POLYCYCLIC COMPOUNDS AS POTENT ALPHA2-ADRENOCEPTOR ANTAGONISTS

FIELD OF THE INVENTION

The present invention relates to pharmacologically active arylquinolizine derivatives and related compounds and to their pharmaceutically acceptable salts and esters thereof, as well as to pharmaceutical compositions containing them and to their use as alpha2 antagonists.

BACKGROUND OF THE INVENTION

Some compounds exhibiting alpha adrenergic activity are well known in the art. It is also generally known and accepted in the art that those compounds may be used for the treatment of a wide variety of diseases and conditions of the peripheric system and the central nervous system (CNS).

The alpha adrenergic receptors can be divided on a pharmacological basis into alpha1- and alpha2-adrenoceptors, which can both be further divided into subtypes. Three genetically encoded subtypes, namely alpha2A-, alpha2B- and alpha2C-adrenoceptors, have been discovered in human. Accordingly, alpha2-adrenoceptors in humans have been subdivided into three pharmacological subtypes known as alpha2A-, alpha2B- and alpha2C-adrenoceptors. A fourth, pharmacologically defined subtype, alpha2D, is known in rodents and in some other mammals, and it corresponds to the genetically defined alpha2A-adrenoceptors.

The alpha2-adrenoceptor subtypes have distinct tissue distributions and functional roles. For instance, while alpha2A-adrenoceptors are widely expressed in various tissues, alpha2C-adrenoceptors are concentrated in the CNS, and they appear to play a role in the modulation of specific CNS-mediated behavioural and physiological responses.

Compounds that are non-specific to any of the above-mentioned alpha2 subtypes, and compounds that are specific to certain alpha2 subtypes, are already known. For example, atipamezole is a non-specific alpha2 antagonist. Atipamezole has been described in, for example, EP-A-183 492 (cf. p.13, compound XV) and Haapalinna, A. et al., *Naunyn-Schmiedeberg's Arch. Pharmacol.* **356** (1997) 570-582. U.S. Patent No. 5,902,807 describes compounds that are selective antagonists for the alpha2C subtype and may be used in the treatment of mental illness, e.g. mental disturbance induced by stress. Such compounds include, for example, MK-912 and BAM-1303. Furthermore, WO-A-99 28300 discloses substituted imidazole derivatives having agonist-like activity for alpha2B- or 2B/2C-adrenoceptors. In addition, WO 01/64645 relates to derivatives of quinoline useful as alpha2 antagonists, as well as to selective alpha2C antagonist agents. The disclosures of all documents cited above in this paragraph are incorporated by reference herein.

Several arylquinolizine derivatives and related compounds have been described in the literature, some of which possess valuable pharmaceutical effects. For example, U.S. Patents No. 4,806,545 and 4,044,012 describe 1,1-disubstituted indolo[2,3-*a*]quinolizidines useful as vasodilators and antihypoxic agents. Further, substituted arylquinolizine derivatives, described for example in U.S. Patent No. 4,686,226 possessing alpha2-adrenoceptor antagonistic activity are useful for example as antidepressant, antihypertensive, or antidiabetic agents or platelet aggregation inhibitors. In addition, U.S. Patent No. 3,492,303 relates to indolo[2,3-*a*]quinolizidines useful as central nervous system depressants.

SUMMARY OF THE INVENTION

An object of the present invention is to provide further antagonists of alpha2-adrenoceptors that can be used for the treatment of diseases or conditions of the peripheric or central nervous system where alpha2-antagonists are indicated to be useful. Accordingly, an object of the present invention is to provide further compounds to be used as alpha2 antagonist agents in the treatment of mammals, including humans and animals.

The invention also provides compounds useful as selective alpha2C antagonist agents for the treatment of various disorders or conditions of the central nervous system where alpha2C antagonists are indicated to be useful.

BRIEF DESCRIPTION OF THE DRAWINGS

Figures 1a and b show the results from two separate locomotor activity tests where the locomotor activity of mice was tested after injections of vehicle or amphetamine (amph) (4 micromol/kg). The mice were pre-treated (20 min before amphetamine) either with vehicle, the subtype non-selective alpha2-antagonist atipamezole (1 micromol/kg) or the alpha2C-antagonists, compound K (3 micromol/kg)(Fig a) or compound L (3 micromol/kg)(Fig b). * $p<0.05$, ** $p<0.01$ and *** $p<0.001$ compared to vehicle + amph –group (1-way ANOVA + LSD –test).

Figure 2 shows alpha2-agonist-induced sedation (measured as locomotor inhibition) in mice. The non-selective alpha2-antagonist atipamezole (Ati) antagonised the sedative effects of the alpