ia), (Ib), (Ic) and (Id) are purified according to a conventional purification technique, are separated, when desired, into their optical isomers
 10 and are converted, when desired, into their addition salts with a pharmaceutically acceptable acid.

Compounds of formula (Ie), a particular case of the compounds of formula (I) wherein X represents the group of formula -CH₂O-CH(CH₃)- :



15 wherein R₁, R₂, R₃, n and Ar are as defined hereinbefore,

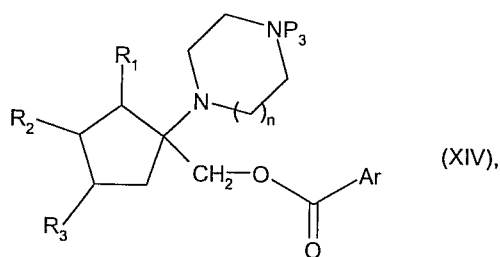
can also be obtained by condensation of the compound of formula (IX) with the compound of formula (XIII) :



wherein Ar is as defined hereinbefore,

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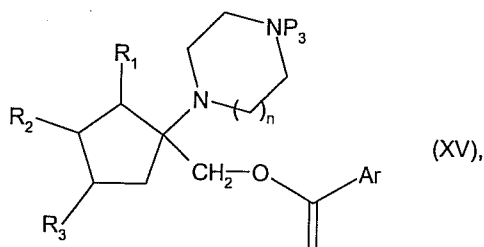
to yield the compound of formula (XIV) :



wherein R_1 , R_2 , R_3 , n , Ar and P_3 are as defined hereinbefore,

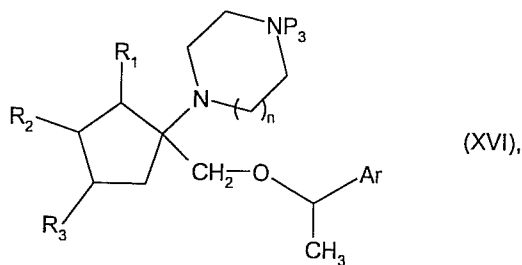
which is reacted with bis(cyclopentadienyl)dimethyltitanium to yield the compound of formula (XV) :

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wherein R_1 , R_2 , R_3 , n , Ar and P_3 are as defined hereinbefore,

which is hydrogenated to yield the compound of formula (XVI) :



15 wherein R_1 , R_2 , R_3 , n , Ar and P_3 are as defined hereinbefore,

the amine function of which is deprotected to yield the compound of formula (Ie),

which is separated, when desired, into its optical isomers and is converted, when desired, into its addition salts with a pharmaceutically acceptable acid.

5 The compounds of the present invention are serotonin reuptake inhibitors and NK₁ antagonists. They are useful as medicaments in the treatment of depressive states, anxiety states, impulsive disorders, aggressive behaviours, drug abuse, obesity and appetite disorders, pain and inflammation, dementias, psychotic states, disturbances of chronobiological rhythms, nausea and gastrointestinal disorders.

10 The present invention relates also to pharmaceutical compositions comprising, as active ingredient, a compound of formula (I), or an addition salt thereof with a pharmaceutically acceptable acid, in combination with one or more pharmaceutically acceptable, inert, non-toxic excipients or carriers.

15 Among the pharmaceutical compositions according to the invention there may be mentioned more especially those that are suitable for oral, parenteral (intravenous, intramuscular or subcutaneous), per- or trans-cutaneous, nasal, rectal, perlingual, ocular or respiratory administration, and especially tablets or dragées, sublingual tablets, gelatin capsules, capsules, suppositories, creams, ointments, dermal gels, injectable or drinkable preparations, aerosols, eye drops and nose drops.

20 The useful dosage varies according to the age and weight of the patient, the administration route, the nature and severity of the disorder, and the administration of any associated treatments and ranges from 0.5 to 500 mg per day in one or more administrations.

The Examples that follow illustrate the invention. The starting materials used are known products or are prepared according to known procedures. The various Preparations yield synthesis intermediates that are of use in preparation of the compounds of the invention.

25 The structures of the compounds described in the Examples were determined according to customary spectrophotometric techniques (infra-red, nuclear magnetic resonance, mass spectrometry).

A compound of configuration (1 α) is understood to be a compound selected from the compounds of absolute configurations (1R) and (1S), it being understood that when the (1 α) compound represents the compound of configuration (1R) the (1 β) compound represents the other enantiomer.

- 5 A compound of configuration (1 α') is understood to be a compound selected from the compounds of absolute configurations (1R) and (1S), it being understood that when the (1 α') compound represents the compound configuration (1R) the (1 β') represents the other enantiomer.

10 A compound of configuration (1RS) is understood to be a racemic mixture of the 2 enantiomers of absolute configurations (1R) and (1S).

PREPARATION 1 : (1RS)-1-[4-(tert-butyloxycarbonyl)-1-piperazinyl]-1-indan-carboxylic acid.

Step A : Benzyl (1RS)-1-[(tert-butyloxycarbonyl)amino]-1-indancarboxylate.

15 To 0.140 mol of 1-[(tert-butyloxycarbonyl)amino]-1-indancarboxylic acid there are added 750 ml of dimethylformamide and then 0.147 mol of caesium carbonate. Stirring is then carried out for 2 hours 30 minutes at ambient temperature and there is then poured in, dropwise, over 1/2 hour, 0.145 mol of benzyl bromide dissolved in 150 ml of dimethylformamide, and stirring is carried out for 20 hours at ambient temperature.

20 The mineral salts are filtered off and the solvent is evaporated off. The residue is redissolved in ethyl acetate and washed with water. The organic phase is dried and then evaporated to yield the expected product.

IR ν : 3284 nm^{-1} -NH
1735-1672 cm^{-1} >C=O

Step B : Benzyl (1RS)-1-amino-1-indancarboxylate hydrochloride.

0.471 mol of the compound obtained in the step above are added to 2 litres of ethyl acetate. A stream of hydrogen chloride gas is passed through for 1 hour 15 minutes, with stirring, and then stirring is continued for 20 hours at ambient temperature. The expected product is
5 obtained by evaporation of the ethyl acetate.

IR ν : 1741 cm^{-1} $>\text{C}=\text{O}$

Step C : Benzyl (1RS)-1-[4-(para-toluenesulphonyl)-1-piperazinyl]-1-indancarboxylate.

To 0.235 mol of the compound obtained in the step above there are added 750 ml of dimethylformamide, 750 ml of diisopropylethylamine and 0.235 mol of *N,N*-bis(2-
10 chloroethyl)para-toluenesulphonamide. Refluxing is carried out for 48 hours and then the solvents are evaporated off. The residue is dissolved in ethyl acetate and washed with water. The organic phase is dried and evaporated. The residue is purified by chromatography on silica gel, using a 98/2 methylene chloride/ethyl acetate mixture as eluant, to yield the expected product.

15 IR ν $\text{C}=\text{O}$ 1728 cm^{-1}
 asymmetric SO_2 1348 cm^{-1}
 symmetric SO_2 1164 cm^{-1}

Step D : (1RS)-1-[4-(Para-toluenesulphonyl)-1-piperazinyl]-1-indancarboxylic acid.

To 0.181 mol of the compound obtained in the step above there are added 620 ml of
20 dioxane, and then 620 ml of 1N sodium hydroxide solution and 360 ml of water. Refluxing is carried out for 20 hours and then the dioxane is evaporated off. Neutralisation is carried out by adding 620 ml of 1N hydrochloric acid, and then extraction with methylene chloride is carried out. The organic phase is dried and evaporated. The residue is crystallised from ethyl ether and then filtered off to yield the expected product.

25 IR ν OH 1800-3000 cm^{-1}
 $\text{C}=\text{O}$ 1706 cm^{-1}
 $\text{C}=\text{O}$ 1596 cm^{-1}

SO₂ 1348-1165 cm⁻¹

CH... 772-732 cm⁻¹

Step E : (1RS)-1-(1-Piperazinyl)-1-indancarboxylic acid dihydrobromide.

To 100 ml of a 30 % solution of hydrobromic acid in acetic acid there are added 40 ml of acetic acid, 12.5 mmol of naphthalene and 12.5 mmol of the compound obtained in the step above. Refluxing is carried out for 1 hour, followed by concentration. The residue is taken up in water, and the aqueous phase is washed with ethyl acetate and then evaporated. The solid residue is washed with acetonitrile and then dried to yield the expected product.

IR ν C=O 1740 cm⁻¹

10 **Step F : (1RS)-1-[4-(tert-Butyloxycarbonyl)-1-piperazinyl]-1-indancarboxylic acid.**

To 9.26 mmol of the compound obtained in the step above there are added 40 ml of dioxane and 37 ml of 1N sodium hydroxide solution. To the resulting solution there is added, dropwise and at ambient temperature, a solution of 10.2 mmol of di-tert-butyl dicarbonate in 100 ml of dioxane. Stirring is carried out for 5 hours and then the dioxane is evaporated off. The pH is brought to 4-5 using 1N hydrochloric acid, and saturation with sodium chloride and extraction with ethyl acetate are carried out. The organic phase is dried and evaporated to yield the expected product.

IR ν OH 2200-2300 cm⁻¹

C=O 1624-1731 cm⁻¹

20 **PREPARATION 2 : 2-[4-(tert-Butyloxycarbonyl)-1-piperazinyl]-2-indancarboxylic acid.**

The expected product is obtained according to the procedure described in Preparation 1, replacing, in Step A, the 1-[(tert-butyloxycarbonyl)amino]-1-indancarboxylic acid by 2-[(tert-butyloxycarbonyl)amino]-2-indancarboxylic acid and the benzyl bromide by 1-bromoethane.

EXAMPLE 1 : 1-[(1RS)-1-(3,5-Dibromobenzyloxymethyl)indan-1-yl]piperazine dihydrochloride.

Step A : Benzyl (1RS)-1-[4-(tert-butyloxycarbonyl)-1-piperazinyl]-1-indancarboxylate.

To 63.5 mmol of the compound of Preparation 1 there are added 550 ml of dimethyl-
5 formamide and 66 mmol of caesium carbonate; stirring is carried out for 2 hours at
ambient temperature and there is then added, dropwise over ½ hour, a solution of
65.7 mmol of benzyl bromide in 50 ml of dimethylformamide. Stirring is continued for
20 hours at ambient temperature and the solvent is then evaporated off. The residue is
taken up in ethyl acetate; the organic phase is washed with water, dried and evaporated to
10 yield the expected product in the form of a colourless oil.

Step B : (1RS)-1-[4-(tert-Butyloxycarbonyl)-1-piperazinyl]-1-hydroxymethylindan.

To 250 ml of tetrahydrofuran and 63.2 mmol of lithium aluminium hydride there is added,
over 1 hour 15 minutes, whilst maintaining the temperature of the reaction mixture below
20°C, a solution of 57.5 mmol of the compound obtained in the step above in 550 ml of
15 tetrahydrofuran. After addition, stirring is continued for 1/2 hour at 20°C; hydrolysis is
then carried out with 50 ml of isopropanol, followed by 50 ml of saturated sodium chloride
solution. Filtration is carried out and the filtrate is evaporated; the residue is redissolved in
ethyl acetate and washed with water. The dried and evaporated organic phase yields the
expected product.

20 IR v OH 3440 cm⁻¹
 C=O 1691 cm⁻¹

Step C : 4-(tert-Butyloxycarbonyl)-1-[(1RS)-1-(3,5-dibromobenzyloxymethyl)indan-1-yl]piperazine.

To 30 ml of dimethylformamide and 5.4 mmol of sodium hydride 95 % there is added,
25 over 10 minutes, a solution of 3.6 mmol of the compound obtained in the step above in
50 ml of dimethylformamide. Heating at 50-60°C is carried out for 1/2 hour and the

temperature is then allowed to return to ambient temperature. 0.36 mmol of tetrabutylammonium iodide is then added and then, over 10 minutes, a solution of 5.4 mmol of 3,5-dibromobenzyl bromide in 30 ml of dimethylformamide. Stirring is continued for 20 hours at ambient temperature.

- 5 The solvent is evaporated off, and the residue is then redissolved in ethyl acetate. Washing with water and with sodium chloride solution is carried out. The organic phase is dried and evaporated. The product is purified by chromatography on silica gel (eluant: CH₂Cl₂/AcOEt 90/10) to yield the expected product.

IR ν C=O 1688 cm⁻¹

10 **Step D :** *1-[(1RS)-1-(3,5-Dibromobenzyloxymethyl)indan-1-yl]piperazine dihydrochloride.*

- To 2.75 mmol of the compound obtained in the step above dissolved in 30 ml of ethyl acetate there are added 15 ml of a 1N solution of hydrochloric acid in dioxane. After stirring for 20 hours at ambient temperature, the precipitate obtained is filtered off, washed
15 with ethyl acetate and then redissolved in water. After evaporation and drying, the expected product is obtained.

Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated	45.60	4.74	5.06	12.82
20 Found	45.95	4.80	5.12	13.16

EXAMPLE 2 : *1-[(1RS)-1-(3,5-Dimethylbenzyloxymethyl)indan-1-yl]piperazine dihydrochloride.*

The expected product is obtained according to the procedure described in Example 1, replacing the 3,5-dibromobenzyl bromide in Step C by 3,5-dimethylbenzyl bromide.

25 Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated	65.24	7.62	6.62	16.75
Found	65.71	7.49	6.53	16.46

EXAMPLE 3 : 1-[2-(3,5-Dimethylbenzyloxymethyl)indan-2-yl]piperazine dihydrochloride.

Step A : 2-[4-(*tert*-Butyloxycarbonyl)-1-piperazinyl]-2-hydroxymethylindan.

The expected product is obtained according to the procedure described in Steps A and B of Example 1, replacing the compound of Preparation 1 in Step A by the compound of Preparation 2.

Step B : 1-[2-(3,5-Dimethylbenzyloxymethyl)indan-2-yl]piperazine dihydrochloride.

The expected product is obtained according to the procedure described in Steps C and D of Example 1, starting from the compound obtained in Step A above and 3,5-dimethylbenzyl bromide.

Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated	65.24	7.62	6.62	16.75
15 Found	65.92	7.52	6.64	16.91

EXAMPLE 4 : (1RS)-N-(3,5-Dibromobenzyl)-1-(1-piperazinyl)-1-indancarboxamide dihydrochloride.

Step A : (1RS)-N-(3,5-Dibromobenzyl)-1-[4-(*tert*-butyloxycarbonyl)-1-piperazinyl]-1-indancarboxamide.

To 2 mmol of the compound of Preparation 1 there are added 50 ml of dimethylformamide, 2 mmol of 3,5-dibromobenzylamine, 2 mmol of 1-hydroxybenzotriazole and 2 mmol of dicyclohexylcarbodiimide. Stirring for 20 hours at ambient temperature and then evaporation are carried out. The residue is then taken up in ethyl acetate. The dicyclohexylurea formed is removed by filtration; the organic phase is then washed with saturated sodium bicarbonate solution, followed by saturated sodium chloride solution.

After drying, evaporation and purification by chromatography on silica gel (eluant: CH₂Cl₂/AcOEt 95/5), the expected product is obtained.

IR ν NH 3347 cm⁻¹
 C=O 1668 cm⁻¹

5 **Step B : (1RS)-N-(3,5-Dibromobenzyl)-1-(1-piperazinyl)-1-indancarboxamide dihydrochloride.**

To 1.6 mmol of the compound obtained in the step above dissolved in 30 ml of ethyl acetate there are added 15 ml of a 4N solution of hydrochloric acid in dioxane, and the reaction mixture is then stirred for 20 hours at ambient temperature. The precipitate
 10 obtained is filtered off and then redissolved in 5 ml of water.

After evaporating off the water and drying, the expected product is obtained.

Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated	44.55	4.45	7.42	12.52
15 Found	44.92	4.61	7.44	11.54

EXAMPLE 5 : N-[3,5-Bis(trifluoromethyl)benzyl]-2-(1-piperazinyl)-2-indan-carboxamide dihydrochloride.

The expected product is obtained according to the procedure of Example 4, starting from the compound of Preparation 2 and 3,5-bis(trifluoromethyl)benzylamine.

20 Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated	51.44	4.63	7.72	11.88
Found	51.42	4.73	7.71	10.82

EXAMPLE 6 : [3,5-Bis(trifluoromethyl)phenyl]-N-{[2-(1-piperazinyl)indan-2-yl]-methyl}methanamine trihydrochloride.

To 3 mmol of the compound of Example 5 dissolved in 80 ml of tetrahydrofuran there are added, under nitrogen and over 20 minutes, 30 mmol of a 2N solution of borane dimethyl sulphide in tetrahydrofuran. The reaction mixture is then refluxed for 18 hours and subsequently returned to ambient temperature. 50 ml of 4N hydrochloric acid are then added dropwise and refluxing is subsequently carried out again for 20 hours, before evaporating off the solvents, making alkaline with sodium hydroxide solution and extracting the reaction mixture with ethyl acetate. The organic phase is washed with saturated sodium chloride solution, dried and then evaporated. After purification by chromatography, conversion into a salt using hydrochloric acid and evaporation, the expected product is obtained after drying.

Elemental microanalysis :

	% C	% H	% N	% Cl
15 <i>Calculated</i>	49.69	5.02	7.56	17.22
<i>Found</i>	49.77	5.01	7.38	17.37

EXAMPLE 7 : N-Benzyl-N-methyl-2-(1-piperazinyl)-2-indancarboxamide dihydrochloride.

The expected product is obtained according to the procedure of Example 4, starting from the compound of Preparation 2 and N-benzyl-N-methylamine.

Elemental microanalysis :

	% C	% H	% N	% Cl
<i>Calculated</i>	63.66	6.99	9.95	15.37
<i>Found</i>	63.64	6.71	10.24	15.86

EXAMPLE 8 : 1-[(1 α)-1-(3,5-Dimethylbenzyloxymethyl)indan-1-yl]piperazine dihydrochloride.

The expected product is obtained by separation of the compound of Example 2 on a chiral HPLC column.

5 **EXAMPLE 9 : 1-[(1 β)-1-(3,5-Dimethylbenzyloxymethyl)indan-1-yl]piperazine dihydrochloride.**

The expected product is the second of the enantiomers obtained by separation of the compound of Example 2 on a chiral HPLC column.

10 **EXAMPLE 10 : (1RS)-N-[3,5-Bis(trifluoromethyl)benzyl]-1-(1-piperazinyl)-1-indan-carboxamide dihydrochloride.**

The expected product is obtained according to the procedure of Example 4, replacing the 3,5-dibromobenzylamine in Step A by 3,5-bis(trifluoromethyl)benzylamine.

Elemental microanalysis :

	% C	% H	% N	% Cl
15 <i>Calculated</i>	50.75	4.63	7.72	13.03
<i>Found</i>	51.08	4.86	7.79	13.45

EXAMPLE 11 : (1RS)-N-Benzyl-N-methyl-1-(1-piperazinyl)-1-indancarboxamide dihydrochloride.

20 The expected product is obtained according to the procedure of Example 4, starting from the compound of Preparation 1 and N-methylbenzylamine.

Elemental microanalysis :

	% C	% H	% N	% Cl
<i>Calculated</i>	62.56	6.92	9.95	16.79
<i>Found</i>	62.27	6.86	9.73	17.91

**EXAMPLE 12 : 1-[2-(Biphenyl-4-ylmethoxymethyl)indan-2-yl]piperazine
dihydrochloride.**

The expected product is obtained according to the procedure of Example 1, starting from the compound of Preparation 2 and biphenyl-4-ylmethyl bromide.

5 Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated	68.78	6.84	5.94	15.04
Found	69.38	7.09	5.99	15.03

10 **EXAMPLE 13 : 1-[2-(3,5-Dimethoxybenzyloxymethyl)indan-2-yl]piperazine
dihydrochloride.**

The expected product is obtained according to the procedure of Example 1, starting from the compound of Preparation 2 and 3,5-dimethoxybenzyl bromide.

Elemental microanalysis :

15

	% C	% H	% N	% Cl
Calculated	60.66	7.08	6.15	15.57
Found	60.96	7.30	6.07	15.71

**EXAMPLE 14 : 1-[2-(3,5-Dichlorobenzyloxymethyl)indan-2-yl]piperazine
dihydrochloride.**

20 The expected product is obtained according to the procedure of Example 1, starting from the compound of Preparation 2 and 3,5-dichlorobenzyl bromide.

Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated	54.33	5.64	6.03	30.55
Found	54.08	5.31	6.12	30.15

EXAMPLE 15 : 1-[2-(3,4-Dichlorobenzyloxymethyl)indan-2-yl]piperazine dihydrochloride.

The expected product is obtained according to the procedure of Example 1, starting from the compound of Preparation 2 and 3,4-dichlorobenzyl bromide.

5 **Elemental microanalysis :**

	% C	% H	% N	% Cl
Calculated	54.33	5.64	6.03	30.55
Found	53.99	5.46	6.03	29.99

10 **EXAMPLE 16 : 1-[2-(3,5-Dibromobenzyloxymethyl)indan-2-yl]piperazine dihydrochloride.**

The expected product is obtained according to the procedure of Example 1, starting from the compound of Preparation 2 and 3,5-dibromobenzyl bromide.

Elemental microanalysis :

15

	% C	% H	% N	% Cl
Calculated	45.60	4.74	5.06	12.82
Found	45.48	4.83	5.03	12.79

EXAMPLE 17 : 1-[2-[3,5-Bis(trifluoromethyl)benzyloxymethyl]indan-2-yl]-piperazine dihydrochloride.

20 The expected product is obtained according to the procedure of Example 1, starting from the compound of Preparation 2 and 3,5-bis(trifluoromethyl)benzyl bromide.

Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated	51.99	4.93	5.27	13.34
Found	52.48	5.05	5.34	13.12

**EXAMPLE 18 : (1RS)-N-Benzyl-1-(1-piperazinyl)-1-indancarboxamide
dihydrochloride.**

The expected product is obtained according to the procedure of Example 4, replacing the 3,5-dibromobenzylamine in Step A by benzylamine.

5 Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated	61.77	6.66	10.29	17.36
Found	61.63	7.06	10.24	17.38

10 **EXAMPLE 19 : 1-[2-(Naphth-2-ylmethoxymethyl)indan-2-yl]piperazine
dihydrochloride.**

The expected product is obtained according to the procedure of Example 1, starting from the compound of Preparation 2 and naphth-2-ylmethyl bromide.

Elemental microanalysis :

	% C	% H	% N	% Cl
15 Calculated	67.41	6.79	6.29	15.92
Found	66.99	7.18	6.29	15.69

**EXAMPLE 20 : (1RS)-N-[3,5-Bis(trifluoromethyl)benzyl]-N-methyl-1-(1-
piperazinyl)-1-indancarboxamide dihydrochloride.**

20 The expected product is obtained according to the procedure of Example 4, starting from the compound of Preparation 1 and N-methyl-3,5-bis(trifluoromethyl)benzylamine.

Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated	51.62	4.87	7.53	12.70
Found	51.40	4.85	7.48	11.77

EXAMPLE 21 : N-(3,5-Dichlorobenzyl)-2-(1-piperazinyl)-2-indancarboxamide dihydrochloride.

The expected product is obtained according to the procedure of Example 4, starting from the compound of Preparation 2 and 3,5-dichlorobenzylamine.

5 **Elemental microanalysis :**

	% C	% H	% N	% Cl
<i>Calculated</i>	52.85	5.28	8.80	29.71
<i>Found</i>	53.30	5.34	9.00	28.89

10 **EXAMPLE 22 : (1 α)-N-[(1S)-1-Phenethyl]-1-(1-piperazinyl)-1-indancarboxamide dihydrochloride.**

Step A : (1RS)-N-[(1S)-1-Phenethyl]-1-[4-(tert-butyloxycarbonyl)-1-piperazinyl]-1-indancarboxamide.

The expected product is obtained according to the procedure described in Step A of Example 4, starting from the compound of Preparation 1 and (1S)-1-phenethylamine.

15 **Step B :** (1 α)-N-[(1S)-1-Phenethyl]-1-[4-(tert-butyloxycarbonyl)-1-piperazinyl]-1-indancarboxamide.

The expected product is obtained by separation, by means of chromatography on silica, of the diastereoisomeric mixture obtained in Step A.

20 **Step C :** (1 α)-N-[(1S)-1-Phenethyl]-1-(1-piperazinyl)-1-indancarboxamide dihydrochloride.

Starting from the compound obtained in Step B, the expected product is obtained according to the procedure described in Step B of Example 4.

Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated	62.56	6.92	9.95	16.79
Found	62.69	7.21	9.85	16.54

5 **EXAMPLE 23 : (1 β)-N-[(1S)-1-Phenethyl]-1-(1-piperazinyl)-1-indancarboxamide dihydrochloride.**

The expected product is obtained according to the procedure described in Step B of Example 4, starting from the second of the diastereoisomers separated in Step B of Example 22.

10 Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated	62.56	6.92	9.95	16.79
Found	62.57	7.08	9.90	16.32

15 **EXAMPLE 24 : (1 α)-N-[(1R)-1-Phenethyl]-1-(1-piperazinyl)-1-indancarboxamide dihydrochloride.**

Step A : (1RS)-N-[(1R)-1-Phenethyl]-1-[4-(tert-butyloxycarbonyl)-1-piperazinyl]-1-indancarboxamide.

The expected product is obtained according to the procedure described in Step A of Example 4, starting from the compound of Preparation 1 and (1R)-1-phenethylamine.

20 **Step B : (1 α)-N-[(1R)-1-Phenethyl]-1-[4-(tert-butyloxycarbonyl)-1-piperazinyl]-1-indancarboxamide.**

The expected product is obtained by separation, by means of chromatography on silica, of the diastereoisomeric mixture obtained in Step A.

Step C: (1 α)-N-[(1R)-1-Phenethyl]-1-(1-piperazinyl)-1-indancarboxamide dihydrochloride.

The expected product is obtained according to the procedure described in Step B of Example 4, starting from the compound obtained in Step B.

5 **Elemental microanalysis** :

	% C	% H	% N	% Cl
Calculated	62.56	6.92	9.95	16.79
Found	62.69	7.21	9.85	16.54

10 **EXAMPLE 25 : (1 β)-N-[(1R)-1-Phenethyl]-1-(1-piperazinyl)-1-indancarboxamide dihydrochloride.**

The expected product is obtained according to the procedure described in Step B of Example 4, starting from the second of the diastereoisomers separated in Step B of Example 24.

Elemental microanalysis :

15

	% C	% H	% N	% Cl
Calculated	62.56	6.92	9.95	16.79
Found	62.71	7.25	9.92	16.27

EXAMPLE 26 : (1RS)-N-(2-Phenethyl)-1-(1-piperazinyl)-1-indancarboxamide dihydrochloride.

20 The expected product is obtained according to the procedure of Example 4, replacing the 3,5-dibromobenzylamine in Step A by 2-phenethylamine.

Elemental microanalysis :

25

	% C	% H	% N	% Cl
Calculated	62.56	6.92	9.95	16.79
Found	62.34	7.17	9.83	16.65

EXAMPLE 27 : (1RS)-N-(3,4-Dichlorobenzyl)-1-(1-piperazinyl)-1-indancarboxamide dihydrochloride.

The expected product is obtained according to the procedure of Example 4, replacing the 3,5-dibromobenzylamine in Step A by 3,4-dichlorobenzylamine.

5 **Elemental microanalysis :**

	% C	% H	% N	% Cl
<i>Calculated</i>	52.85	5.28	8.80	29.71
<i>Found</i>	53.26	5.52	8.83	28.98

10 **EXAMPLE 28 : 2-(1-Piperazinyl)-N-(3-pyridylmethyl)-2-indancarboxamide trihydrochloride.**

The expected product is obtained according to the procedure of Example 4, starting from the compound of Preparation 2 and 3-pyridylmethylamine.

Elemental microanalysis :

	% C	% H	% N	% Cl
15 <i>Calculated</i>	53.88	6.10	12.57	23.86
<i>Found</i>	53.94	6.20	12.30	23.76

EXAMPLE 29 : 2-(1-Piperazinyl)-N-(2-thienylmethyl)-2-indancarboxamide dihydrochloride.

20 The expected product is obtained according to the procedure of Example 4, starting from the compound of Preparation 2 and 2-thienylmethylamine.

Elemental microanalysis :

	% C	% H	% N	% S	% Cl
<i>Calculated</i>	55.07	6.08	10.14	7.74	17.11
<i>Found</i>	54.96	6.07	10.75	7.53	16.56

EXAMPLE 30 : 2-(1-Piperazinyl)-N-[4-(trifluoromethyl)benzyl]-2-indan-carboxamide dihydrochloride.

The expected product is obtained according to the procedure of Example 4, starting from the compound of Preparation 2 and 4-(trifluoromethyl)benzylamine.

5 **Elemental microanalysis** :

	% C	% H	% N	% Cl
Calculated	55.47	5.50	8.82	14.88
Found	55.13	5.43	8.93	14.98

10 **EXAMPLE 31 : N-(2-Phenethyl)-2-(1-piperazinyl)-2-indancarboxamide dihydrochloride.**

The expected product is obtained according to the procedure of Example 4, starting from the compound of Preparation 2 and 2-phenethylamine.

Elemental microanalysis :

	% C	% H	% N	% Cl
15 Calculated	62.56	6.92	9.95	16.79
Found	63.42	6.91	10.06	16.63

EXAMPLE 32 : N-(1-Naphthylmethyl)-2-(1-piperazinyl)-2-indancarboxamide dihydrochloride.

20 The expected product is obtained according to the procedure of Example 4, starting from the compound of Preparation 2 and 1-naphthylmethylamine.

Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated	65.50	6.38	9.17	15.47
Found	65.86	6.52	9.83	14.72

EXAMPLE 33 : (1RS)-N-(2,4-Dichlorobenzyl)-1-(1-piperazinyl)-1-indancarboxamide dihydrochloride.

The expected product is obtained according to the procedure of Example 4, replacing the 3,5-dibromobenzylamine in Step A by 2,4-dichlorobenzylamine.

5 Elemental microanalysis :

	% C	% H	% N	% Cl
<i>Calculated</i>	52.85	5.28	8.80	29.71
<i>Found</i>	53.69	5.31	8.84	30.27

10 **EXAMPLE 34 : (1RS)-1-(1-Piperazinyl)-N-(3-thienylmethyl)-1-indancarboxamide dihydrochloride.**

The expected product is obtained according to the procedure of Example 4, replacing the 3,5-dibromobenzylamine in Step A by 3-thienylmethylamine.

Elemental microanalysis :

	% C	% H	% N	% S	% Cl
15 <i>Calculated</i>	55.07	6.08	10.14	7.74	17.11
<i>Found</i>	55.68	6.33	10.28	7.62	17.79

EXAMPLE 35 : (1RS)-1-(1-Piperazinyl)-N-(2-thienylmethyl)-1-indancarboxamide dihydrochloride.

20 The expected product is obtained according to the procedure of Example 4, replacing the 3,5-dibromobenzylamine in Step A by 2-thienylmethylamine.

Elemental microanalysis :

	% C	% H	% N	% S	% Cl
<i>Calculated</i>	55.07	6.08	10.14	7.74	17.11
<i>Found</i>	55.73	6.35	10.30	7.76	17.49

EXAMPLE 36 : (1RS)-N-(3,5-Dichlorobenzyl)-1-(1-piperazinyl)-1-indancarboxamide dihydrochloride.

The expected product is obtained according to the procedure of Example 4, replacing the 3,5-dibromobenzylamine in Step A by 3,5-dichlorobenzylamine.

5 **Elemental microanalysis :**

	% C	% H	% N	% Cl
<i>Calculated</i>	66.94	6.45	8.67	14.64
<i>Found</i>	66.26	6.41	8.57	14.09

10 **EXAMPLE 37 : N-(Biphenyl-4-ylmethyl)-2-(1-piperazinyl)-2-indancarboxamide dihydrochloride.**

The expected product is obtained according to the procedure of Example 4, starting from the compound of Preparation 2 and biphenyl-4-ylmethylamine.

Elemental microanalysis :

15

	% C	% H	% N	% Cl
<i>Calculated</i>	66.94	6.45	8.67	14.64
<i>Found</i>	66.26	6.41	8.57	14.09

EXAMPLE 38 : N-(3,5-Dimethylbenzyl)-2-(1-piperazinyl)-2-indancarboxamide dihydrochloride.

20 The expected product is obtained according to the procedure of Example 4, starting from the compound of Preparation 2 and 3,5-dimethylbenzylamine.

Elemental microanalysis :

	% C	% H	% N	% Cl
<i>Calculated</i>	63.30	7.16	9.63	16.25
<i>Found</i>	63.50	7.28	10.23	16.19

EXAMPLE 39 : N-[(1R)-1-Phenethyl]-2-(1-piperazinyl)-2-indancarboxamide dihydrochloride.

The expected product is obtained according to the procedure of Example 4, starting from the compound of Preparation 2 and (1R)-1-phenethylamine.

5 Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated	62.56	6.92	9.95	16.79
Found	62.49	7.03	10.44	16.97

10 **EXAMPLE 40 : N-[(1S)-1-Phenethyl]-2-(1-piperazinyl)-2-indancarboxamide dihydrochloride.**

The expected product is obtained according to the procedure of Example 4, starting from the compound of Preparation 2 and (1S)-1-phenethylamine.

Elemental microanalysis :

	% C	% H	% N	% Cl
15 Calculated	62.56	6.92	9.95	16.79
Found	62.83	7.10	10.34	16.19

EXAMPLE 41 : (1RS)-N-(2-Methoxybenzyl)-1-(1-piperazinyl)-1-indancarboxamide dihydrochloride.

20 The expected product is obtained according to the procedure of Example 4, starting from the compound of Preparation 1 and 2-methoxybenzylamine.

Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated	60.27	6.67	9.58	16.17
Found	59.71	6.91	9.41	15.88

EXAMPLE 42 : (1*RS*)-N-(3,5-Dimethylbenzyl)-1-(1-piperazinyl)-1-indancarboxamide dihydrochloride.

The expected product is obtained according to the procedure of Example 4, starting from the compound of Preparation 1 and 3,5-dimethylbenzylamine.

5 **Elemental microanalysis :**

	% C	% H	% N	% Cl
<i>Calculated</i>	63.30	7.16	9.63	16.25
<i>Found</i>	62.89	7.53	9.44	16.06

10 **EXAMPLE 43 : 2-(1-Piperazinyl)-N-(3-thienylmethyl)-2-indancarboxamide dihydrochloride.**

The expected product is obtained according to the procedure of Example 4, starting from the compound of Preparation 2 and 3-thienylmethylamine.

Elemental microanalysis :

15

	% C	% H	% N	% S	% Cl
<i>Calculated</i>	55.07	6.08	10.14	7.74	17.11
<i>Found</i>	55.34	6.53	9.93	7.96	17.70

EXAMPLE 44 : N-(3,5-Difluorobenzyl)-2-(1-piperazinyl)-2-indancarboxamide dihydrochloride.

20 The expected product is obtained according to the procedure of Example 4, starting from the compound of Preparation 2 and 3,5-difluorobenzylamine.

Elemental microanalysis :

	% C	% H	% N	% Cl
<i>Calculated</i>	56.76	5.67	9.46	15.96
<i>Found</i>	57.26	5.74	9.45	15.41

EXAMPLE 45 : N-(4-Methoxybenzyl)-2-(1-piperazinyl)-2-indancarboxamide dihydrochloride.

The expected product is obtained according to the procedure of Example 4, starting from the compound of Preparation 2 and 4-methoxybenzylamine.

5 Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated	60.27	6.67	9.58	16.17
Found	59.45	6.79	10.41	16.36

10 **EXAMPLE 46 : N-(4-Bromobenzyl)-2-(1-piperazinyl)-2-indancarboxamide dihydrochloride.**

The expected product is obtained according to the procedure of Example 4, starting from the compound of Preparation 2 and 4-bromobenzylamine.

Elemental microanalysis :

	% C	% H	% N	% Cl
15 Calculated	51.76	5.38	8.62	14.55
Found	52.30	5.36	8.90	13.95

EXAMPLE 47 : N-(3-Bromobenzyl)-2-(1-piperazinyl)-2-indancarboxamide dihydrochloride.

20 The expected product is obtained according to the procedure of Example 4, starting from the compound of Preparation 2 and 3-bromobenzylamine.

Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated	51.76	5.38	8.62	14.55
Found	52.08	5.60	8.84	14.43

EXAMPLE 48 : N-(4-Chlorobenzyl)-2-(1-piperazinyl)-2-indancarboxamide dihydrochloride.

The expected product is obtained according to the procedure of Example 4, starting from the compound of Preparation 2 and 4-chlorobenzylamine.

5 Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated	56.96	5.92	9.49	24.02
Found	57.22	6.03	9.46	24.07

EXAMPLE 49 : N-Benzyl-2-(1-piperazinyl)-2-indancarboxamide dihydrochloride.

- 10 The expected product is obtained according to the procedure of Example 4, starting from the compound of Preparation 2 and benzylamine.

Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated	61.77	6.66	10.29	17.36
15 Found	61.09	6.74	10.24	16.80

EXAMPLE 50 : (1RS)-N-(3,5-Dibromobenzyl)-N-methyl-1-(1-piperazinyl)-1-indan-carboxamide dihydrochloride.

The expected product is obtained according to the procedure of Example 4, starting from the compound of Preparation 1 and N-methyl-3,5-dibromobenzylamine.

20 Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated	45.54	4.69	7.24	12.22
Found	45.11	4.73	7.14	12.96

EXAMPLE 51 : (1RS)-1-[1-(3,5-Bis(trifluoromethyl)benzyloxymethyl)indan-1-yl]-piperazine dihydrochloride.

The expected product is obtained according to the procedure of Example 1, starting from the compound of Preparation 1 and 3,5-bis(trifluoromethyl)benzyl bromide.

5 Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated	51.99	4.93	5.27	13.34
Found	52.31	4.77	5.28	13.54

10 **EXAMPLE 52 : 1-[(1RS)-1-(3,5-Dichlorobenzyloxymethyl)indan-1-yl]piperazine dihydrochloride.**

The expected product is obtained according to the procedure of Example 1, starting from the compound of Preparation 1 and 3,5-dichlorobenzyl bromide.

Elemental microanalysis :

	% C	% H	% N	% Cl
15 Calculated	54.33	5.64	6.03	30.55
Found	54.97	5.81	6.00	29.88

EXAMPLE 53 : 1-[(1RS)-1-(3-(Trifluoromethyl)benzyloxymethyl)indan-1-yl]-piperazine dihydrochloride.

20 The expected product is obtained according to the procedure of Example 1, starting from the compound of Preparation 1 and 3-(trifluoromethyl)benzyl bromide.

Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated	57.03	5.87	6.05	15.30
Found	56.75	6.33	5.81	15.16

EXAMPLE 54 : 2-(1-Piperazinyl)-N-(2-pyridylmethyl)-2-indancarboxamide trihydrochloride.

The expected product is obtained according to the procedure of Example 4, starting from the compound of Preparation 2 and 2-pyridylmethylanine.

5 Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated	53.88	6.10	12.57	23.86
Found	52.54	6.13	12.00	23.85

10 **EXAMPLE 55 : 2-(1-Piperazinyl)-N-(3-pyridylmethyl)-2-indancarboxamide trihydrochloride.**

The expected product is obtained according to the procedure of Example 4, starting from the compound of Preparation 2 and 3-pyridylmethylanine.

Elemental microanalysis :

15

	% C	% H	% N	% Cl
Calculated	53.88	6.10	12.57	23.86
Found	53.92	5.94	12.43	24.62

EXAMPLE 56 : N-(2-Bromobenzyl)-2-(1-piperazinyl)-2-indancarboxamide dihydrochloride.

20 The expected product is obtained according to the procedure of Example 4, starting from the compound of Preparation 2 and 2-bromobenzylanine.

Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated	51.76	5.38	8.62	14.55
Found	52.54	5.33	8.66	13.77

EXAMPLE 57 : N-(4-Fluorobenzyl)-2-(1-piperazinyl)-2-indancarboxamide dihydrochloride.

The expected product is obtained according to the procedure of Example 4, starting from the compound of Preparation 2 and 4-fluorobenzylamine.

5 Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated	59.16	6.15	9.86	16.63
Found	58.93	6.04	9.69	16.81

10 **EXAMPLE 58 : N-(4-Methylbenzyl)-2-(1-piperazinyl)-2-indancarboxamide dihydrochloride.**

The expected product is obtained according to the procedure of Example 4, starting from the compound of Preparation 2 and 4-methylbenzylamine.

Elemental microanalysis :

15

	% C	% H	% N	% Cl
Calculated	62.56	6.92	9.95	16.79
Found	62.15	6.60	9.78	17.06

EXAMPLE 59 : N-(3,5-Dibromobenzyl)-2-(1-piperazinyl)-2-indancarboxamide dihydrochloride.

20 The expected product is obtained according to the procedure of Example 4, starting from the compound of Preparation 2 and 3,5-dibromobenzylamine.

Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated	44.55	4.45	7.42	12.52
Found	44.53	4.76	7.35	12.22

EXAMPLE 60 : N-[3,5-Bis(trifluoromethyl)benzyl]-N-methyl-2-(1-piperazinyl)-2-indancarboxamide dihydrochloride.

The expected product is obtained according to the procedure of Example 4, starting from the compound of Preparation 2 and N-methyl-3,5-bis(trifluoromethyl)benzylamine.

5 Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated	53.37	4.94	7.78	9.84
Found	53.21	5.15	7.63	9.78

10 **EXAMPLE 61 : 2-(1-Piperazinyl)-N-[4-(trifluoromethyl)benzyl]-2-indancarboxamide dihydrochloride.**

The expected product is obtained according to the procedure of Example 4, starting from the compound of Preparation 2 and 4-(trifluoromethyl)benzylamine.

Elemental microanalysis :

	% C	% H	% N	% Cl
15 Calculated	55.47	5.50	8.82	14.88
Found	55.24	5.32	8.62	14.70

EXAMPLE 62 : N-(2-Naphthylmethyl)-2-(1-piperazinyl)-2-indancarboxamide dihydrochloride.

20 The expected product is obtained according to the procedure of Example 4, starting from the compound of Preparation 2 and 2-naphthylmethylamine.

Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated	65.50	6.38	9.17	15.47
Found	66.04	6.22	9.00	15.29

EXAMPLE 63 : N-(3,5-Difluorobenzyl)-2-(1-piperaziny)-2-indancarboxamide dihydrochloride.

The expected product is obtained according to the procedure of Example 4, starting from the compound of Preparation 2 and 3,5-difluorobenzylamine.

5 Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated	56.76	5.67	9.46	15.96
Found	56.87	5.81	9.49	15.99

10 **EXAMPLE 64 : (1RS)-1-[1-(3-Fluoro-5-(trifluoromethyl)benzyloxymethyl)indan-1-yl]piperazine dihydrochloride.**

The expected product is obtained according to the procedure of Example 1, starting from the compound of Preparation 1 and 3-fluoro-5-(trifluoromethyl)benzyl bromide.

Elemental microanalysis :

15

	% C	% H	% N	% Cl
Calculated	54.89	5.44	5.82	14.73
Found	54.78	5.58	5.79	14.65

EXAMPLE 65 : (1RS)-1-(1-Piperaziny)-N-[3-(trifluoromethyl)benzyl]-1-indan-carboxamide dihydrochloride.

20 The expected product is obtained according to the procedure of Example 4, starting from the compound of Preparation 1 and 3-(trifluoromethyl)benzylamine.

Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated	55.47	5.50	8.82	14.88
Found	56.07	5.78	8.79	14.73

EXAMPLE 66 : (1RS)-1-(1-Piperazinyl)-N-methyl-N-[3-(trifluoromethyl)benzyl]-1-indancarboxamide dihydrochloride.

The expected product is obtained according to the procedure of Example 4, starting from the compound of Preparation 1 and N-methyl-3-(trifluoromethyl)benzylamine.

5 Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated	56.33	5.76	8.57	14.46
Found	56.10	5.78	8.47	14.72

10 **EXAMPLE 67 : N-(3,5-Dichlorobenzyl)-N-methyl-2-(1-piperazinyl)-2-indan-carboxamide dihydrochloride.**

The expected product is obtained according to the procedure of Example 4, starting from the compound of Preparation 2 and N-methyl-3,5-dichlorobenzylamine.

Elemental microanalysis :

15

	% C	% H	% N	% Cl
Calculated	53.79	5.54	8.55	28.87
Found	54.52	5.50	8.68	27.84

EXAMPLE 68 : (1RS)-N-(3,5-Difluorobenzyl)-N-methyl-1-(1-piperazinyl)-1-indan-carboxamide dihydrochloride.

20 The expected product is obtained according to the procedure of Example 4, starting from the compound of Preparation 1 and N-methyl-3,5-difluorobenzylamine.

Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated	57.65	5.94	9.17	15.47
Found	57.73	6.29	9.06	15.71

EXAMPLE 69 : (1RS)-N-[3-Fluoro-5-(trifluoromethyl)benzyl]-N-methyl-1-(1-piperazinyl)-1-indancarboxamide dihydrochloride.

The expected product is obtained according to the procedure of Example 4, starting from the compound of Preparation 1 and N-methyl-3-fluoro-5-(trifluoromethyl)benzylamine.

5 Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated	54.34	5.35	8.27	13.95
Found	53.78	5.68	8.11	14.83

10 **EXAMPLE 70 : (1RS)-1-[1-(3,5-Difluorobenzyloxymethyl)indan-1-yl]piperazine dihydrochloride.**

The expected product is obtained according to the procedure of Example 1, starting from the compound of Preparation 1 and 3,5-difluorobenzyl bromide.

Elemental microanalysis :

15

	% C	% H	% N	% Cl
Calculated	58.47	6.08	6.49	16.44
Found	58.36	6.04	6.49	16.30

EXAMPLE 71 : N-(3,5-Dibromobenzyl)-N-methyl-2-(1-piperazinyl)-2-indan-carboxamide dihydrochloride.

20 The expected product is obtained according to the procedure of Example 4, starting from the compound of Preparation 2 and N-methyl-3,5-dibromobenzylamine.

Mass spectrometry : ESI : $[M+H]^+$ m/z 506.0

EXAMPLE 72 : N-[3-(Trifluoromethyl)benzyl]-N-methyl-2-(1-piperazinyl)-2-indan-carboxamide dihydrochloride.

25 The expected product is obtained according to the procedure of Example 4, starting from the compound of Preparation 2 and N-methyl-3-(trifluoromethyl)benzylamine.

Mass spectrometry : ESI : $[M+H]^+$ m/z 418.2

EXAMPLE 73 : N-(3,5-Difluorobenzyl)-N-methyl-2-(1-piperazinyl)-2-indan-carboxamide dihydrochloride.

The expected product is obtained according to the procedure of Example 4, starting from the compound of Preparation 2 and N-methyl-3,5-difluorobenzylamine.

5 Mass spectrometry : ESI : $[M+H]^+$ m/z 386.2

EXAMPLE 74 : N-(3,5-Dimethylbenzyl)-N-methyl-2-(1-piperazinyl)-2-indan-carboxamide dihydrochloride.

The expected product is obtained according to the procedure of Example 4, starting from the compound of Preparation 2 and N-methyl-3,5-dimethylbenzylamine.

10 Mass spectrometry : ESI : $[M+H]^+$ m/z 378.3

EXAMPLE 75 : N-Benzyl-N-methyl-[2-(1-piperazinyl)indan-2-yl]methanamine trihydrochloride.

The expected product is obtained according to the procedure of Example 6, starting from the compound of Example 7.

15 Mass spectrometry : ESI : $[M+H]^+$ m/z 336.2

EXAMPLE 76 : N-[3-Fluoro-5-(trifluoromethyl)benzyl]-2-(1-piperazinyl)-2-indan-carboxamide dihydrochloride.

The expected product is obtained according to the procedure of Example 4, starting from the compound of Preparation 2 and 3-fluoro-5-(trifluoromethyl)benzylamine.

20 Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated	53.45	5.10	8.50	14.34
Found	53.55	5.29	8.73	13.74

EXAMPLE 77 : N-(3,5-Difluorobenzyl)-N-methyl-[2-(1-piperazinyl)indan-2-yl]-methanamine trihydrochloride.

The expected product is obtained according to the procedure of Example 6, starting from the compound of Example 73.

5 Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated	54.95	6.29	8.74	22.12
Found	54.98	6.49	8.51	22.00

10 **EXAMPLE 78 : N-3,5-(Dimethylbenzyl)-N-methyl-[2-(1-piperazinyl)indan-2-yl]-methanamine trihydrochloride.**

The expected product is obtained according to the procedure of Example 6, starting from the compound of Example 74.

Mass spectrometry : ESI : $[M+H]^+$ m/z 364.3

15 **EXAMPLE 79 : N-(3,5-Dichlorobenzyl)-N-methyl-[2-(1-piperazinyl)indan-2-yl]-methanamine trihydrochloride.**

The expected product is obtained according to the procedure of Example 6, starting from the compound of Example 67.

Mass spectrometry : ESI : $[M+H]^+$ m/z 404.2

20 **EXAMPLE 80 : N-[3-Fluoro-5-(trifluoromethyl)benzyl]-N-methyl-2-(1-piperazinyl)-2-indancarboxamide dihydrochloride.**

The expected product is obtained according to the procedure of Example 4, starting from the compound of Preparation 2 and N-methyl-3-fluoro-5-(trifluoromethyl)benzylamine.

Mass spectrometry : ESI : $[M+H]^+$ m/z 436.2

EXAMPLE 81 : N-[3-Fluoro-5-(trifluoromethyl)benzyl]-N-methyl-[2-(1-piperazinyl)-indan-2-yl]methanamine dihydrochloride.

The expected product is obtained according to the procedure of Example 6, starting from the compound of Example 80.

5 Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated	55.88	5.91	8.50	14.34
Found	55.50	6.32	7.98	14.47

10 **EXAMPLE 82 : N-[3-(Trifluoromethyl)benzyl]-N-methyl-[2-(1-piperazinyl)-indan-2-yl]methanamine dihydrochloride.**

The expected product is obtained according to the procedure of Example 6, starting from the compound of Example 72.

Elemental microanalysis :

15

	% C	% H	% N	% Cl
Calculated	57.99	6.35	8.82	14.88
Found	57.60	6.70	8.59	14.33

EXAMPLE 83 : N-[3,5-Bis(trifluoromethyl)benzyl]-N-methyl-[2-(1-piperazinyl)-indan-2-yl]methanamine dihydrochloride.

20 The expected product is obtained according to the procedure of Example 6, starting from the compound of Example 60.

Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated	52.95	5.37	7.72	13.02
Found	52.87	5.80	7.42	12.74

EXAMPLE 84 : (1RS)-N-(3,5-Dibromobenzyl)-N-ethyl-1-(1-piperazinyl)-1-indan-carboxamide dihydrochloride.

The expected product is obtained according to the procedure of Example 4, starting from the compound of Preparation 1 and N-ethyl-3,5-dibromobenzylamine.

5 Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated	46.49	4.92	7.07	11.93
Found	46.42	5.16	6.96	11.59

10 **EXAMPLE 85 : (1RS)-N-(3,5-Dichlorobenzyl)-N-methyl-1-(1-piperazinyl)-1-indan-carboxamide dihydrochloride.**

The expected product is obtained according to the procedure of Example 4, starting from the compound of Preparation 1 and N-methyl-3,5-dichlorobenzylamine.

Elemental microanalysis :

	% C	% H	% N	% Cl
15 Calculated	53.79	5.54	8.55	28.87
Found	54.22	5.61	8.67	29.81

EXAMPLE 86 : (1 α)-N-(3,5-Dimethylbenzyl)-1-(1-piperazinyl)-1-indancarboxamide dihydrochloride.

Step A: Benzyl (1 α)-1-[4-(tert-butyloxycarbonyl)-1-piperazinyl]-1-indancarboxylate.

20 The expected product is the first of the enantiomers obtained by separation on a chiral HPLC column of the compound obtained in Step A of Example 1.

Step B: (1 α)-1-[4-(tert-Butyloxycarbonyl)-1-piperazinyl]-1-indancarboxylic acid.

The expected product is obtained according to the procedure described in Step F of Preparation 1, starting from the compound of Step A above.

Step C: *(1 α)-N-(3,5-Dimethylbenzyl)-1-(1-piperazinyl)-1-indancarboxamide dihydrochloride.*

The expected product is obtained according to the procedure of Example 4, starting from the compound of Step B above and 3,5-dimethylbenzylamine.

5 **Elemental microanalysis :**

	% C	% H	% N	% Cl
Calculated	63.30	7.16	9.63	16.25
Found	62.93	7.30	9.50	16.40

EXAMPLE 87 : *(1 β)-N-(3,5-Dimethylbenzyl)-1-(1-piperazinyl)-1-indancarboxamide dihydrochloride.*

10

Step A: *(1 β)-1-[4-(tert-Butyloxycarbonyl)-1-piperazinyl]-1-indancarboxylic acid.*

The expected product is obtained according to the procedure described in Step F of Preparation 1, starting from the second of the enantiomers separated in Step A of Example 86.

15 **Step B:** *(1 β)-N-(3,5-Dimethylbenzyl)-1-(1-piperazinyl)-1-indancarboxamide dihydrochloride*

The expected product is obtained according to the procedure of Example 4, starting from the compound of Step A above and 3,5-dimethylbenzylamine.

Elemental microanalysis :

20

	% C	% H	% N	% Cl
Calculated	63.30	7.16	9.63	16.25
Found	63.46	7.24	9.61	16.77

EXAMPLE 88 : N-(3,5-Dibromobenzyl)-N-methyl-[2-(1-piperazinyl)indan-2-yl]-methanamine dihydrochloride.

The expected product is obtained according to the procedure of Example 6, starting from the compound of Example 71.

5 Mass spectrometry : ESI : $[M+H]^+$ m/z 492.1

EXAMPLE 89 : (1 α)-N-[(1 α')-1-(3,5-Dimethylphenyl)ethyl]-1-(1-piperazinyl)-1-indancarboxamide dihydrochloride.

Step A : (1 α)-N-[(1RS)-1-(3,5-Dimethylphenyl)ethyl]-1-[4-(tert-butyloxycarbonyl)-1-piperazinyl]-1-indancarboxamide.

10 The expected product is obtained according to the procedure described in Step A of Example 4, starting from the compound obtained in Step B of Example 86 and (RS)-1-(3,5-dimethylphenyl)ethylamine.

Step B : (1 α)-N-[(1 α')-1-(3,5-Dimethylphenyl)ethyl]-1-[4-(tert-butyloxycarbonyl)-1-piperazinyl]-1-indancarboxamide.

15 The expected product is obtained by chromatography on silica (eluant: dichloromethane/ethyl acetate) of the diastereoisomeric mixture obtained in Step A.

Step C : (1 α)-N-[(1 α')-1-(3,5-Dimethylphenyl)ethyl]-1-(1-piperazinyl)-1-indancarboxamide dihydrochloride.

20 The expected product is obtained according to the procedure described in Step B of Example 4, starting from the compound obtained in Step B above.

Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated	63.99	7.38	9.33	15.74
Found	63.16	7.59	9.09	15.93

EXAMPLE 90 : (1 α)-N-[(1 β ')-1-(3,5-Dimethylphenyl)ethyl]-1-(1-piperazinyl)-1-indancarboxamide dihydrochloride.

The expected product is obtained according to the procedure described in Step B of Example 4, starting from the second of the diastereoisomers separated in Step B of Example 89.

Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated	63.99	7.38	9.33	15.74
Found	64.35	7.60	9.39	15.45

EXAMPLE 91 : (1 β)-N-[(1 α ')-1-(3,5-Dimethylphenyl)ethyl]-1-(1-piperazinyl)-1-indancarboxamide dihydrochloride.

Step A : (1 β)-N-[(1RS)-1-(3,5-Dimethylphenyl)ethyl]-1-[4-(tert-butyloxycarbonyl)-1-piperazinyl]-1-indancarboxamide.

The expected product is obtained according to the procedure described in Step A of Example 4, starting from the compound obtained in Step A of Example 87 and (RS)-1-(3,5-dimethylphenyl)ethylamine.

Step B : (1 β)-N-[(1 α ')-1-(3,5-Dimethylphenyl)ethyl]-1-[4-(tert-butyloxycarbonyl)-1-piperazinyl]-1-indancarboxamide.

The expected product is obtained by chromatography on silica (eluant: dichloromethane/ethyl acetate) of the diastereoisomeric mixture obtained in Step A.

Step C : (1 β)-N-[(1 α ')-1-(3,5-Dimethylphenyl)ethyl]-1-(1-piperazinyl)-1-indancarboxamide dihydrochloride.

The expected product is obtained according to the procedure described in Step B of Example 4, starting from the compound obtained in Step B above.

Elemental microanalysis :

	% C	% H	% N	% Cl
<i>Calculated</i>	63.99	7.38	9.33	15.74
<i>Found</i>	64.49	7.75	9.57	15.33

5 **EXAMPLE 92 : (1 β)-N-[(1 β')-1-(3,5-Dimethylphenyl)ethyl]-1-(1-piperazinyl)-1-indancarboxamide dihydrochloride.**

The expected product is obtained according to the procedure described in Step B of Example 4, starting from the second of the diastereoisomers separated in Step B of Example 91.

10 Elemental microanalysis :

	% C	% H	% N	% Cl
<i>Calculated</i>	63.99	7.38	9.33	15.74
<i>Found</i>	64.00	7.66	9.31	16.13

15 **EXAMPLE 93 : (1RS)-N-(3,5-Dimethylbenzyl)-N-methyl-1-(1-piperazinyl)-1-indancarboxamide dihydrochloride.**

The expected product is obtained according to the procedure of Example 4, starting from the compound of Preparation 1 and N-methyl-3,5-dimethylbenzylamine.

Elemental microanalysis :

	% C	% H	% N	% Cl
20 <i>Calculated</i>	63.99	7.38	9.33	15.75
<i>Found</i>	64.79	7.38	9.57	14.78

EXAMPLE 94 : (1 α)-N-[(1S)-2-Hydroxy-1-phenylethyl]-1-(1-piperazinyl)-1-indan-carboxamide dihydrochloride.

Step A : (1RS)-N-[(1S)-2-Hydroxy-1-phenylethyl]-1-[4-(tert-butyloxycarbonyl)-1-piperazinyl]-1-indancarboxamide.

- 5 The expected product is obtained according to the procedure described in Step A of Example 4, starting from the compound of Preparation 1 and (S)-2-phenylglycinol.

Step B : (1 α)-N-[(1S)-2-Hydroxy-1-phenylethyl]-1-[4-(tert-butyloxycarbonyl)-1-piperazinyl]-1-indancarboxamide.

- 10 The expected product is obtained by separation, by means of chromatography on silica (eluant: dichloromethane/ethyl acetate), of the diastereoisomeric mixture obtained in Step A.

Step C : (1 α)-N-[(1S)-2-Hydroxy-1-phenylethyl]-1-(1-piperazinyl)-1-indancarboxamide dihydrochloride.

- 15 The expected product is obtained according to the procedure described in Step B of Example 4, starting from the compound obtained in Step B above.

Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated	60.27	6.67	9.58	16.17
Found	59.95	6.43	9.35	16.25

- 20 **EXAMPLE 95 :** (1 β)-N-[(1S)-2-Hydroxy-1-phenylethyl]-1-(1-piperazinyl)-1-indan-carboxamide dihydrochloride.

The expected product is obtained according to the procedure described in Step B of Example 4, starting from the second of the diastereoisomers separated in Step B of Example 94.

Elemental microanalysis :

	% C	% H	% N	% Cl
<i>Calculated</i>	60.27	6.67	9.58	16.17
<i>Found</i>	59.95	6.64	9.50	16.42

5 **EXAMPLE 96 : N-[(1R)-1-(3,5-Dimethylphenyl)ethyl]-2-(1-piperazinyl)-2-indan-carboxamide dihydrochloride.**

The expected product is obtained according to the procedure of Example 4, starting from the compound of Preparation 2 and (R)-1-(3,5-dimethylphenyl)ethylamine.

Elemental microanalysis :

10

	% C	% H	% N	% Cl
<i>Calculated</i>	63.99	7.38	9.33	15.74
<i>Found</i>	64.34	7.04	9.45	16.22

EXAMPLE 97 : N-{[2-(1-Piperazinyl)indan-2-yl]methyl}-3,5-bis(trifluoromethyl)-benzamide dihydrochloride.

15 **Step A : 2-Azidomethyl-2-[4-(tert-butyloxycarbonyl)-1-piperazinyl]-2-indan.**

The expected product is obtained by reaction of the compound obtained in Step A of Example 3 with diphenylphosphoryl azide (DPPA) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), according to the procedure described in *J. Org Chem.* 1993, 58, 5886-5888, and then purification by chromatography on silica (eluant: dichloromethane/ethyl acetate 98/2).

20 IR : N₃ : 2095 cm⁻¹ CO : 1692 cm⁻¹

Step B : 2-Aminomethyl-2-[4-(tert-butyloxycarbonyl)-1-piperazinyl]-2-indan.

2.35 mmol of the compound obtained in Step A above are dissolved in 80 ml of tetrahydrofuran, 2.59 mmol of triphenylphosphine are then added and stirring is carried out for ¼ hour. 10 ml of water are then added and stirring is continued for 24 hours. After
25 evaporating off the solvents, the product is purified by chromatography on silica (eluant: dichloromethane/methanol/ammonia 85/15/1) to yield the expected product.

Step C : *N-{{2-[4-(tert-Butyloxycarbonyl)-1-piperazinyl]indan-2-yl}methyl}-3,5-bis(trifluoromethyl)benzamide*

2 mmol of the amine obtained in Step B above are dissolved in 15 ml of tetrahydrofuran, cooling to 0°C is then carried out, and a solution of 2 mmol of 3,5-bis(trifluoromethyl)-benzoyl chloride in 5 ml of tetrahydrofuran is added dropwise. Stirring is then carried out for 1 hour, the solvent is evaporated off and the residue is redissolved in methylene chloride and washed successively with sodium bicarbonate solution, with 10 % citric acid solution and then with water. After evaporation and chromatography on silica (eluant: dichloromethane/ethyl acetate 98/2), the expected product is recovered.

10 **Step D :** *N-{{2-(1-Piperazinyl)indan-2-yl}methyl}-3,5-bis(trifluoromethyl)benzamide dihydrochloride.*

The expected product is obtained according to the procedure described in Step D of Example 1, starting from the compound obtained in Step C above.

Elemental microanalysis :

15		% C	% H	% N	% Cl
	<i>Calculated</i>	50.75	4.63	7.72	13.03
	<i>Found</i>	51.52	4.84	7.72	12.72

EXAMPLE 98 : *N-[(1 α)-1-(3,5-Dibromophenyl)ethyl]-2-(1-piperazinyl)-2-indan-carboxamide dihydrochloride.*

20 The expected product is obtained according to the procedure of Example 4, starting from the compound of Preparation 2 and (1 α)-1-(3,5-dibromophenyl)ethylamine.

Melting point : 178-180°C.

EXAMPLE 99 : N-[(1S)-1-(3,5-Dimethylphenyl)ethyl]-2-(1-piperazinyl)-2-indan-carboxamide dihydrochloride.

The expected product is obtained according to the procedure of Example 4, starting from the compound of Preparation 2 and (S)-1-(3,5-dimethylphenyl)ethylamine.

5 Melting point : 175°C.

EXAMPLE 100 : N-[(1β)-1-(3,5-Dibromophenyl)ethyl]-2-(1-piperazinyl)-2-indan-carboxamide dihydrochloride.

The expected product is obtained according to the procedure of Example 4, starting from the compound of Preparation 2 and (1β)-1-(3,5-dibromophenyl)ethylamine.

10 Melting point : 192-194°C.

EXAMPLE 101 : (1α)-N-[(1α')-1-(3,5-Bis(trifluoromethyl)phenyl)ethyl]-1-(1-piperazinyl)indancarboxamide dihydrochloride.

Step A : (1α')-1-[3,5-Bis(trifluoromethyl)phenyl]ethylamine.

(1RS)-1-[3,5-Bis(trifluoromethyl)phenyl]ethylamine is converted into a salt using (L)-
15 tartaric acid, the mixture of diastereoisomers thereby obtained is separated and then reconversion to the base is carried out on each of the two diastereoisomers.

The expected product is the first of the enantiomers thereby obtained.

Step B : (1RS)-N-[(1α')-1-(3,5-Bis(trifluoromethyl)phenyl)ethyl]-1-[4-(tert-butylloxycarbonyl)-1-piperazinyl]-1-indancarboxamide dihydrochloride.

20 The expected product is obtained according to the procedure described in Step A of Example 4, starting from Preparation 1 and the compound obtained in Step A above.

Step C: (1 α)-N-[(1 α')-1-(3,5-Bis(trifluoromethyl)phenyl)ethyl]-1-[4-(tert-butylloxycarbonyl)-1-piperazinyl]-1-indancarboxamide dihydrochloride.

The expected product is obtained by separation, by means of chromatography on silica (eluant: dichloromethane/ethyl acetate), of the diastereoisomeric mixture obtained in
5 Step B.

Step D: (1 α)-N-[(1 α')-1-(3,5-Bis(trifluoromethyl)phenyl)ethyl]-1-(1-piperazinyl)-indancarboxamide dihydrochloride.

The expected product is obtained according to the procedure described in Step B of Example 4, starting from the compound obtained in Step C above.

10 **Elemental microanalysis :**

	% C	% H	% N	% Cl
Calculated	51.62	4.87	7.53	12.70
Found	52.46	5.10	7.50	12.06

EXAMPLE 102 : (1 β)-N-[(1 α')-1-(3,5-Bis(trifluoromethyl)phenyl)ethyl]-1-(1-piperazinyl)indancarboxamide dihydrochloride.
15

The expected product is obtained according to the procedure described in Step B of Example 4, starting from the second of the diastereoisomers separated in Step C of Example 101.

Elemental microanalysis :

20

	% C	% H	% N	% Cl
Calculated	51.62	4.87	7.53	12.70
Found	51.97	5.00	7.38	11.79

EXAMPLE 103 : (1 α)-N-[(1 β')-1-(3,5-Bis(trifluoromethyl)phenyl)ethyl]-1-(1-piperazinyl)indancarboxamide dihydrochloride.

Step A : (1 β')-1-[3,5-Bis(trifluoromethyl)phenyl]ethylamine.

The expected product is the second of the enantiomers obtained in Step A of Example 101.

5 **Step B :** (1RS)-N-[(1 β')-1-(3,5-Bis(trifluoromethyl)phenyl)ethyl]-1-[4-(tert-butyloxycarbonyl)-1-piperazinyl]-1-indancarboxamide dihydrochloride.

The expected product is obtained according to the procedure described in Step A of Example 4, starting from the compound of Preparation 1 and the compound obtained in Step A above.

10 **Step C :** (1 α)-N-[(1 β')-1-(3,5-Bis(trifluoromethyl)phenyl)ethyl]-1-[4-(tert-butyloxycarbonyl)-1-piperazinyl]-1-indancarboxamide dihydrochloride.

The expected product is obtained by separation, by means of chromatography on silica (eluant: dichloromethane/ethyl acetate), of the diastereoisomeric mixture obtained in Step B.

15 **Step D :** (1 α)-N-[(1 β')-1-(3,5-Bis(trifluoromethyl)phenyl)ethyl]-1-(1-piperazinyl)-indancarboxamide dihydrochloride.

The expected product is obtained according to the procedure described in Step B of Example 4, starting from the compound obtained in Step C above.

Elemental microanalysis :

20		% C	% H	% N	% Cl
	Calculated	51.62	4.87	7.53	12.70
	Found	51.05	4.68	7.24	12.25

EXAMPLE 104 : (1 β)-N-[(1 β')-1-(3,5-Bis(trifluoromethyl)phenyl)ethyl]-1-(1-piperazinyl)indancarboxamide dihydrochloride.

The expected product is obtained according to the procedure described in Step B of Example 4, starting from the second of the diastereoisomers separated in Step C of Example 103.

Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated	51.62	4.87	7.53	12.70
Found	52.43	5.16	7.52	11.94

EXAMPLE 105 : 1-[(1RS)-1-(3-Bromo-5-fluorobenzyloxymethyl)indan-1-yl]-piperazine dihydrochloride.

The expected product is obtained according to the procedure of Example 1, starting from the compound of Preparation 1 and 3-bromo-5-fluorobenzyl bromide.

Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated	51.24	5.32	5.69	14.40
Found	51.96	5.28	5.56	14.36

EXAMPLE 106 : 1-[(1RS)-1-(3-Chloro-5-fluorobenzyloxymethyl)indan-1-yl]-piperazine dihydrochloride.

The expected product is obtained according to the procedure of Example 1, starting from the compound of Preparation 1 and 3-chloro-5-fluorobenzyl bromide.

Mass spectrometry : ESI (H_2O/CH_3CN) : $[M+H]^+$ m/z 375.2 Th

EXAMPLE 107 : 1-[2-(3,5-Difluorobenzyloxymethyl)indan-2-yl]piperazine dihydrochloride.

The expected product is obtained according to the procedure of Example 1, starting from the compound of Preparation 2 and 3,5-difluorobenzyl bromide.

5 Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated	58.47	6.08	6.49	16.44
Found	58.49	6.07	6.47	17.04

10 **EXAMPLE 108 : N-[(1S)-1-(3,5-Dimethylphenyl)ethyl]-N-methyl-2-(1-piperazinyl)-2-indancarboxamide dihydrochloride.**

The expected product is obtained according to the procedure of Example 4, starting from the compound of Preparation 2 and N-[(1S)-1-(3,5-dimethylphenyl)ethyl]-N-methylamine.

Elemental microanalysis :

15

	% C	% H	% N	% Cl
Calculated	64.65	7.60	9.05	15.27
Found	64.66	7.66	9.29	15.18

EXAMPLE 109 : N-[(1R)-1-(3,5-Dimethylphenyl)ethyl]-N-methyl-2-(1-piperazinyl)-2-indancarboxamide dihydrochloride.

20 The expected product is obtained according to the procedure of Example 4, starting from the compound of Preparation 2 and N-[(1R)-1-(3,5-dimethylphenyl)ethyl]-N-methylamine.

Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated	64.65	7.60	9.05	15.27
Found	64.66	7.66	9.29	15.18

EXAMPLE 110 : 1-[2-(3-Bromo-5-fluorobenzyloxymethyl)indan-2-yl]piperazine, dihydrochloride.

The expected product is obtained according to the procedure of Example 1, starting from the compound of Preparation 2 and 3-bromo-5-fluorobenzyl bromide.

5 Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated	51.24	5.32	5.69	14.40
Found	51.37	5.33	5.67	14.72

10 **EXAMPLE 111: N-[(1R)-1-(3,5-Dichlorophenyl)ethyl]-2-(1-piperazinyl)-2-indan-carboxamide dihydrochloride.**

The expected product is obtained according to the procedure of Example 4, starting from the compound of Preparation 2 and (1R)-1-(3,5-dichlorophenyl)ethylamine.

Elemental microanalysis :

15

	% C	% H	% N	% Cl
Calculated	53.79	5.54	8.55	28.87
Found	54.58	5.55	8.45	28.63

EXAMPLE 112 : 1-[2-(3-Fluoro-5-(trifluoromethyl)benzyloxymethyl)indan-2-yl]-piperazine dihydrochloride.

20 The expected product is obtained according to the procedure of Example 1, starting from the compound of Preparation 2 and 3-fluoro-5-(trifluoromethyl)benzyl bromide.

Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated	54.89	5.44	5.82	14.73
Found	55.40	5.53	5.69	14.90

EXAMPLE 113 : N-[(1S)-1-(3,5-Bis(trifluoromethyl)phenyl)ethyl]-2-(1-piperazinyl)-2-indancarboxamide dihydrochloride.

The expected product is obtained according to the procedure of Example 4, starting from the compound of Preparation 2 and (1S)-1-[3,5-bis(trifluoromethyl)phenyl]ethylamine.

5 Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated	51.62	4.87	7.53	12.70
Found	51.10	4.77	7.22	12.30

10 **EXAMPLE 114 : 1-[2-(3-Chloro-5-fluorobenzyloxymethyl)indan-2-yl]piperazine dihydrochloride.**

The expected product is obtained according to the procedure of Example 1, starting from the compound of Preparation 2 and 3-chloro-5-fluorobenzyl bromide.

Elemental microanalysis :

	% C	% H	% N	% Cl
15 Calculated	56.33	5.85	6.26	23.75
Found	56.40	6.00	6.25	23.67

EXAMPLE 115 : (1 α)-N-[(1 α')-1-(3,5-Dibromophenyl)ethyl]-1-(1-piperazinyl)-indancarboxamide dihydrochloride.

Step A : (1 α')-1-[3,5-Dibromophenyl]ethylamine.

20 (1RS)-1-[3,5-Dibromophenyl]ethylamine is converted into a salt using (L)-tartaric acid, the mixture of diastereoisomers thereby obtained is separated and then reconversion to the base is carried out on each of the two diastereoisomers.

The expected product is the first of the enantiomers thereby obtained.

Step B : *(1RS)-N-[(1 α')-1-(3,5-Dibromophenyl)ethyl]-1-[4-(tert-butyloxycarbonyl)-1-piperazinyl]-1-indancarboxamide dihydrochloride.*

The expected product is obtained according to the procedure described in Step A of Example 4, starting from Preparation 1 and the compound obtained in Step A above.

5 **Step C :** *(1 α)-N-[(1 α')-1-(3,5-Dibromophenyl)ethyl]-1-[4-(tert-butyloxycarbonyl)-1-piperazinyl]-1-indancarboxamide dihydrochloride.*

The expected product is obtained by separation, by means of chromatography on silica (eluant: dichloromethane/ethyl acetate), of the diastereoisomeric mixture obtained in Step B.

10 **Step D :** *(1 α)-N-[(1 α')-1-(3,5-Dibromophenyl)ethyl]-1-(1-piperazinyl)indancarboxamide dihydrochloride.*

The expected product is obtained according to the procedure described in Step B of Example 4, starting from the compound obtained in Step C above.

Elemental microanalysis :

15	% C	% H	% N	% Cl
	<i>Calculated</i>	45.54	4.69	7.24
	<i>Found</i>	45.94	4.77	7.02
				11.32

EXAMPLE 116 : *(1 β)-N-[(1 α')-1-(3,5-Dibromophenyl)ethyl]-1-(1-piperazinyl)-indancarboxamide dihydrochloride.*

20 The expected product is obtained according to the procedure described in Step B of Example 4, starting from the second of the diastereoisomers separated in Step C of Example 115.

Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated	45.54	4.69	7.24	12.22
Found	45.58	4.80	6.98	11.64

5 **EXAMPLE 117 : (1 α)-N-[(1 β')-1-(3,5-Dibromophenyl)ethyl]-1-(1-piperazinyl)-indancarboxamide dihydrochloride.**

Step A : (1 β')-1-[3,5-Dibromophenyl]ethylamine.

The expected product is the second of the enantiomers obtained in Step A of Example 115.

10 **Step B :** (1RS)-N-[(1 β')-1-(3,5-Dibromophenyl)ethyl]-1-[4-(tert-butyloxycarbonyl)-1-piperazinyl]-1-indancarboxamide dihydrochloride.

The expected product is obtained according to the procedure described in Step A of Example 4, starting from the compound of Preparation 1 and the compound obtained in Step A above.

15 **Step C :** (1 α)-N-[(1 β')-1-(3,5-Dibromophenyl)ethyl]-1-[4-(tert-butyloxycarbonyl)-1-piperazinyl]-1-indancarboxamide dihydrochloride.

The expected product is obtained by separation, by means of chromatography on silica (eluant: dichloromethane/ethyl acetate), of the diastereoisomeric mixture obtained in Step B.

20 **Step D :** (1 α)-N-[(1 β')-1-(3,5-Dibromophenyl)ethyl]-1-(1-piperazinyl)indancarboxamide dihydrochloride.

The expected product is obtained according to the procedure described in Step B of Example 4, starting from the compound obtained in Step C above.

Elemental microanalysis :

	% C	% H	% N	% Cl
<i>Calculated</i>	45.54	4.69	7.24	12.22
<i>Found</i>	45.70	4.76	7.06	11.08

5 **EXAMPLE 118 : (1 β)-N-[(1 β')-1-(3,5-Dibromophenyl)ethyl]-1-(1-piperazinyl)-indancarboxamide dihydrochloride.**

The expected product is obtained according to the procedure described in Step B of Example 4, starting from the second of the diastereoisomers separated in Step C of Example 117.

10 Elemental microanalysis :

	% C	% H	% N	% Cl
<i>Calculated</i>	45.54	4.69	7.24	12.22
<i>Found</i>	45.53	4.56	7.10	12.08

15 **EXAMPLE 119 : N-[(1 α)-1-(3,5-Dichlorophenyl)ethyl]-N-methyl-2-(1-piperazinyl)-2-indancarboxamide dihydrochloride.**

Step A : *N-[(1RS)-1-(3,5-Dichlorophenyl)ethyl]-N-methyl-2-(1-piperazinyl)-2-indancarboxamide.*

The expected product is obtained according to the procedure of Example 4, starting from the compound of Preparation 2 and N-methyl-1-(3,5-dichlorophenyl)ethylamine.

20 **Step B :** *N-[(1 α)-1-(3,5-Dichlorophenyl)ethyl]-N-methyl-2-(1-piperazinyl)-2-indancarboxamide.*

The compound obtained in the step above is separated by HPLC chromatography, on a chiral phase, of the racemic compound obtained in the step above.

The expected product is the first of the enantiomers thereby separated.

Step C: *N-[(1 α)-1-(3,5-Dichlorophenyl)ethyl]-N-methyl-2-(1-piperazinyl)-2-indancarboxamide dihydrochloride.*

The expected product is obtained by conversion of the compound obtained in the step above into a salt using hydrochloric acid.

5 **Elemental microanalysis :**

	% C	% H	% N	% Cl
<i>Calculated</i>	54.67	5.78	8.32	14.03
<i>Found</i>	54.73	5.88	8.26	13.89

10 **EXAMPLE 120 :** *N-[(1 β)-1-(3,5-Dichlorophenyl)ethyl]-N-methyl-2-(1-piperazinyl)-2-indancarboxamide dihydrochloride.*

The second of the enantiomers separated in Step B of Example 119 is converted into a salt using hydrochloric acid to yield the expected product.

Elemental microanalysis :

15

	% C	% H	% N	% Cl
<i>Calculated</i>	54.67	5.78	8.32	14.03
<i>Found</i>	54.95	5.96	8.15	13.41

EXAMPLE 121 : *N-[(1 α)-1-(3,5-Difluorophenyl)ethyl]-2-(1-piperazinyl)-2-indancarboxamide dihydrochloride.*

Step A: *N-[(1RS)-1-(3,5-Difluorophenyl)ethyl]-2-(1-piperazinyl)-2-indancarboxamide.*

20 The expected product is obtained according to the procedure of Example 4, starting from the compound of Preparation 2 and 1-(3,5-difluorophenyl)ethylamine.

Step B: *N-[(1 α)-1-(3,5-Difluorophenyl)ethyl]-2-(1-piperazinyl)-2-indancarboxamide.*

The compound obtained in the step above is separated by HPLC chromatography, on a chiral phase, of the racemic compound obtained in the step above.

The expected product is the first of the enantiomers thereby separated.

Step C: *N-[(1 α)-1-(3,5-Difluorophenyl)ethyl]-2-(1-piperazinyl)-2-indancarboxamide dihydrochloride.*

The expected product is obtained by conversion of the compound obtained in the step above into a salt using hydrochloric acid.

Elemental microanalysis :

5		% C	% H	% N	% Cl
	Calculated	57.65	5.94	9.17	15.47
	Found	57.87	5.86	9.08	15.47

EXAMPLE 122 : *N-[(1 β)-1-(3,5-Difluorophenyl)ethyl]-2-(1-piperazinyl)-2-indan-carboxamide dihydrochloride.*

- 10 The second of the enantiomers separated in Step B of Example 121 is converted into a salt using hydrochloric acid to yield the expected product.

Elemental microanalysis :

		% C	% H	% N	% Cl
	Calculated	57.65	5.94	9.17	15.47
15	Found	58.30	5.88	9.14	15.61

EXAMPLE 123 : *(1 α)-N-[(1RS)-1-[3,5-Bis(trifluoromethyl)phenyl]ethyl]-N-methyl-1-(1-piperazinyl)-1-indancarboxamide dihydrochloride.*

- 20 The expected product is obtained according to the procedure of Example 4, starting from the compound obtained in Step B of Example 86 and (RS)-N-methyl-1-[3,5-bis(trifluoromethyl)phenyl]ethylamine.

Elemental microanalysis :

		% C	% H	% N	% Cl
	Calculated	52.46	5.11	7.34	12.39
	Found	52.16	5.37	6.93	11.94

EXAMPLE 124 : (1 β)-N-[(1RS)-1-[3,5-Bis(trifluoromethyl)phenyl]ethyl]-N-methyl-1-(1-piperazinyl)-1-indancarboxamide dihydrochloride.

The expected product is obtained according to the procedure of Example 4, starting from the compound obtained in Step A of Example 87 and (RS)-N-methyl-1-[3,5-bis(trifluoromethyl)phenyl]ethylamine.

Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated	52.46	5.11	7.34	12.39
Found	52.99	5.15	7.20	12.21

EXAMPLE 125 : (1 α)-N-[(1 α')-1-(3,5-Difluorophenyl)ethyl]-1-(1-piperazinyl)-1-indancarboxamide dihydrochloride.

Step A : (1 α)-N-[(1RS)-1-(3,5-Difluorophenyl)ethyl]-1-[4-(tert-butyloxycarbonyl)-1-piperazinyl]-1-indancarboxamide.

The expected product is obtained according to the procedure described in Step A of Example 4, starting from the compound obtained in Step B of Example 86 and (RS)-1-(3,5-difluorophenyl)ethylamine.

Step B : (1 α)-N-[(1 α')-1-(3,5-Difluorophenyl)ethyl]-1-[4-(tert-butyloxycarbonyl)-1-piperazinyl]-1-indancarboxamide.

The expected product is obtained by chromatography on silica (eluant: dichloromethane/ethyl acetate) of the diastereoisomeric mixture obtained in Step A.

Step C : (1 α)-N-[(1 α')-1-(3,5-Difluorophenyl)ethyl]-1-(1-piperazinyl)-1-indancarboxamide dihydrochloride.

The expected product is obtained according to the procedure described in Step B of Example 4, starting from the compound obtained in Step B above.

Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated	57.65	5.94	9.17	15.47
Found	57.22	6.30	8.85	15.62

5 **EXAMPLE 126 : (1 α)-N-[(1 β)-1-(3,5-Difluorophenyl)ethyl]-1-(1-piperazinyl)-1-indancarboxamide dihydrochloride.**

The expected product is obtained according to the procedure described in Step B of Example 4, starting from the second of the diastereoisomers separated in Step B of Example 125.

10 Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated	57.65	5.94	9.17	15.47
Found	57.15	6.31	8.84	15.38

15 **EXAMPLE 127 : (1 β)-N-[(1 α')-1-(3,5-Difluorophenyl)ethyl]-1-(1-piperazinyl)-1-indancarboxamide dihydrochloride.**

Step A : (1 β)-N-[(1RS)-1-(3,5-Difluorophenyl)ethyl]-1-[4-(tert-butyloxycarbonyl)-1-piperazinyl]-1-indancarboxamide.

20 The expected product is obtained according to the procedure described in Step A of Example 4, starting from the compound obtained in Step A of Example 87 and (RS)-1-(3,5-difluorophenyl)ethylamine.

Step B : (1 β)-N-[(1 α')-1-(3,5-Difluorophenyl)ethyl]-1-[4-(tert-butyloxycarbonyl)-1-piperazinyl]-1-indancarboxamide.

The expected product is obtained by chromatography on silica (eluant: dichloromethane/ethyl acetate) of the diastereoisomeric mixture obtained in Step A.

Step C: (1 β)-N-[(1 α')-1-(3,5-Difluorophenyl)ethyl]-1-(1-piperazinyl)-1-indan-carboxamide dihydrochloride.

The expected product is obtained according to the procedure described in Step B of Example 4, starting from the compound obtained in Step B above.

5 **Elemental microanalysis :**

	% C	% H	% N	% Cl
Calculated	57.65	5.94	9.17	15.47
Found	57.38	6.36	8.88	15.69

10 **EXAMPLE 128 :** (1 β)-N-[(1 β')-1-(3,5-Difluorophenyl)ethyl]-1-(1-piperazinyl)-1-indancarboxamide dihydrochloride.

The expected product is obtained according to the procedure described in Step B of Example 4, starting from the second of the diastereoisomers separated in Step B of Example 127.

Elemental microanalysis :

15

	% C	% H	% N	% Cl
Calculated	57.65	5.94	9.17	15.47
Found	57.38	6.33	8.87	15.34

EXAMPLE 129 : N-(3-Chloro-5-fluorobenzyl)-2-(1-piperazinyl)-2-indancarboxamide dihydrochloride.

20 The expected product is obtained according to the procedure of Example 4, starting from the compound of Preparation 2 and 3-chloro-5-fluorobenzylamine.

Elemental microanalysis :

25

	% C	% H	% N	% Cl
Calculated	54.74	5.47	9.12	15.39
Found	55.24	5.61	9.06	15.29

EXAMPLE 130 : N-[(1S)-1-(3,5-Dichlorophenyl)ethyl]-2-(1-piperazinyl)-2-indan-carboxamide dihydrochloride.

The expected product is obtained according to the procedure of Example 4, starting from the compound of Preparation 2 and (1S)-1-[3,5-dichlorophenyl]ethylamine.

5 Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated	53.79	5.54	8.55	28.87
Found	54.53	5.59	8.52	28.80

10 **EXAMPLE 131 : (1 α)-N-[(1 α')-1-(3,5-Dichlorophenyl)ethyl]-1-(1-piperazinyl)-indancarboxamide dihydrochloride**

Step A : (1 α)-N-[(1RS)-1-(3,5-Dichlorophenyl)ethyl]-1-[4-(tert-butyloxycarbonyl)-1-piperazinyl]-1-indancarboxamide.

15 The expected product is obtained according to the procedure described in Step A of Example 4, starting from the compound obtained in Step B of Example 86 and (RS)-1-(3,5-dichlorophenyl)ethylamine.

Step B : (1 α)-N-[(1 α')-1-(3,5-Dichlorophenyl)ethyl]-1-[4-(tert-butyloxycarbonyl)-1-piperazinyl]-1-indancarboxamide.

The expected product is obtained by chromatography on silica (eluant: dichloromethane/ethyl acetate) of the diastereoisomeric mixture obtained in Step A.

20 **Step C :** (1 α)-N-[(1 α')-1-(3,5-Dichlorophenyl)ethyl]-1-(1-piperazinyl)-1-indancarboxamide dihydrochloride.

The expected product is obtained according to the procedure described in Step B of Example 4, starting from the compound obtained in Step B above.

Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated	53.79	5.54	8.55	28.87
Found	54.21	5.69	8.04	28.87

5 **EXAMPLE 132 : (1 α)-N-[(1 β')-1-(3,5-Dichlorophenyl)ethyl]-1-(1-piperazinyl)-1-indancarboxamide dihydrochloride.**

The expected product is obtained according to the procedure described in Step B of Example 4, starting from the second of the diastereoisomers separated in Step B of Example 131.

10 Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated	53.79	5.54	8.55	28.87
Found	54.26	5.40	8.04	28.03

15 **EXAMPLE 133 : (1 β)-N-[(1 α')-1-(3,5-Dichlorophenyl)ethyl]-1-(1-piperazinyl)-1-indancarboxamide dihydrochloride.**

Step A : (1 β)-N-[(1RS)-1-(3,5-Dichlorophenyl)ethyl]-1-[4-(tert-butyloxycarbonyl)-1-piperazinyl]-1-indancarboxamide.

20 The expected product is obtained according to the procedure described in Step A of Example 4, starting from the compound obtained in Step A of Example 87 and (RS)-1-(3,5-dichlorophenyl)ethylamine.

Step B : (1 β)-N-[(1 α')-1-(3,5-Dichlorophenyl)ethyl]-1-[4-(tert-butyloxycarbonyl)-1-piperazinyl]-1-indancarboxamide.

The expected product is obtained by chromatography on silica (eluant: dichloromethane/ethyl acetate) of the diastereoisomeric mixture obtained in Step A.

Step C: (1 β)-N-[(1 α')-1-(3,5-Dichlorophenyl)ethyl]-1-(1-piperazinyl)-1-indan-carboxamide dihydrochloride.

The expected product is obtained according to the procedure described in Step B of Example 4, starting from the compound obtained in Step B above.

5 **Elemental microanalysis :**

	% C	% H	% N	% Cl
<i>Calculated</i>	53.79	5.54	8.55	28.87
<i>Found</i>	54.00	5.54	8.08	28.19

10 **EXAMPLE 134 : (1 β)-N-[(1 β')-1-(3,5-Dichlorophenyl)ethyl]-1-(1-piperazinyl)-1-indancarboxamide dihydrochloride.**

The expected product is obtained according to the procedure described in Step B of Example 4, starting from the second of the diastereoisomers separated in Step B of Example 133.

Elemental microanalysis :

15

	% C	% H	% N	% Cl
<i>Calculated</i>	53.79	5.54	8.55	28.87
<i>Found</i>	53.80	5.62	7.93	27.54

EXAMPLE 135 : N-(3-Chloro-5-fluorobenzyl)-N-methyl-2-(1-piperazinyl)-2-indan-carboxamide dihydrochloride.

20 The expected product is obtained according to the procedure of Example 4, starting from the compound of Preparation 2 and N-methyl-3-chloro-5-fluorobenzylamine.

Elemental microanalysis :

25

	% C	% H	% N	% Cl
<i>Calculated</i>	55.65	5.73	8.85	22.40
<i>Found</i>	55.54	5.95	8.81	22.55

EXAMPLE 136 : N-[(1 α)-1-(3,5-Difluorophenyl)ethyl]-N-methyl-2-(1-piperazinyl)-2-indancarboxamide dihydrochloride.

Step A : N-[(1RS)-1-(3,5-Difluorophenyl)ethyl]-N-methyl-2-(1-piperazinyl)-2-indancarboxamide.

- 5 The expected product is obtained according to the procedure of Example 4, starting from the compound of Preparation 2 and N-methyl-1-(3,5-difluorophenyl)ethylamine.

Step B : N-[(1 α)-1-(3,5-Difluorophenyl)ethyl]-N-methyl-2-(1-piperazinyl)-2-indancarboxamide.

- 10 The compound obtained in the step above is separated by HPLC chromatography, on a chiral phase, of the racemic compound obtained in the step above.

The expected product is the first of the enantiomers thereby separated.

Step C : N-[(1 α)-1-(3,5-Difluorophenyl)ethyl]-N-methyl-2-(1-piperazinyl)-2-indancarboxamide dihydrochloride.

- 15 The expected product is obtained by conversion of the compound obtained in the step above into a salt using hydrochloric acid.

Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated	58.48	6.19	8.89	15.01
Found	57.93	6.09	8.62	15.18

- 20 **EXAMPLE 137 : N-[(1 β)-1-(3,5-Difluorophenyl)ethyl]-N-methyl-2-(1-piperazinyl)-2-indancarboxamide dihydrochloride.**

The second of the enantiomers separated in Step B of Example 136 is converted into a salt using hydrochloric acid to yield the expected product.

Elemental microanalysis :

	% C	% H	% N	% Cl
<i>Calculated</i>	58.48	6.19	8.89	15.01
<i>Found</i>	57.83	6.35	8.64	15.56

5 **EXAMPLE 138 :** (1 α)-N-[(1 α')-1-(3,5-Dibromophenyl)ethyl]-N-methyl-1-(1-piperazinyl)indancarboxamide dihydrochloride

Step A : (1 α)-N-[(1RS)-1-(3,5-Dibromophenyl)ethyl]-N-methyl-1-[4-(tert-butyloxy-carbonyl)-1-piperazinyl]-1-indancarboxamide.

10 The expected product is obtained according to the procedure described in Step A of Example 4, starting from the compound obtained in Step B of Example 86 and (RS)-N-methyl-1-(3,5-dibromophenyl)ethylamine.

Step B : (1 α)-N-[(1 α')-1-(3,5-Dibromophenyl)ethyl]-N-methyl-1-[4-(tert-butyloxy-carbonyl)-1-piperazinyl]-1-indancarboxamide.

15 The expected product is obtained by chromatography on silica (eluant: dichloromethane/ethyl acetate) of the diastereoisomeric mixture obtained in Step A.

Step C : (1 α)-N-[(1 α')-1-(3,5-Dibromophenyl)ethyl]-N-methyl-1-(1-piperazinyl)-1-indancarboxamide dihydrochloride.

The expected product is obtained according to the procedure described in Step B of Example 4, starting from the compound obtained in Step B above.

20 Elemental microanalysis :

	% C	% H	% N	% Cl
<i>Calculated</i>	46.49	4.92	7.07	11.93
<i>Found</i>	46.62	5.05	6.78	11.01

EXAMPLE 139 : (1 α)-N-[(1 β')-1-(3,5-Dibromophenyl)ethyl]-N-methyl-1-(1-piperazinyl)-1-indancarboxamide dihydrochloride.

The expected product is obtained according to the procedure described in Step B of Example 4, starting from the second of the diastereoisomers separated in Step B of Example 138.

Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated	46.49	4.92	7.07	11.93
Found	46.14	5.05	6.65	11.14

EXAMPLE 140 : N-[(1 α)-1-[3,5-Bis(trifluoromethyl)phenyl]ethyl]-N-methyl-2-(1-piperazinyl)-2-indancarboxamide dihydrochloride.

Step A : N-[(1RS)-1-[3,5-Bis(trifluoromethyl)phenyl]ethyl]-N-methyl-2-(1-piperazinyl)-2-indancarboxamide.

The expected product is obtained according to the procedure of Example 4, starting from the compound of Preparation 2 and N-methyl-1-[3,5-bis(trifluoromethyl)phenyl]-ethylamine.

Step B : N-[(1 α)-1-[3,5-Bis(trifluoromethyl)phenyl]ethyl]-N-methyl-2-(1-piperazinyl)-2-indancarboxamide

The compound obtained in the step above is separated by HPLC chromatography, on a chiral phase, of the racemic compound obtained in the step above.

The expected product is the first of the enantiomers thereby separated.

Step C: *N*-{(1 α)-1-[3,5-Bis(trifluoromethyl)phenyl]ethyl}-*N*-methyl-2-(1-piperazinyl)-2-indancarboxamide dihydrochloride.

The expected product is obtained by conversion of the compound obtained in the step above into a salt using hydrochloric acid.

5 Elemental microanalysis :

	% C	% H	% N	% Cl
<i>Calculated</i>	52.46	5.11	7.34	12.39
<i>Found</i>	53.00	5.39	7.20	12.03

10 **EXAMPLE 141** : *N*-{(1 β)-1-[3,5-Bis(trifluoromethyl)phenyl]ethyl}-*N*-methyl-2-(1-piperazinyl)-2-indancarboxamide hydrochloride.

The second of the enantiomers separated in Step B of Example 140 is converted into a salt using hydrochloric acid to yield the expected product.

Elemental microanalysis :

	% C	% H	% N	% Cl
15 <i>Calculated</i>	56.03	5.27	7.84	6.61
<i>Found</i>	56.54	5.44	7.66	6.49

EXAMPLE 142 : *N*-[(1*R*)-1-Phenylethyl]-*N*-methyl-2-(1-piperazinyl)-2-indancarboxamide dihydrochloride.

20 The expected product is obtained according to the procedure of Example 4, starting from the compound of Preparation 2 and (1*R*)-*N*-methyl-1-phenethylamine.

Elemental microanalysis :

	% C	% H	% N	% Cl
<i>Calculated</i>	63.30	7.16	9.63	16.25
<i>Found</i>	63.25	7.34	9.35	16.78

EXAMPLE 143 : N-[(1*S*)-1-Phenylethyl]-N-methyl-2-(1-piperazinyl)-2-indan-carboxamide dihydrochloride.

The expected product is obtained according to the procedure of Example 4, starting from the compound of Preparation 2 and (1*S*)-N-methyl-1-phenethylamine.

5 Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated	63.30	7.16	9.63	16.25
Found	63.81	7.29	9.48	16.72

10 **EXAMPLE 144 : (1 α)-N-[(1*S*)-1-Phenylethyl]-N-methyl-1-(1-piperazinyl)-1-indan-carboxamide dihydrochloride.**

The expected product is obtained according to the procedure of Example 4, starting from the compound obtained in Step B of Example 86 and (1*S*)-N-methyl-1-phenethylamine.

Elemental microanalysis :

15

	% C	% H	% N	% Cl
Calculated	63.30	7.16	9.63	16.25
Found	62.68	7.29	9.25	16.04

EXAMPLE 145 : (1 β)-N-[(1*S*)-1-Phenylethyl]-N-methyl-1-(1-piperazinyl)-1-indan-carboxamide dihydrochloride.

20 The expected product is obtained according to the procedure of Example 4, starting from the compound obtained in Step A of Example 87 and (1*S*)-N-methyl-1-phenethylamine.

Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated	63.30	7.16	9.63	16.25
Found	63.51	7.54	9.47	16.06

EXAMPLE 146 : (1 β)-N-[(1*R*)-1-Phenylethyl]-N-methyl-1-(1-piperazinyl)-1-indan-carboxamide dihydrochloride.

The expected product is obtained according to the procedure of Example 4, starting from the compound obtained in Step A of Example 87 and (1*R*)-N-methyl-1-phenethylamine.

5 Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated	63.30	7.16	9.63	16.25
Found	63.63	7.67	9.68	15.51

10 **EXAMPLE 147 : (1 α)-N-[(1*R*)-1-Phenylethyl]-N-methyl-1-(1-piperazinyl)-1-indan-carboxamide dihydrochloride.**

The expected product is obtained according to the procedure of Example 4, starting from the compound obtained in Step B of Example 86 and (1*R*)-N-methyl-1-phenethylamine.

Elemental microanalysis :

15

	% C	% H	% N	% Cl
Calculated	63.30	7.16	9.63	16.25
Found	62.87	7.16	9.06	15.95

EXAMPLE 148 : N-[(1 α)-1-(3,5-Dibromophenyl)ethyl]-N-methyl-2-(1-piperazinyl)-2-indancarboxamide dihydrochloride.

20 Step A : *N-[(1*RS*)-1-(3,5-Dibromophenyl)ethyl]-N-methyl-2-(1-piperazinyl)-2-indan-carboxamide.*

The expected product is obtained according to the procedure of Example 4, starting from the compound of Preparation 2 and N-methyl-1-(3,5-dibromophenyl)ethylamine.

Step B: *N-[(1 α)-1-(3,5-Dibromophenyl)ethyl]-N-methyl-2-(1-piperazinyl)-2-indan-carboxamide*

The compound obtained in the step above is separated by HPLC chromatography, on a chiral phase, of the racemic compound obtained in the step above.

- 5 The expected product is the first of the enantiomers thereby separated.

Step C: *N-[(1 α)-1-(3,5-Dibromophenyl)ethyl]-N-methyl-2-(1-piperazinyl)-2-indan-carboxamide dihydrochloride.*

The expected product is obtained by conversion of the compound obtained in the step above into a salt using hydrochloric acid.

- 10 Mass spectrometry : $[M+H]^+ = 519.1$

EXAMPLE 149 : *N-[(1 β)-1-(3,5-Dibromophenyl)ethyl]-N-methyl-2-(1-piperazinyl)-2-indancarboxamide dihydrochloride.*

The second of the enantiomers separated in Step B of Example 148 is converted into a salt using hydrochloric acid to yield the expected product.

- 15 Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated	46.49	4.92	7.07	11.93
Found	46.99	4.85	6.90	11.28

EXAMPLE 150 : *(RS)-1-{2-[(1-(3,5-Dimethylphenyl)ethoxy)methyl]indan-2-yl}-piperazine dihydrochloride.*

20

Step A : *tert-Butyl (RS)-4-(2-[(3,5-dimethylbenzoyl)oxy]methyl)indan-2-yl)-1-piperazinecarboxylate*

- 25 To 4.8 g of the compound obtained in Step A of Example 3 and 2.16 g of 3,5-dimethylbenzoic acid dissolved in 10 ml of methylene chloride there are added, at 0°C, 2.76 g of 1-

(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 150 mg of dimethylaminopyridine. After stirring for 20 hours at ambient temperature, the solvent is evaporated off, the residue is redissolved in ethyl acetate, and then the organic phase is washed with water, dried and evaporated. The residue obtained is purified by chromatography on silica gel (eluant: dichloromethane/ethyl acetate 92.5/7.5) to yield the expected product.

Melting point : 139°C.

Step B : tert-Butyl 4-[2-({1-(3,5-dimethylphenyl)vinyl}oxy)methyl]indan-2-yl)-1-piperazinecarboxylate

To 4.55 g of the product obtained in the step above, dissolved in 40 ml of tetrahydrofuran, there are added 19.4 ml of a 1M solution of dimethyltitanocene in toluene. The mixture is then heated at reflux under nitrogen. After stirring for 6 hours under reflux, a further 9.7 ml of the titanocene solution are added and refluxing is continued for 18 hours. After returning to ambient temperature, 300 ml of pentane are added and the mixture is filtered. The filtrate is evaporated and the residue is then chromatographed on silica gel (eluant: dichloromethane/ethyl acetate 90/10) to yield the expected product.

Melting point : 128°C.

Step C : tert-Butyl (RS)-4-(2-({1-(3,5-dimethylphenyl)ethoxy}methyl}indan-2-yl)-1-piperazinecarboxylate

To 1.6 g of the product obtained in the step above, dissolved in 40 ml of toluene and 20 ml of anhydrous ethanol, there are added, after degassing, 165 mg (5 % molar) of tris(triphenylphosphine)rhodium chloride. The mixture is then hydrogenated for 20 hours at ambient temperature and atmospheric pressure. After evaporating off the solvents and chromatographing on silica gel (eluant: dichloromethane/ethyl acetate 80/20), the expected product is obtained.

IR : >=CO 1688 cm^{-1} .

Step D : *(RS)-1-{2-[(1-(3,5-Dimethylphenyl)ethoxy)methyl]indan-2-yl}piperazine dihydrochloride*

The expected product is obtained by reaction of the compound obtained in the step above with hydrochloric acid.

5 **Elemental microanalysis :**

	% C	% H	% N	% Cl
<i>Calculated</i>	65.90	7.83	6.40	16.21
<i>Found</i>	66.36	8.34	6.43	15.98

10 **EXAMPLE 151 :** *1-{2-[(1 α)-1-(3,5-Dichlorophenyl)ethoxy)methyl]indan-2-yl}-piperazine dihydrochloride.*

Step A : *tert-Butyl (RS)-4-(2-{[1-(3,5-dichlorophenyl)ethoxy)methyl]indan-2-yl}-1-piperazinecarboxylate*

15 The expected product is obtained according to the procedure described in Steps A to C of Example 150, replacing the 3,5-dimethylbenzoic acid in Step A by 3,5-dichlorobenzoic acid.

Step B : *tert-Butyl 4-(2-{[(1 α)-1-(3,5-dichlorophenyl)ethoxy)methyl]indan-2-yl}-1-piperazinecarboxylate*

The compound obtained in the step above is separated by HPLC chromatography, on a chiral phase, of the racemic compound obtained in the step above.

20 The expected product is the first of the enantiomers thereby separated.

Step C : *1-{2-[(1 α)-1-(3,5-Dichlorophenyl)ethoxy)methyl]indan-2-yl}piperazine dihydrochloride.*

The expected product is obtained by reaction of the compound obtained in the step above with hydrochloric acid.

Elemental microanalysis :

	% C	% H	% N	% Cl
<i>Calculated</i>	55.25	5.90	5.86	29.65
<i>Found</i>	55.17	6.29	5.65	28.95

5 **EXAMPLE 152 : 1-{2-(((1 β)-1-(3,5-Dichlorophenyl)ethoxy)methyl)indan-2-yl}-piperazine dihydrochloride.**

The second of the enantiomers separated in Step B of Example 151 is reacted with hydrochloric acid to yield the expected product.

Elemental microanalysis :

10

	% C	% H	% N	% Cl
<i>Calculated</i>	55.25	5.90	5.86	29.65
<i>Found</i>	55.63	6.24	5.65	29.48

EXAMPLE 153 : 1-{(1 α)-1-(((1 α')-1-(3,5-Difluorophenyl)ethoxy)methyl)indan-1-yl}-piperazine dihydrochloride.

15 **Step A : (1 α)-1-[4-(*tert*-Butyloxycarbonyl)-1-piperazinyl]-1-hydroxymethylindan.**

The expected product is the first of the enantiomers obtained by separation on a chiral HPLC column of the compound obtained in Step B of Example 1.

Step B : *tert*-Butyl 4-((1 α)-1-(((1*RS*)-1-(3,5-difluorophenyl)ethoxy)methyl)indan-1-yl)-1-piperazinecarboxylate

20 The expected product is obtained according to the procedure described in Steps A to C of Example 150, starting from the compound obtained in the step above and 3,5-difluorobenzoic acid.

Step C: *tert-Butyl 4-((1 α)-1-(((1 α')-1-(3,5-difluorophenyl)ethoxy)methyl)indan-1-yl)-1-piperazinecarboxylate*

The compound obtained in the step above is separated by chromatography on silica. The expected product is the first of the diastereoisomers thereby separated.

5 **Step D:** *1-((1 α)-1-(((1 α')-1-(3,5-Difluorophenyl)ethoxy)methyl)indan-1-yl)piperazine dihydrochloride*

The expected product is obtained by reaction of the compound obtained in the step above with hydrochloric acid.

Elemental microanalysis :

10		% C	% H	% N	% Cl
	<i>Calculated</i>	59.33	6.34	6.29	15.92
	<i>Found</i>	60.09	6.38	5.88	16.00

EXAMPLE 154 : *1-((1 α)-1-(((1 β')-1-(3,5-Difluorophenyl)ethoxy)methyl)indan-1-yl)-piperazine dihydrochloride.*

15 The expected product is obtained by reaction of the second of the diastereoisomers separated in Step C of Example 153 with hydrochloric acid.

Elemental microanalysis :

		% C	% H	% N	% Cl
	<i>Calculated</i>	59.33	6.34	6.29	15.92
20	<i>Found</i>	58.86	6.18	6.05	15.85

EXAMPLE 155 : *1-((1 β)-1-(((1 α')-1-(3,5-Difluorophenyl)ethoxy)methyl)indan-1-yl)-piperazine dihydrochloride.*

Step A: *(1 β)-1-[4-(tert-Butyloxycarbonyl)-1-piperazinyl]-1-hydroxymethylindan.*

25 The expected product is the second of the enantiomers obtained by separation on a chiral HPLC column of the compound obtained in Step B of Example 1.

Step B: *tert-Butyl 4-((1 β)-1-{[(1*RS*)-1-(3,5-difluorophenyl)ethoxy]methyl}indan-1-yl)-1-piperazinecarboxylate*

The expected product is obtained according to the procedure described in Steps A to C of Example 150, starting from the compound obtained in the step above and 3,5-difluorobenzoic acid.

Step C: *tert-Butyl 4-((1 β)-1-{[(1 α')-1-(3,5-difluorophenyl)ethoxy]methyl}indan-1-yl)-1-piperazinecarboxylate*

The compound obtained in the step above is separated by chromatography on silica. The expected product is the first of the diastereoisomers thereby separated.

Step D: *1-{[(1 β)-1-{[(1 α')-1-(3,5-Difluorophenyl)ethoxy]methyl}indan-1-yl]piperazine dihydrochloride*

The expected product is obtained by reaction of the compound obtained in the step above with hydrochloric acid.

Elemental microanalysis :

15	% C	% H	% N	% Cl
	<i>Calculated</i>	59.33	6.34	6.29
	<i>Found</i>	58.91	6.38	6.12
			15.92	16.07

EXAMPLE 156 : *1-{[(1 β)-1-[(1 β')-1-(3,5-Difluorophenyl)ethoxy]methyl}indan-1-yl}-piperazine dihydrochloride.*

The expected product is obtained by reaction of the second of the diastereoisomers separated in Step C of Example 155 with hydrochloric acid.

Elemental microanalysis :

	% C	% H	% N	% Cl
	<i>Calculated</i>	59.33	6.34	6.29
25	<i>Found</i>	59.58	6.41	5.93
				15.94

EXAMPLE 157 : 1-{2-[(1 α)-1-(3,5-Dibromophenyl)ethoxy)methyl]indan-2-yl}-piperazine dihydrochloride.

Step A : *tert-Butyl (RS)-4-(2-{[1-(3,5-dibromophenyl)ethoxy]methyl}indan-2-yl)-1-piperazinecarboxylate*

- 5 The expected product is obtained according to the procedure described in Steps A to C of Example 150, replacing the 3,5-dimethylbenzoic acid in Step A by 3,5-dibromobenzoic acid.

Step B : *tert-Butyl 4-(2-{[(1 α)-1-(3,5-dibromophenyl)ethoxy]methyl}indan-2-yl)-1-piperazinecarboxylate*

- 10 The compound obtained in the step above is separated by HPLC chromatography, on a chiral phase, of the racemic compound obtained in the step above.
The expected product is the first of the enantiomers thereby separated.

Step C : *1-{2-[(1 α)-1-(3,5-Dibromophenyl)ethoxy)methyl]indan-2-yl}piperazine dihydrochloride.*

- 15 The expected product is obtained by reaction of the compound obtained in the step above with hydrochloric acid.

Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated	46.59	4.98	4.94	12.50
20 Found	47.21	4.73	4.95	12.54

EXAMPLE 158 : 1-{2-[(1 β)-1-(3,5-Dibromophenyl)ethoxy)methyl]indan-2-yl}-piperazine dihydrochloride.

The second of the enantiomers separated in Step B of Example 157 is reacted with hydrochloric acid to yield the expected product.

5 **Elemental microanalysis :**

	% C	% H	% N	% Cl
Calculated	46.59	4.98	4.94	12.50
Found	46.73	4.70	4.95	12.70

10 **EXAMPLE 159 : 1-{(1 α)-1-[(1 α')-1-[3,5-Bis(trifluoromethyl)phenyl]ethoxy)-methyl]indan-1-yl}piperazine dihydrochloride.**

Step A : tert-Butyl 4-((1 α)-1-[(1RS)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy)methyl]-indan-1-yl)-1-piperazinecarboxylate

15 The expected product is obtained according to the procedure described in Steps A to C of Example 150, starting from the compound obtained in Step A of Example 153 and 3,5-bis(trifluoromethyl)benzoic acid.

Step B : tert-Butyl 4-((1 α)-1-[(1 α')-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy)methyl]-indan-1-yl)-1-piperazinecarboxylate

The compound obtained in the step above is separated by chromatography on silica. The expected product is the first of the diastereoisomers thereby separated.

20 **Step C : 1-{(1 α)-1-[(1 α')-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy)methyl]indan-1-yl}-piperazine dihydrochloride**

The expected product is obtained by reaction of the compound obtained in the step above with hydrochloric acid.

Elemental microanalysis :

	% C	% H	% N	% Cl
<i>Calculated</i>	52.85	5.17	5.14	13.00
<i>Found</i>	52.93	5.38	5.00	13.11

5 **EXAMPLE 160 : 1-{(1 α)-1-[(1 β ')-1-[3,5-Bis(trifluoromethyl)phenyl]ethoxy)methyl]-indan-1-yl}piperazine dihydrochloride.**

The expected product is obtained by reaction of the second of the diastereoisomers separated in Step B of Example 159 with hydrochloric acid.

Elemental microanalysis :

	% C	% H	% N	% Cl
<i>Calculated</i>	52.85	5.17	5.14	13.00
<i>Found</i>	53.35	5.16	5.09	12.63

EXAMPLE 161 : 1-{(1 β)-1-[(1 α ')-1-[3,5-Bis(trifluoromethyl)phenyl]ethoxy)methyl]-indan-1-yl}piperazine dihydrochloride.

15 **Step A : *tert*-Butyl 4-((1 β)-1-[(1 RS)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy)methyl]-indan-1-yl)-1-piperazinecarboxylate**

The expected product is obtained according to the procedure described in Steps A to C of Example 150, starting from the compound obtained in Step A of Example 155 and 3,5-bis(trifluoromethyl)benzoic acid.

20 **Step B : *tert*-Butyl 4-((1 β)-1-[(1 α ')-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy)methyl]-indan-1-yl)-1-piperazinecarboxylate**

The compound obtained in the step above is separated by chromatography on silica. The expected product is the first of the diastereoisomers thereby separated.

Step C: 1-[(1 β)-1-[(1 α')-1-[3,5-Bis(trifluoromethyl)phenyl]ethoxy)methyl]indan-1-yl]-piperazine dihydrochloride

The expected product is obtained by reaction of the compound obtained in the step above with hydrochloric acid.

5 **Elemental microanalysis :**

	% C	% H	% N	% Cl
Calculated	52.85	5.17	5.14	13.00
Found	52.96	5.19	4.91	12.76

10 **EXAMPLE 162 :** 1-[(1 β)-1-[(1 β')-1-[3,5-Bis(trifluoromethyl)phenyl]ethoxy)methyl]-indan-1-yl]piperazine dihydrochloride.

The expected product is obtained by reaction of the second of the diastereoisomers separated in Step B of Example 161 with hydrochloric acid.

Elemental microanalysis :

	% C	% H	% N	% Cl
15 Calculated	52.85	5.17	5.14	13.00
Found	53.37	5.18	4.94	12.78

EXAMPLE 163 (1 α)-N-[(1 α')-1-(3,5-Difluorophenyl)ethyl]-N-methyl-1-(1-piperazinyl)-1-indancarboxamide dihydrochloride.

20 **Step A :** (1 α)-N-[(1RS)-1-(3,5-Difluorophenyl)ethyl]-N-methyl-1-[4-(tert-butyloxy-carbonyl)-1-piperazinyl]-1-indancarboxamide.

The expected product is obtained according to the procedure described in Step A of Example 4, starting from the compound obtained in Step B of Example 86 and (RS)-N-methyl-1-(3,5-difluorophenyl)ethylamine.

Step B : (1 α)-N-[(1 α')-1-(3,5-Difluorophenyl)ethyl]-N-methyl-1-[4-(tert-butyloxy-carbonyl)-1-piperazinyl]-1-indancarboxamide.

The expected product is obtained by chromatography on silica (eluant: dichloromethane/ethyl acetate) of the diastereoisomeric mixture obtained in Step A.

5 **Step C** : (1 α)-N-[(1 α')-1-(3,5-Difluorophenyl)ethyl]-N-methyl-1-(1-piperazinyl)-1-indancarboxamide dihydrochloride.

The expected product is obtained according to the procedure described in Step B of Example 4, starting from the compound obtained in Step B above.

Mass spectrometry ESI/FIA/HR and MS/MS : [M+H]⁺=400.

EXAMPLE 164 : (1 α)-N-[(1 β')-1-(3,5-Difluorophenyl)ethyl]-N-methyl-1-(1-piperazinyl)-1-indancarboxamide dihydrochloride.

The expected product is obtained according to the procedure described in Step B of Example 4, starting from the second of the diastereoisomers separated in Step B of Example 163.

Elemental microanalysis :

15	% C	% H	% N	% Cl
Calculated	58.48	6.19	8.89	15.01
Found	57.89	5.96	8.43	15.40

EXAMPLE 165 : (1 β)-N-[(1 α')-1-(3,5-Difluorophenyl)ethyl]-N-methyl-1-(1-piperazinyl)-1-indancarboxamide dihydrochloride.

20 **Step A** : (1 β)-N-[(1RS)-1-(3,5-Difluorophenyl)ethyl]-N-methyl-1-[4-(tert-butyloxycarbonyl)-1-piperazinyl]-1-indancarboxamide.

The expected product is obtained according to the procedure described in Step A of Example 4, starting from the compound obtained in Step A of Example 87 and (RS)-N-methyl-1-(3,5-difluorophenyl)ethylamine.

Step B : *(1 β)-N-[(1 α')-1-(3,5-Difluorophenyl)ethyl]-N-methyl-1-[4-(tert-butyloxy-carbonyl)-1-piperazinyl]-1-indancarboxamide.*

The expected product is obtained by chromatography on silica (eluant: dichloromethane/ethyl acetate) of the diastereoisomeric mixture obtained in Step A.

5 **Step C :** *(1 β)-N-[(1 α')-1-(3,5-Difluorophenyl)ethyl]-N-methyl-1-(1-piperazinyl)-1-indancarboxamide dihydrochloride.*

The expected product is obtained according to the procedure described in Step B of Example 4, starting from the compound obtained in Step B above.

Elemental microanalysis :

10		% C	% H	% N	% Cl
	<i>Calculated</i>	58.48	6.19	8.89	15.01
	<i>Found</i>	58.31	5.95	8.40	14.17

EXAMPLE 166 : *(1 β)-N-[(1 β')-1-(3,5-Difluorophenyl)ethyl]-N-methyl-1-(1-piperazinyl)-1-indancarboxamide dihydrochloride.*

15 The expected product is obtained according to the procedure described in Step B of Example 4, starting from the second of the diastereoisomers separated in Step B of Example 165.

Mass spectrometry ESI/FIA/HR and MS/MS : [M+H]⁺=400.

EXAMPLE 167 (1 α)-N-[(1 α')-1-(3,5-Dichlorophenyl)ethyl]-N-methyl-1-(1-piperazinyl)-1-indancarboxamide dihydrochloride.

Step A: (1 α)-N-[(1RS)-1-(3,5-Dichlorophenyl)ethyl]-N-methyl-1-[4-(tert-butyloxycarbonyl)-1-piperazinyl]-1-indancarboxamide.

- 5 The expected product is obtained according to the procedure described in Step A of Example 4, starting from the compound obtained in Step B of Example 86 and (RS)-N-methyl-1-(3,5-dichlorophenyl)ethylamine.

Step B: (1 α)-N-[(1 α')-1-(3,5-Dichlorophenyl)ethyl]-N-methyl-1-[4-(tert-butyloxycarbonyl)-1-piperazinyl]-1-indancarboxamide.

- 10 The expected product is obtained by chromatography on silica (eluant: dichloromethane/ethyl acetate) of the diastereoisomeric mixture obtained in Step A.

Step C: (1 α)-N-[(1 α')-1-(3,5-Dichlorophenyl)ethyl]-N-methyl-1-(1-piperazinyl)-1-indancarboxamide dihydrochloride.

- The expected product is obtained according to the procedure described in Step B of
15 Example 4, starting from the compound obtained in Step B above.

Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated	54.67	5.78	8.32	14.03
Found	55.18	5.79	8.06	12.57

- 20 **EXAMPLE 168 :** (1 α)-N-[(1 β')-1-(3,5-Dichlorophenyl)ethyl]-N-methyl-1-(1-piperazinyl)-1-indancarboxamide dihydrochloride.

The expected product is obtained according to the procedure described in Step B of Example 4, starting from the second of the diastereoisomers separated in Step B of Example 167.

Elemental microanalysis :

	% C	% H	% N	% Cl
<i>Calculated</i>	54.67	5.78	8.32	14.03
<i>Found</i>	53.93	5.78	7.90	14.03

5 **EXAMPLE 169 :** (1 β)-N-[(1 α')-1-(3,5-Dichlorophenyl)ethyl]-N-methyl-1-(1-piperazinyl)-1-indancarboxamide dihydrochloride.

Step A : (1 β)-N-[(1RS)-1-(3,5-Dichlorophenyl)ethyl]-N-methyl-1-[4-(tert-butylloxycarbonyl)-1-piperazinyl]-1-indancarboxamide.

10 The expected product is obtained according to the procedure described in Step A of Example 4, starting from the compound obtained in Step A of Example 87 and (RS)-N-methyl-1-(3,5-dichlorophenyl)ethylamine.

Step B : (1 β)-N-[(1 α')-1-(3,5-Dichlorophenyl)ethyl]-N-methyl-1-[4-(tert-butylloxycarbonyl)-1-piperazinyl]-1-indancarboxamide.

15 The expected product is obtained by chromatography on silica (eluant: dichloromethane/ethyl acetate) of the diastereoisomeric mixture obtained in Step A.

Step C : (1 β)-N-[(1 α')-1-(3,5-Dichlorophenyl)ethyl]-N-methyl-1-(1-piperazinyl)-1-indancarboxamide dihydrochloride.

The expected product is obtained according to the procedure described in Step B of Example 4, starting from the compound obtained in Step B above.

Mass spectrometry ESI/FIA/HR and MS/MS : [M+H]⁺=432.

EXAMPLE 170 : (1 β)-N-[(1 β')-1-(3,5-Dichlorophenyl)ethyl]-N-methyl-1-(1-piperazinyl)-1-indancarboxamide dihydrochloride.

The expected product is obtained according to the procedure described in Step B of Example 4, starting from the second of the diastereoisomers separated in Step B of Example 169.

Mass spectrometry ESI/FIA/HR and MS/MS : [M+H]⁺=432.

EXAMPLE 171 : 1-{2-[(1RS)-1-(3,5-Difluorophenyl)ethoxy)methyl]indan-2-yl}-piperazine dihydrochloride.

The expected product is obtained according to the procedure of Example 150, replacing the 3,5-dimethylbenzoic acid in Step A by 3,5-difluorobenzoic acid.

Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated	59.33	6.34	6.29	15.92
Found	59.46	6.61	6.15	15.40

EXAMPLE 172 : 1-{2-[(1RS)-1-[3,5-Bis(trifluoromethyl)phenyl]ethoxy)methyl]-indan-2-yl}piperazine dihydrochloride.

The expected product is obtained according to the procedure of Example 150, replacing the 3,5-dimethylbenzoic acid in Step A by 3,5-bis(trifluoromethyl)benzoic acid.

Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated	52.85	5.17	5.14	13.00
Found	52.82	5.14	5.05	12.77

EXAMPLE 173 : 1-{2-[(1 α)-1-Phenylethoxy)methyl]indan-2-yl}piperazine dihydrochloride.

Step A : *tert-Butyl (RS)-4-(2-{[1-phenylethoxy)methyl]indan-2-yl)-1-piperazine-carboxylate*

- 5 The expected product is obtained according to the procedure described in Steps A to C of Example 150, replacing the 3,5-dimethylbenzoic acid in Step A by benzoic acid.

Step B : *tert-Butyl 4-(2-{[(1 α)-1-phenylethoxy)methyl]indan-2-yl)-1-piperazine-carboxylate*

- 10 The compound obtained in the step above is separated by HPLC chromatography, on a chiral phase, of the racemic compound obtained in the step above.

The expected product is the first of the enantiomers thereby separated.

Step C : *1-{2-[(1 α)-1-Phenylethoxy)methyl]indan-2-yl}piperazine dihydrochloride.*

The expected product is obtained by reaction of the compound obtained in the step above with hydrochloric acid.

- 15 **Elemental microanalysis :**

	% C	% H	% N	% Cl
<i>Calculated</i>	64.54	7.39	6.84	17.32
<i>Found</i>	60.57	6.80	5.99	17.32

EXAMPLE 174 : 1-{2-[(1 β)-1-Phenylethoxy)methyl]indan-2-yl}piperazine dihydrochloride.

20

The second of the enantiomers separated in Step B of Example 173 is reacted with hydrochloric acid to yield the expected product.

Elemental microanalysis :

	% C	% H	% N	% Cl
<i>Calculated</i>	64.54	7.39	6.84	17.32
<i>Found</i>	64.96	6.97	6.43	16.82

5

EXAMPLE 175 : 1-[(1 α)-1-(3,5-Difluorobenzyloxymethyl)indan-1-yl]piperazine dihydrochloride.

Step A : (1 α)-1-[4-(tert-Butyloxycarbonyl)-1-piperazinyl]-1-hydroxymethylindan.

The expected product is obtained according to the procedure described in Step B of Example 1, starting from the compound obtained in Step A of Example 86.

10 **Step B : 1-[(1 α)-1-(3,5-Difluorobenzyloxymethyl)indan-1-yl]piperazine dihydrochloride.**

The expected product is obtained according to the procedure described in Steps C and D of Example 1, starting from the compound obtained in the step above and 3,5-difluorobenzyl
15 bromide.

Elemental microanalysis :

	% C	% H	% N	% Cl
<i>Calculated</i>	58.47	6.08	6.49	16.44
<i>Found</i>	58.67	6.17	6.27	16.52

20 **EXAMPLE 176 : 1-[(1 β)-1-(3,5-Difluorobenzyloxymethyl)indan-1-yl]piperazine dihydrochloride.**

Step A : (1 β)-1-[4-(tert-Butyloxycarbonyl)-1-piperazinyl]-1-hydroxymethylindan.

The expected product is obtained according to the procedure described in Step B of Example 1, starting from the second of the enantiomers separated in Step A of Example 86.

Step B : 1-[(1 β)-1-(3,5-Difluorobenzyloxymethyl)indan-1-yl]piperazine dihydrochloride.

The expected product is obtained according to the procedure described in Steps C and D of Example 1, starting from the compound obtained in the step above and 3,5-difluorobenzyl
5 bromide.

Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated	58.47	6.08	6.49	16.44
Found	58.37	6.24	6.17	16.40

10 **EXAMPLE 177 :** (1 α)-N-(3,5-Difluorobenzyl)-N-methyl-1-(1-piperazinyl)-1-indan-carboxamide dihydrochloride.

The expected product is obtained according to the procedure of Example 4, starting from the compound obtained in Step B of Example 86 and N-methyl-3,5-difluorobenzylamine.

Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated	57.65	5.94	9.17	15.47
15 Found	57.21	5.99	8.36	15.47

EXAMPLE 178 : (1 β)-N-(3,5-Difluorobenzyl)-N-methyl-1-(1-piperazinyl)-1-indan-carboxamide dihydrochloride.

The expected product is obtained according to the procedure of Example 4, starting from the compound obtained in Step A of Example 87 and N-methyl-3,5-difluorobenzylamine.

Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated	57.65	5.94	9.17	15.47
20 Found	58.14	6.16	8.84	14.96

EXAMPLE 179 : (1 α)-N-(3,5-Dichlorobenzyl)-N-methyl-1-(1-piperazinyl)-1-indan-carboxamide dihydrochloride.

The expected product is obtained according to the procedure of Example 4, starting from the compound obtained in Step B of Example 86 and N-methyl-3,5-dichlorobenzylamine.

Elemental microanalysis :

	% C	% H	% N	% Cl
5 <i>Calculated</i>	53.79	5.54	8.55	28.87
<i>Found</i>	53.17	6.03	8.18	29.05

EXAMPLE 180 : (1 β)-N-(3,5-Dichlorobenzyl)-N-methyl-1-(1-piperazinyl)-1-indan-carboxamide dihydrochloride.

The expected product is obtained according to the procedure of Example 4, starting from the compound obtained in Step A of Example 87 and N-methyl-3,5-dichlorobenzylamine.

10 Elemental microanalysis :

	% C	% H	% N	% Cl
<i>Calculated</i>	53.79	5.54	8.55	28.87
<i>Found</i>	54.00	5.49	8.07	29.08

15 **EXAMPLE 181 : (1 α)-N-(3-Chloro-5-fluorobenzyl)-N-methyl-1-(1-piperazinyl)-1-indancarboxamide dihydrochloride.**

The expected product is obtained according to the procedure of Example 4, starting from the compound obtained in Step B of Example 86 and N-methyl-3-chloro-5-fluorobenzylamine.

Elemental microanalysis :

	% C	% H	% N	% Cl
<i>Calculated</i>	55.65	5.73	8.85	22.40
20 <i>Found</i>	55.21	6.19	8.46	22.33

EXAMPLE 182 : (1 β)-N-(3-Chloro-5-fluorobenzyl)-N-methyl-1-(1-piperazinyl)-1-indancarboxamide dihydrochloride.

The expected product is obtained according to the procedure of Example 4, starting from the compound obtained in Step A of Example 87 and N-methyl-3-chloro-5-fluorobenzylamine.

Elemental microanalysis :

	% C	% H	% N	% Cl
5 <i>Calculated</i>	55.65	5.73	8.85	22.40
<i>Found</i>	55.10	6.11	8.45	22.08

EXAMPLE 183 : N-[(1 α)-1-(3-Chloro-5-fluorophenyl)ethyl]-N-methyl-2-(1-piperazinyl)-2-indancarboxamide hydrochloride.

10 Step A : *N-[(1RS)-1-(3-Chloro-5-fluorophenyl)ethyl]-N-methyl-2-(1-piperazinyl)-2-indancarboxamide.*

The expected product is obtained according to the procedure of Example 4, starting from the compound of Preparation 2 and N-methyl-1-(3-chloro-5-fluorophenyl)ethylamine.

Step B : *N-[(1 α)-1-(3-Chloro-5-fluorophenyl)ethyl]-N-methyl-2-(1-piperazinyl)-2-indancarboxamide*

15 The compound obtained in the step above is separated by HPLC chromatography, on a chiral phase, of the racemic compound obtained in the step above.

The expected product is the first of the enantiomers thereby separated.

Step C : *N-[(1 α)-1-(3-Chloro-5-fluorophenyl)ethyl]-N-methyl-2-(1-piperazinyl)-2-indancarboxamide hydrochloride.*

20 The expected product is obtained by conversion of the compound obtained in the step above into a salt using hydrochloric acid.

Elemental microanalysis :

	% C	% H	% N	% Cl
<i>Calculated</i>	58.70	6.10	8.93	18.83
<i>Found</i>	58.82	6.22	8.81	18.73

5

EXAMPLE 184 : N-[(1 β)-1-(3-Chloro-5-fluorophenyl)ethyl]-N-methyl-2-(1-piperazinyl)-2-indancarboxamide hydrochloride.

The second of the enantiomers separated in Step B of Example 183 is converted into a salt using hydrochloric acid to yield the expected product.

10 Elemental microanalysis :

	% C	% H	% N	% Cl
<i>Calculated</i>	58.70	6.10	8.93	18.83
<i>Found</i>	59.03	6.23	8.78	19.38

15 **EXAMPLE 185 (1 α)-N-[(1 α')-1-(3-Chloro-5-fluorophenyl)ethyl]-N-methyl-1-(1-piperazinyl)-1-indancarboxamide dihydrochloride.**

Step A : (1 α)-N-[(1RS)-1-(3-Chloro-5-fluorophenyl)ethyl]-N-methyl-1-[4-(tert-butyloxycarbonyl)-1-piperazinyl]-1-indancarboxamide.

20 The expected product is obtained according to the procedure described in Step A of Example 4, starting from the compound obtained in Step B of Example 86 and (RS)-N-methyl-1-(3-chloro-5-fluorophenyl)ethylamine.

Step B : (1 α)-N-[(1 α')-1-(3-Chloro-5-fluorophenyl)ethyl]-N-methyl-1-[4-(tert-butyloxycarbonyl)-1-piperazinyl]-1-indancarboxamide.

25 The expected product is obtained by chromatography on silica (eluant: dichloromethane/ethyl acetate) of the diastereoisomeric mixture obtained in Step A.

Step C: *(1 α)-N-[(1 α')-1-(3-Chloro-5-fluorophenyl)ethyl]-N-methyl-1-(1-piperazinyl)-1-indancarboxamide dihydrochloride.*

The expected product is obtained according to the procedure described in Step B of Example 4, starting from the compound obtained in Step B above.

5 **Elemental microanalysis :**

	% C	% H	% N	% Cl
Calculated	56.51	5.98	8.60	21.76
Found	57.14	6.01	8.47	20.75

10 **EXAMPLE 186 :** *(1 α)-N-[(1 β')-1-(3-Chloro-5-fluorophenyl)ethyl]-N-methyl-1-(1-piperazinyl)-1-indancarboxamide dihydrochloride.*

The expected product is obtained according to the procedure described in Step B of Example 4, starting from the second of the diastereoisomers separated in Step B of Example 185.

Elemental microanalysis :

15

	% C	% H	% N	% Cl
Calculated	56.51	5.98	8.60	21.76
Found	57.38	5.83	8.51	20.89

EXAMPLE 187 : *(1 β)-N-[(1 α')-1-(3-Chloro-5-fluorophenyl)ethyl]-N-methyl-1-(1-piperazinyl)-1-indancarboxamide dihydrochloride.*

20 **Step A:** *(1 β)-N-[(1RS)-1-(3-Chloro-5-fluorophenyl)ethyl]-N-methyl-1-[4-(tert-butyloxycarbonyl)-1-piperazinyl]-1-indancarboxamide.*

The expected product is obtained according to the procedure described in Step A of Example 4, starting from the compound obtained in Step A of Example 87 and (RS)-N-methyl-1-(3-chloro-5-fluorophenyl)ethylamine.

Step B : (1 β)-N-[(1 α')-1-(3-Chloro-5-fluorophenyl)ethyl]-N-methyl-1-[4-(tert-butylloxycarbonyl)-1-piperazinyl]-1-indancarboxamide.

The expected product is obtained by chromatography on silica (eluant: dichloromethane/ethyl acetate) of the diastereoisomeric mixture obtained in Step A.

5 **Step C** : (1 β)-N-[(1 α')-1-(3-Chloro-5-fluorophenyl)ethyl]-N-methyl-1-(1-piperazinyl)-1-indancarboxamide dihydrochloride.

The expected product is obtained according to the procedure described in Step B of Example 4, starting from the compound obtained in Step B above.

Elemental microanalysis :

10		% C	% H	% N	% Cl
	Calculated	56.51	5.98	8.60	21.76
	Found	57.05	5.98	8.39	21.05

15 **EXAMPLE 188** : (1 β)-N-[(1 β')-1-(3-Chloro-5-fluorophenyl)ethyl]-N-methyl-1-(1-piperazinyl)-1-indancarboxamide dihydrochloride.

The expected product is obtained according to the procedure described in Step B of Example 4, starting from the second of the diastereoisomers separated in Step B of Example 187.

Elemental microanalysis :

20		% C	% H	% N	% Cl
	Calculated	56.51	5.98	8.60	21.76
	Found	57.15	6.02	8.38	21.14

EXAMPLE 189 : N-[3-Chloro-5-fluorobenzyl]-N-methyl-5,6-difluoro-2-(1-piperazinyl)-2-indancarboxamide hydrochloride.

Step A : 4,5-Difluorophthalic acid.

5 35 g (0.161 mol) of 4,5-dichlorophthalic anhydride, 32.7g of potassium fluoride and 140 ml of sulpholane are introduced into an autoclave. The reaction mixture is then heated at 180°C for 24 hours and is then, after returning to ambient temperature, poured into 500 ml of 1N sodium hydroxide solution and washed 3 times with ether. The aqueous phase is acidified to pH = 1 using hydrochloric acid and is then extracted with ether. The
10 ether phase is washed with water, dried and evaporated to yield the expected product.

Step B : (4,5-Difluoro-2-hydroxymethylphenyl)methanol.

To a solution of 0.198 mol of sodium borohydride in 150 ml of tetrahydrofuran there is
15 added, over 20 minutes and maintaining the temperature at 20°C, a solution of 8.25 mmol of the compound obtained in the step above in 150 ml of tetrahydrofuran. After stirring for 3 hours at ambient temperature, there is added, over 30 minutes and maintaining the temperature at 20°C, a solution of 8.25 mmol of iodine in 150 ml of tetrahydrofuran. After stirring overnight at ambient temperature, the reaction mixture is cooled using an iced
20 water bath and then 45 ml of 3N hydrochloric acid are added dropwise. After stirring for a further 30 minutes, ethyl ether is added. The insoluble matter that forms is filtered off. The ether and tetrahydrofuran are then evaporated off, ethyl ether is added and then the solution obtained is washed with a 1N solution of sodium thiosulphate, with 3N sodium hydroxide solution and then with water to yield, after drying and evaporation, the expected product.

25

Step C : 1,2-Bis-bromomethyl-4,5-difluorobenzene.

To 0.195 mol of the compound obtained in the step above in 1.25 litres of ether there is added, dropwise, over 1 hour 30 minutes, a solution of 0.916 mol of phosphorus tribromide
30 in 300 ml of ether. The reaction mixture is then stirred overnight at ambient temperature; it is subsequently poured into 1 litre of ice-cold water and separated. The organic phase is

then washed with 1N sodium hydroxide solution and then with water and finally with saturated sodium chloride solution before being dried and concentrated to yield the expected product.

5 **Step D :** *2-(Benzhydrylidene-amino)-5,6-difluoroindan-2-carboxylic acid ethyl ester.*

To 0.374 mol of sodium hydride 95 % in 160 ml of tetrahydrofuran there is added, over 40 minutes and maintaining the temperature of the reaction mixture below 5°C, a solution of 0.17 mol of the compound obtained in the step above and 0.17 mol of (benzhydrylidene-amino)acetic acid ethyl ester in 300 ml of tetrahydrofuran. After stirring overnight at ambient temperature, the reaction mixture is filtered and concentrated to yield the expected product.

Step E : *Ethyl 2-amino-5,6-difluoro-2-indancarboxylate hydrochloride.*

To 0.17 mol of the compound obtained in the step above, dissolved in 500 ml of dioxane, there are added 510 ml of 1N hydrochloric acid, and then the reaction mixture is stirred overnight at ambient temperature. The dioxane is then evaporated off; the residue obtained is subsequently made solid by stirring up with 1.5 litres of ether and is filtered off, washed and then dried to yield the expected product.

15 **Step F :** *2-[4-(tert-Butyloxycarbonyl)-1-piperazinyl]-5,6-difluoro-2-indan-carboxylic acid.*

The expected product is obtained according to the procedure described in Steps C to F of Preparation 1, starting from the compound obtained in the step above.

20 **Step G :** *N-[3-Chloro-5-fluorobenzyl]-N-methyl-5,6-difluoro-2-(1-piperazinyl)-2-indancarboxamide hydrochloride.*

The expected product is obtained according to the procedure of Example 4, starting from the compound obtained in the step above and N-methyl-3-chloro-5-fluorobenzylamine.

Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated	55.71	5.10	8.86	14.95
Found	55.85	5.43	9.03	15.61

5 **EXAMPLE 190 : N-(3-Chloro-5-fluorobenzyl)-N-methyl-2-(1-piperazinyl)-2,3-dihydro-1H-cyclopenta[b]naphthalene-2-carboxamide hydrochloride**

Step A : 2,3-Bis(bromomethyl)naphthalene.

10 To 0.454 mol of 2,3-dimethyl-naphthalene in 710 ml of carbon tetrachloride there are added 0.953 mol of N-bromosuccinimide and 45.4 mmol of 2,2'-azobisisobutyronitrile. The reaction mixture is then heated at 65°C for 4 hours and subsequently concentrated and purified by chromatography on silica gel, using a gradient of cyclohexane and dichloromethane (cyclohexane/dichloromethane: 70/30 to 0/100) as eluant, to yield the
15 expected product.

Step B : Ethyl 2-amino-2,3-dihydro-1H-cyclopenta[b]naphthalene-2-carboxylate hydrochloride.

The expected product is obtained according to the procedure described in Steps D to E of Example 189, starting from the compound obtained in the step above.

Step C : 2-[4-(tert-Butoxycarbonyl)-1-piperazinyl]-2,3-dihydro-1H-cyclopenta[b]-naphthalene-2-carboxylic acid

20

The expected product is obtained according to the procedure described in Steps C to F of Preparation 1, starting from the compound obtained in the step above.

Step D : *N-(3-Chloro-5-fluorobenzyl)-N-methyl-2-(1-piperazinyl)-2,3-dihydro-1H-cyclopenta[b]naphthalene-2-carboxamide hydrochloride*

The expected product is obtained according to the procedure of Example 4, starting from the compound obtained in the step above and N-methyl-3-chloro-5-fluorobenzylamine.

Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated	63.94	5.78	8.60	7.26
Found	63.56	5.58	8.23	8.15

EXAMPLE 191 : *N-[3-Chloro-5-fluorobenzyl]-N-methyl-5,6-dichloro-2-(1-piperazinyl)-2-indancarboxamide hydrochloride.*

Step A : *4,5-Dichlorophthalic acid.*

The expected product is obtained by ring-opening of 4,5-dichlorophthalic anhydride using acetic anhydride.

Step B : *Ethyl 2-amino-5,6-dichloro-2-indancarboxylate hydrochloride.*

The expected product is obtained according to the procedure described in Steps B to E of Example 189, starting from the compound obtained in the step above.

Step C : *2-[4-(tert-Butyloxycarbonyl)-1-piperazinyl]-5,6-dichloro-2-indancarboxylic acid.*

The expected product is obtained according to the procedure described in Steps C to F of Preparation 1, starting from the compound obtained in the step above.

Step D: *N-[3-Chloro-5-fluorobenzyl]-N-methyl-5,6-dichloro-2-(1-piperazinyl)-2-indancarboxamide hydrochloride.*

The expected product is obtained according to the procedure of Example 4, starting from
5 the compound obtained in the step above and N-methyl-3-chloro-5-fluorobenzylamine.

Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated	52.09	4.77	8.28	27.96
Found	52.77	4.65	8.21	28.83

10 **EXAMPLE 192 :** *1-[(1 α)-1-(3,5-Difluorobenzylloxymethyl)-5,6-difluoroindan-1-yl]-piperazine dihydrochloride.*

Step A: *3-(3,4-Difluorophenyl)propionyl chloride*

To 0.27 mol of 3,4-difluorocinnamic acid dissolved in dichloroethane there are added
15 20 drops of dimethylformamide and 100 ml of thionyl chloride.

The mixture is then heated at reflux for 5 hours, and is subsequently evaporated to dryness and dried to yield the expected product.

Step B: *5,6-Difluoro-1-indanone*

To 58 g of the acid chloride obtained in the step above, dissolved in dichloroethane, there
20 are added, at 0°C, over 10 minutes and in 3 portions, 51.3 g of aluminium chloride. After stirring at 0°C for 40 minutes, the solution is poured into 600 ml of ice-cold 1N hydrochloric acid.

The mixture is then separated, washed twice with 1N sodium hydroxide solution and then with water and with brine, before being dried, filtered, evaporated and dried to yield the
25 expected product.

Step C: *(1RS)-1-Amino-5,6-difluoro-1-indancarboxylic acid*

To 0.27 mol of the compound obtained in the step above in 650 ml of ethanol and 50 ml of water there are added 113.6 g of ammonium carbonate and then 35.8 g of potassium cyanide.

- 5 The reaction mixture is then heated at 120°C under pressure for 3 hours (the pressure increases to 20 bars).

After cooling, the solvents are evaporated off and the residue is taken up in water. The insoluble material is filtered off and dried.

- 10 The hydantoin thereby obtained is heated in the autoclave for 9 hours at 120°C in 1.4 litres of water, in the presence of 0.17 mol of barium hydroxide.

After cooling, the mixture is filtered; finely divided dry ice (solid carbon dioxide) is added to the filtrate to adjust to pH 7. The mixture is filtered, and then the filtrate is evaporated to dryness to yield the expected product.

Step D: *(1RS)-1-[(tert-Butyloxycarbonyl)amino]-5,6-difluoro-1-indancarboxylic acid*

- 15 To 0.17 mol of the compound obtained in the step above in 1.3 litres of dioxane there are added 398 ml of 1N sodium hydroxide solution and then, at 0-5°C, 0.23 mol of di(tert-butyl) dicarbonate dissolved in 100 ml of dioxane.

After stirring for 48 hours at ambient temperature, the dioxane is evaporated off and the residue is taken up in 425 ml of 1N hydrochloric acid.

- 20 The solution is then saturated with sodium chloride and extracted with ethyl acetate. The organic phases are dried, filtered and evaporated to yield the expected product.

Step E: *(1RS)-1-[4-(tert-Butyloxycarbonyl)-1-piperazinyl]-5,6-difluoro-1-indancarboxylic acid.*

25

The expected compound is obtained according to the procedure of Preparation 1, starting from the compound obtained in the step above.

Step F: *Benzyl (1RS)-1-[4-(tert-butyloxycarbonyl)-1-piperazinyl]-5,6-difluoro-1-indancarboxylate.*

The expected compound is obtained according to the procedure described in Step A of Example 1, starting from the compound obtained in the step above.

Step G: *Benzyl (1 α)-1-[4-(tert-butyloxycarbonyl)-1-piperazinyl]-5,6-difluoro-1-indancarboxylate.*

- 5 The expected product is obtained by separation on a chiral HPLC column of the compound obtained in the step above.

Step H: *1-[(1 α)-1-(3,5-Difluorobenzylloxymethyl)-5,6-difluoroindan-1-yl]piperazine dihydrochloride.*

The expected compound is obtained according to the procedure described in Steps B to D of Example 1, starting from the compound obtained in the step above and 3,5-difluorobenzyl bromide.

Elemental microanalysis :

10		% C	% H	% N	% Cl
	<i>Calculated</i>	53.97	5.18	5.99	15.17
	<i>Found</i>	54.21	5.26	5.56	14.90

EXAMPLE 193 : *1-[(1 β)-1-(3,5-Difluorobenzylloxymethyl)-5,6-difluoroindan-1-yl]-piperazine dihydrochloride.*

- 15 **Step A:** *Benzyl (1 β)-1-[4-(tert-butyloxycarbonyl)-1-piperazinyl]-5,6-difluoro-1-indancarboxylate.*

The expected product is the second of the enantiomers separated in Step G of Example 192.

Step B : *1-[(1 β)-1-(3,5-Difluorobenzyloxymethyl)-5,6-difluoroindan-1-yl]piperazine dihydrochloride.*

The expected compound is obtained according to the procedure described in Steps B to D of Example 1, starting from the compound obtained in the step above and 3,5-difluorobenzyl bromide.

Elemental microanalysis :

	% C	% H	% N	% Cl
5 <i>Calculated</i>	53.97	5.18	5.99	15.17
<i>Found</i>	53.26	5.53	6.44	15.69

EXAMPLE 194 : *1-[(1 α)-1-(3,5-Difluorobenzyloxymethyl)-5,6-dichloroindan-1-yl]-piperazine hydrochloride.*

10 **Step A :** *Benzyl (1RS)-1-[4-(tert-butyloxycarbonyl)-1-piperazinyl]-5,6-dichloro-1-indancarboxylate.*

The expected compound is obtained according to the procedure described in Steps A to F of Example 192, replacing the 3,4-difluorocinnamic acid in Step A by 3,4-dichlorocinnamic acid.

Step B : *Benzyl (1 α)-1-[4-(tert-butyloxycarbonyl)-1-piperazinyl]- 5,6-dichloro-1-indancarboxylate.*

The expected product is obtained by separation on a chiral HPLC column of the compound obtained in the step above.

Step C : *1-[(1 α)-1-(3,5-Difluorobenzyloxymethyl)-5,6-dichloroindan-1-yl]piperazine hydrochloride.*

The expected compound is obtained according to the procedure described in Steps B to D of Example 1, starting from the compound obtained in the step above and 3,5-difluorobenzyl bromide.

Elemental microanalysis :

	% C	% H	% N
5 <i>Calculated</i>	54.39	5.00	6.04
<i>Found</i>	54.97	5.08	5.71

EXAMPLE 195 : *1-[(1 β)-1-(3,5-Difluorobenzyloxymethyl)-5,6-difluoroindan-1-yl]-piperazine hydrochloride.*

10 **Step A :** *Benzyl (1 β)-1-[4-(tert-butyloxycarbonyl)-1-piperazinyl]-5,6-dichloro-1-indancarboxylate.*

The expected product is the second of the enantiomers separated in Step B of Example 194.

Step B : *1-[(1 β)-1-(3,5-Difluorobenzyloxymethyl)-5,6-dichloroindan-1-yl]piperazine hydrochloride.*

15 The expected compound is obtained according to the procedure described in Steps B to D of Example 1, starting from the compound obtained in the step above and 3,5-difluorobenzyl bromide.

Elemental microanalysis :

	% C	% H	% N	% Cl
20 <i>Calculated</i>	54.39	5.00	6.04	22.93
<i>Found</i>	54.54	5.04	5.69	22.89

EXAMPLE 196 : 1-[(1 α)-1-(3-Bromo-5-fluorobenzyloxymethyl)indan-1-yl]-piperazine dihydrochloride.

The expected product is obtained according to the procedure described in Steps B to D of Example 1, starting from the compound obtained in Step A of Example 175 and 3-bromo-5-fluorobenzyl bromide.

Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated	51.24	5.32	5.69	14.40
Found	51.36	5.35	5.46	14.51

EXAMPLE 197 : 1-[(1 β)-1-(3-Bromo-5-fluorobenzyloxymethyl)indan-1-yl]-piperazine dihydrochloride.

The expected product is obtained according to the procedure described in Steps B to D of Example 1, starting from the compound obtained in Step A of Example 176 and 3-bromo-5-fluorobenzyl bromide.

Elemental microanalysis :

	% C	% H	% N	% Cl
Calculated	51.24	5.32	5.69	14.40
Found	51.65	5.38	5.64	14.44

EXAMPLE 198 : N-(3-Fluorobenzyl)-N-methyl-2-(1-piperazinyl)-2-indan-carboxamide dihydrochloride.

The expected product is obtained according to the procedure of Example 4, starting from the compound of Preparation 2 and N-methyl-3-fluorobenzylamine.

EXAMPLE 199 : N-(3-Chlorobenzyl)-N-methyl-2-(1-piperazinyl)-2-indan-carboxamide dihydrochloride.

The expected product is obtained according to the procedure of Example 4, starting from the compound of Preparation 2 and N-methyl-3-chlorobenzylamine.

5 **EXAMPLE 200 : N-(3-Bromobenzyl)-N-methyl-2-(1-piperazinyl)-2-indan-carboxamide dihydrochloride.**

The expected product is obtained according to the procedure of Example 4, starting from the compound of Preparation 2 and N-methyl-3-bromobenzylamine.

10 **EXAMPLE 201 : N-Methyl-N-[3-(trifluoromethyl)benzyl]-2-(1-piperazinyl)-2-indancarboxamide dihydrochloride.**

The expected product is obtained according to the procedure of Example 4, starting from the compound of Preparation 2 and N-methyl-3-(trifluoromethyl)benzylamine.

EXAMPLE 202 : N-(3-Chloro-5-fluoro-2-methoxybenzyl)-N-methyl-2-(1-piperazinyl)-2-indancarboxamide dihydrochloride.

15 The expected product is obtained according to the procedure of Example 4, starting from the compound of Preparation 2 and N-methyl-3-chloro-5-fluoro-2-methoxybenzylamine.

EXAMPLE 203 : N-(5-Chloro-3-fluoro-2-methoxybenzyl)-N-methyl-2-(1-piperazinyl)-2-indancarboxamide dihydrochloride.

20 The expected product is obtained according to the procedure of Example 4, starting from the compound of Preparation 2 and N-methyl-5-chloro-3-fluoro-2-methoxybenzylamine.

EXAMPLE 204 : N-(3-Chloro-5-fluoro-4-methoxybenzyl)-N-methyl-2-(1-piperazinyl)-2-indancarboxamide dihydrochloride.

The expected product is obtained according to the procedure of Example 4, starting from the compound of Preparation 2 and N-methyl-3-chloro-5-fluoro-4-methoxybenzylamine.

5 **EXAMPLE 205 : N-(3,5-Difluoro-2-methoxybenzyl)-N-methyl-2-(1-piperazinyl)-2-indancarboxamide dihydrochloride.**

The expected product is obtained according to the procedure of Example 4, starting from the compound of Preparation 2 and N-methyl-3,5-difluoro-2-methoxybenzylamine.

10 **EXAMPLE 206 : N-(3,5-Difluoro-4-methoxybenzyl)-N-methyl-2-(1-piperazinyl)-2-indancarboxamide dihydrochloride.**

The expected product is obtained according to the procedure of Example 4, starting from the compound of Preparation 2 and N-methyl-3,5-difluoro-4-methoxybenzylamine.

EXAMPLE 207 : N-(3,5-Dichloro-2-methoxybenzyl)-N-methyl-2-(1-piperazinyl)-2-indancarboxamide dihydrochloride.

15 The expected product is obtained according to the procedure of Example 4, starting from the compound of Preparation 2 and N-methyl-3,5-dichloro-2-methoxybenzylamine.

EXAMPLE 208 : N-(3,5-Dichloro-4-methoxybenzyl)-N-methyl-2-(1-piperazinyl)-2-indancarboxamide dihydrochloride.

20 The expected product is obtained according to the procedure of Example 4, starting from the compound of Preparation 2 and N-methyl-3,5-dichloro-4-methoxybenzylamine.

EXAMPLE 209 : N-(3-Cyanobenzyl)-N-methyl-2-(1-piperazinyl)-2-indan-carboxamide dihydrochloride.

The expected product is obtained according to the procedure of Example 4, starting from the compound of Preparation 2 and N-methyl-3-cyanobenzylamine.

5 **EXAMPLE 210 : N-(3-Cyano-5-fluorobenzyl)-N-methyl-2-(1-piperazinyl)-2-indan-carboxamide dihydrochloride.**

The expected product is obtained according to the procedure of Example 4, starting from the compound of Preparation 2 and N-methyl-3-cyano-5-fluorobenzylamine.

10 **EXAMPLE 211 : N-(3-Chloro-5-cyanobenzyl)-N-methyl-2-(1-piperazinyl)-2-indan-carboxamide dihydrochloride.**

The expected product is obtained according to the procedure of Example 4, starting from the compound of Preparation 2 and N-methyl-3-chloro-5-cyanobenzylamine.

EXAMPLE 212 : N-[(2,6-Difluoro-4-pyridyl)methyl]-N-methyl-2-(1-piperazinyl)-2-indancarboxamide dihydrochloride.

15 The expected product is obtained according to the procedure of Example 4, starting from the compound of Preparation 2 and N-[(2,6-difluoro-4-pyridyl)methyl]-N-methylamine.

EXAMPLE 213 : N-[(2-Chloro-6-fluoro-4-pyridyl)methyl]-N-methyl-2-(1-piperazinyl)-2-indancarboxamide dihydrochloride.

20 The expected product is obtained according to the procedure of Example 4, starting from the compound of Preparation 2 and N-[(2-chloro-6-fluoro-4-pyridyl)methyl]-N-methylamine.

EXAMPLE 214 : N-[(2,6-Dichloro-4-pyridyl)methyl]-N-methyl-2-(1-piperazinyl)-2-indancarboxamide dihydrochloride.

The expected product is obtained according to the procedure of Example 4, starting from the compound of Preparation 2 and N-[(2,6-dichloro-4-pyridyl)methyl]-N-methylamine.

5 **EXAMPLE 215 : N-[(4,6-Difluoro-2-pyridyl)methyl]-N-methyl-2-(1-piperazinyl)-2-indancarboxamide dihydrochloride.**

The expected product is obtained according to the procedure of Example 4, starting from the compound of Preparation 2 and N-[(4,6-difluoro-2-pyridyl)methyl]-N-methylamine.

10 **EXAMPLE 216 : N-[(6-Chloro-4-fluoro-2-pyridyl)methyl]-N-methyl-2-(1-piperazinyl)-2-indancarboxamide dihydrochloride.**

The expected product is obtained according to the procedure of Example 4, starting from the compound of Preparation 2 and N-[(6-chloro-4-fluoro-2-pyridyl)methyl]-N-methylamine.

15 **EXAMPLE 217 : N-[(4,6-Dichloro-2-pyridyl)methyl]-N-methyl-2-(1-piperazinyl)-2-indancarboxamide dihydrochloride.**

The expected product is obtained according to the procedure of Example 4, starting from the compound of Preparation 2 and N-[(4,6-dichloro-2-pyridyl)methyl]-N-methylamine.

EXAMPLE 218 : N-[(4-Chloro-6-fluoro-2-pyridyl)methyl]-N-methyl-2-(1-piperazinyl)-2-indancarboxamide dihydrochloride.

20 The expected product is obtained according to the procedure of Example 4, starting from the compound of Preparation 2 and N-[(4-chloro-6-fluoro-2-pyridyl)methyl]-N-methylamine.

PHARMACOLOGICAL STUDY OF COMPOUNDS OF THE INVENTION

EXAMPLE 219 : Determination of the affinity for serotonin reuptake sites in the rat.

The affinity of the compounds for the serotonin (5-HTT) reuptake site is evaluated by competition experiments with [³H]-citalopram on rat frontal cortex membranes. The cortices are homogenised using a Polytron in 40 volumes (weight/volume) of cold Tris-HCl (50mM, pH 7.4) incubation buffer containing 120mM NaCl and 5mM KCl and are then centrifuged for a first time. The sediment is resuspended in the same buffer, incubated for 10 minutes at 37°C and then re-centrifuged. The membranes are washed a further two times and the sediment is then resuspended in an appropriate volume of incubation buffer.

The membranes are then incubated for 2 hours at 25°C with the compound under test in the presence of 0.7nM [³H]-citalopram. Non-specific binding is determined with 10µM fluoxetine. At the end of the incubation period, the samples are filtered through Unifilter GF/B type filters pretreated with PEI (0.5 %) and washed several times with the incubation buffer. The radioactivity retained on the filters is counted after addition of scintillation liquid, with the aid of a scintillation counter. The isotherms obtained are analysed by non-linear regression to determine the IC₅₀ values, which are converted into K_i using the Cheng-Prusoff equation:

$$K_i = IC_{50}/(1 + L/K_d)$$

wherein L represents the concentration of radioligand and K_d is the dissociation constant of [³H]-citalopram on the serotonin reuptake site (0.7nM). The results are expressed as pK_i = -log K_i.

The results obtained for representative compounds of the invention are collated in the following table:

<i>Compound</i>	<i>pKi r5-HTT</i>
Example 1	6.61
Example 2	7.27
Example 3	7.20
Example 68	7.47
Example 69	6.82
Example 70	8.49
Example 85	7.03
Example 135	7.36

EXAMPLE 220 : hNK₁ binding.

The affinity of compounds of the invention was determined by competition experiments in the presence of [³H]-Substance P (Sar-9, MetO²-11,2-propyl-3,4-3H). IM9 human lymphoblast cells endogenously expressing NK₁ receptors are centrifuged and taken up in the incubation buffer containing 50mM TRIS, 150mM NaCl, 4mM CaCl₂, protease inhibitors at 1/100^e (Cocktail SIGMA P8340) and 0.2 % BSA. The volume of incubation buffer is determined so as to obtain a concentration of 5 x 10⁶ cells/ml. The cell preparation is then incubated together with 1.5nM [³H]-Substance P and the compound under test for 90 minutes at ambient temperature. Non-specific binding is determined in the presence of 1μM GR 205171.

At the end of the incubation period, the samples are filtered through Unifilter GF/B type filters pretreated with PEI (0.1 %) and washed several times with the filtration buffer (50mM TRIS, 150mM NaCl, 4mM CaCl₂). The radioactivity retained on the filters is measured by counting after addition of scintillation liquid to the filters. The counts are analysed by non-linear regression, allowing the isotherms to be plotted and the IC₅₀ values to be determined. The latter are converted into inhibition constants (K_i) by means of the Cheng-Prusoff equation:

$$K_i = IC_{50} / (1 + L / K_D)$$

wherein L is the concentration of [³H]-Substance P and K_D is the dissociation constant of [³H]-Substance P for human NK₁ receptors (0.53nM). The results are expressed as pK_i (-log K_i).

The results obtained for representative compounds of the invention are collated in the following table:

<i>Compound</i>	<i>pK_i NK₁</i>
Example 1	8.47
Example 2	7.74
Example 3	6.79
Example 5	6.40
Example 11	6.31
Example 79	6.29

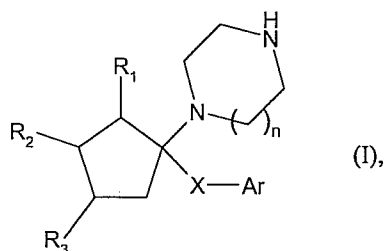
EXAMPLE 221 : Pharmaceutical composition.

Formula for the preparation of 1000 tablets each containing 10 mg of active ingredient:

Compound of Example 1	10 g
Hydroxypropylcellulose	2 g
10 Wheat starch	10 g
Lactose.....	100 g
Magnesium stearate	3 g
Talc	3 g

CLAIMS

1. Compound of formula (I) :



wherein :

- 5 - R_3 represents a hydrogen atom, and R_1 and R_2 together with the carbon atoms carrying them form a benzene, naphthalene or quinoline ring structure, each of those ring structures being optionally substituted by one or more identical or different substituents selected from hydrogen, halogen and linear or branched C_1 - C_6 alkyl optionally substituted by one or more halogen atoms,
- 10 or R_1 represents a hydrogen atom, and R_2 and R_3 together with the carbon atoms carrying them form a benzene, naphthalene or quinoline ring structure, each of those ring structures being optionally substituted by one or more identical or different substituents selected from hydrogen, halogen and linear or branched C_1 - C_6 alkyl optionally substituted by one or more halogen atoms,
- 15 - n represents 1 or 2,
- $-X-$ represents a group selected from $-(CH_2)_m-O-Ak-$, $-(CH_2)_m-NR_4-Ak-$, $-(CO)-NR_4-Ak-$ and $-(CH_2)_m-NR_4-(CO)-$,

m represents an integer between 1 and 6 inclusive, Ak represents a linear or branched C₁-C₆alkylene chain optionally substituted by a hydroxy group, and R₄ represents a hydrogen atom or a linear or branched C₁-C₆alkyl group,

- Ar represents an aryl or heteroaryl group,

5 its optical isomers, and also addition salts thereof with a pharmaceutically acceptable acid,

it being understood that:

optical isomers mean enantiomers and diastereoisomers,

an aryl group means phenyl, biphenyl or naphthyl, each of those groups being optionally substituted by one or more identical or different groups selected from halogen, linear or
10 branched C₁-C₆alkyl, linear or branched C₁-C₆alkoxy, hydroxy, cyano and linear or branched C₁-C₆trihaloalkyl,

a heteroaryl group means an aromatic mono- or bi-cyclic 5- to 12-membered group containing one, two or three hetero atoms selected from oxygen, nitrogen and sulphur, it being understood that the heteroaryl group may be optionally substituted by one or more
15 identical or different groups selected from halogen, linear or branched C₁-C₆alkyl, linear or branched C₁-C₆alkoxy, hydroxy and linear or branched C₁-C₆trihaloalkyl.

2. Compound of formula (I) according to claim 1, wherein R₁ and R₂ together with the carbon atoms carrying them form an optionally substituted benzene ring and R₃ represents a hydrogen atom, or R₂ and R₃ together with the carbon atoms carrying them
20 form an optionally substituted benzene ring and R₁ represents a hydrogen atom.

3. Compound of formula (I) according to either claim 1 or claim 2, wherein n represents 1.

4. Compound of formula (I) according to any one of claims 1 to 3, wherein m represents 1.

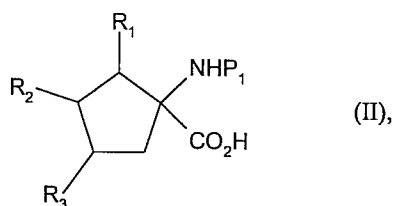
5. Compound of formula (I) according to any one of claims 1 to 4, wherein Ar represents an aryl group.

6. Compound of formula (I) according to claim 1, selected from:

- 1-[(1RS)-1-(3,5-dibromobenzyloxymethyl)indan-1-yl]piperazine, its optical isomers, and also addition salts thereof with a pharmaceutically acceptable acid,
- 1-[(1RS)-1-(3,5-dimethylbenzyloxymethyl)indan-1-yl]piperazine, its optical isomers, and also addition salts thereof with a pharmaceutically acceptable acid,
- 1-[2-(3,5-dimethylbenzyloxymethyl)indan-2-yl]piperazine, and also addition salts thereof with a pharmaceutically acceptable acid,
- N-[(3,5-bis(trifluoromethyl)benzyl]-2-(1-piperazinyl)-2-indancarboxamide, and also addition salts thereof with a pharmaceutically acceptable acid,
- (1RS)-N-benzyl-N-methyl-1-(1-piperazinyl)-1-indancarboxamide, its optical isomers, and also addition salts thereof with a pharmaceutically acceptable acid,
- (1RS)-N-[3,5-bis(trifluoromethyl)benzyl]-N-methyl-1-(1-piperazinyl)-1-indancarboxamide, its optical isomers, and also addition salts thereof with a pharmaceutically acceptable acid,
- (1RS)-N-(3,5-dimethylbenzyl)-1-(1-piperazinyl)-1-indancarboxamide, its optical isomers, and also addition salts thereof with a pharmaceutically acceptable acid,
- N-(3,5-difluorobenzyl)-2-(1-piperazinyl)-2-indancarboxamide, and also addition salts thereof with a pharmaceutically acceptable acid,
- N-(3,5-dichlorobenzyl)-N-methyl-2-(1-piperazinyl)-2-indancarboxamide, and also addition salts thereof with a pharmaceutically acceptable acid,
- (1RS)-N-(3,5-difluorobenzyl)-N-methyl-1-(1-piperazinyl)-1-indancarboxamide, its optical isomers, and also addition salts thereof with a pharmaceutically acceptable acid,
- (1RS)-N-[3-fluoro-5-(trifluoromethyl)benzyl]-N-methyl-1-(1-piperazinyl)-1-indancarboxamide, its optical isomers, and also addition salts thereof with a pharmaceutically acceptable acid,
- (1RS)-1-[1-(3,5-difluorobenzyloxymethyl)indan-1-yl]piperazine, its optical isomers, and also addition salts thereof with a pharmaceutically acceptable acid,

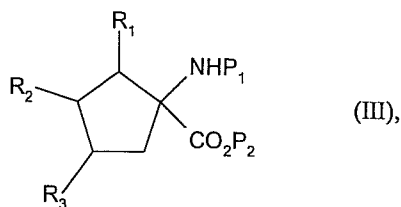
- N-(3-chloro-5-fluorobenzyl)-N-methyl-2-(1-piperaziny)-2-indancarboxamide, and also addition salts thereof with a pharmaceutically acceptable acid,
- 1-[(1RS)-1-(3,5-difluorobenzyloxymethyl)indan-1-yl]piperazine, its optical isomers, and also addition salts thereof with a pharmaceutically acceptable acid,
- 5 - (1RS)-N-(3,5-difluorobenzyl)-N-methyl-1-(1-piperaziny)-1-indancarboxamide, its optical isomers, and also addition salts thereof with a pharmaceutically acceptable acid,
- 1-[(1RS)-1-(3,5-difluorobenzyloxymethyl)-5,6-difluoroindan-1-yl]piperazine, its optical isomers, and also addition salts thereof with a pharmaceutically acceptable acid,
- 10 - and 1-[(1RS)-1-(3-bromo-5-fluorobenzyloxymethyl)indan-1-yl]piperazine, its optical isomers, and also addition salts thereof with a pharmaceutically acceptable acid.

7. Process for the preparation of compounds of formula (I) according to claim 1, starting from the compound of formula (II) :



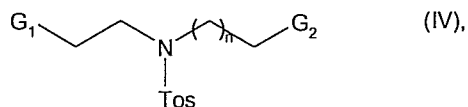
wherein R_1 , R_2 and R_3 are as defined for formula (I) and P_1 represents a protecting group for the amine function,

the acid function of which is protected to yield the compound of formula (III) :



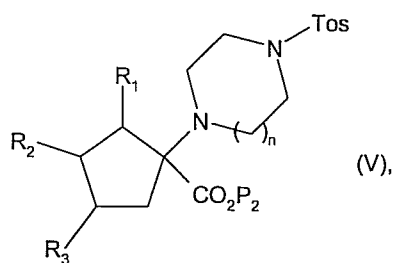
wherein R_1 , R_2 , R_3 and P_1 are as defined hereinbefore and P_2 represents a protecting group for the acid function which is different from P_1 ,

the amine function of which is deprotected before reaction with the compound of formula (IV) :



wherein G_1 and G_2 each represent a halogen atom or a p-toluenesulphonyloxy group, Tos represents a para-toluenesulphonyl group, and n is as defined for formula (I),

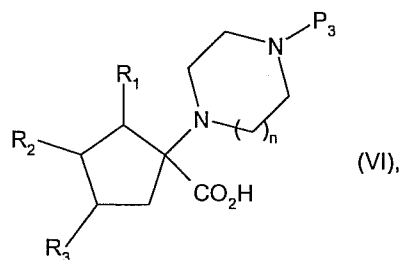
to yield the compound of formula (V) :



wherein R_1 , R_2 , R_3 , P_2 , n and Tos are as defined hereinbefore,

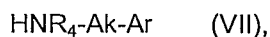
from which the para-toluenesulphonyl group is cleaved,

the acid function is deprotected and then the amine function is protected to yield the compound of formula (VI) :



wherein R_1 , R_2 , R_3 and n are as defined hereinbefore and P_3 represents a protecting group for the amine function,

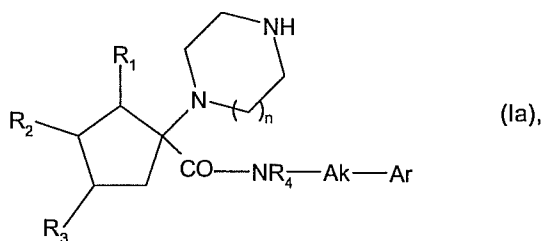
- which compound of formula (VI) is reacted, when it is desired to obtain compounds of formula (I) wherein X represents $-(CO)-NR_4-Ak-$ or $-CH_2-NR_4-Ak$, with a compound of formula (VII) :



wherein R_4 , Ak and Ar are as defined for formula (I),

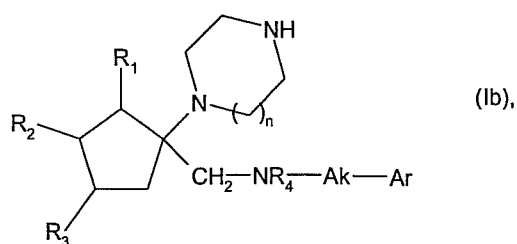
in the presence of one or more coupling agents,

to yield, after deprotection of the ring amine function, compounds of formula (Ia), a particular case of the compounds of formula (I) wherein X represents a group $-(CO)-NR_4-Ak$:



wherein R_1 , R_2 , R_3 , n , R_4 and Ak are as defined hereinbefore and Ar is as defined for formula (I),

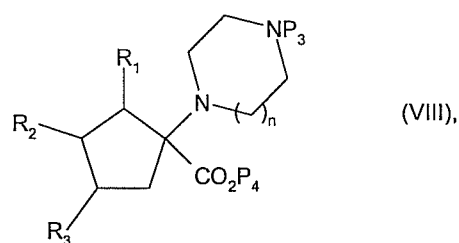
which is reacted, when it is desired to obtain compounds of formula (Ib), a particular case of the compounds of formula (I) wherein X represents a group $-CH_2-NR_4-Ak$, with a reducing agent to yield compounds of formula (Ib) :



wherein R_1 , R_2 , R_3 , n , R_4 , Ak and Ar are as defined hereinbefore,

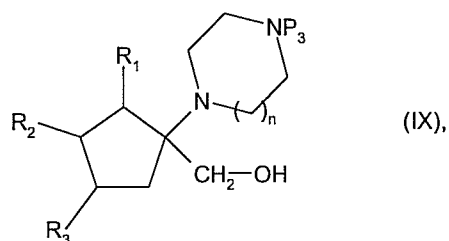
- or which compound of formula (VI) is esterified, when it is desired to obtain compounds of formula (I) wherein X represents a group $-\text{CH}_2-\text{O}Ak-$ or $-\text{CH}_2-\text{NR}_4-(\text{CO})-$,

to yield the compound of formula (VIII) :



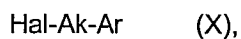
wherein R_1 , R_2 , R_3 , n and P_3 are as defined hereinbefore and P_4 represents a benzyl or linear or branched $\text{C}_1\text{-C}_6$ alkyl group,

which is placed in the presence of a reducing agent to yield the alcohol of formula (IX) :

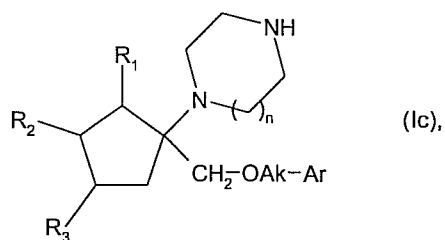


wherein R_1 , R_2 , R_3 , n and P_3 are as defined hereinbefore,

which alcohol of formula (IX) is reacted, when it is desired to obtain compounds of formula (Ic), a particular case of the compounds of formula (I) wherein X represents the group $-\text{CH}_2-\text{O}-\text{Ak}-$, with a compound of formula (X) :

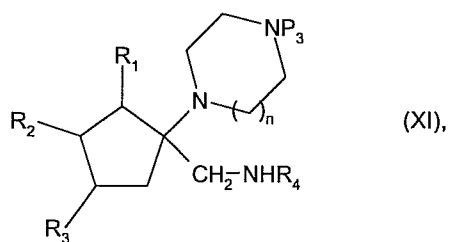


- 5 wherein Ak and Ar are as defined for formula (I) and Hal represents a halogen atom,
to yield, after deprotection of the ring amine function, compounds of formula (Ic) :



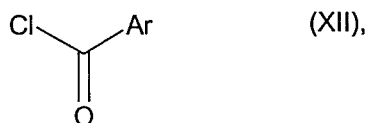
wherein R_1 , R_2 , R_3 , n , Ak and Ar are as defined hereinbefore,

- 10 or which alcohol of formula (IX) is converted by conventional reactions of organic chemistry into an amine of formula (XI) :



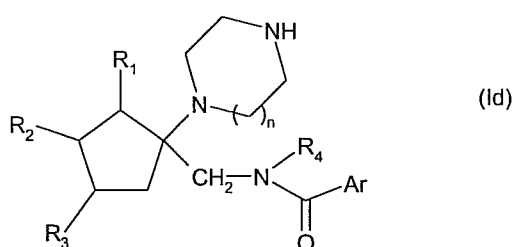
wherein R_1 , R_2 , R_3 , n , R_4 and P_3 are as defined hereinbefore,

which is reacted with a compound of formula (XII) :



wherein Ar is as defined for formula (I),

to yield, after deprotection of the ring amine function, compounds of formula (Id), a particular case of the compounds of formula (I) wherein X represents a group
 5 -CH₂-NR₄-(CO)- :



wherein R₁, R₂, R₃, n, R₄ and Ar are as defined hereinbefore,

which compounds of formulae (Ia), (Ib), (Ic) and (Id) are purified according to a conventional purification technique, are separated, when desired, into their optical
 10 isomers and are converted, when desired, into their addition salts with a pharmaceutically acceptable acid.

8. Pharmaceutical composition comprising, as active ingredient, a compound according to any one of claims 1 to 6, in combination with one or more pharmaceutically acceptable, inert, non-toxic carriers.

15 9. Use of compounds of formula (I) according to any one of claims 1 to 6 in the manufacture of medicaments for use as serotonin reuptake inhibitors and NK₁ antagonists.

10. Use of compounds of formula (I) according to any one of claims 1 to 6 in the manufacture of medicaments for use in the treatment of depressive states, anxiety states,

impulsive disorders, aggressive behaviours, drug abuse, obesity and appetite disorders, pain and inflammation, dementias, psychotic states, disturbances of chronobiological rhythms, nausea or gastrointestinal disorders.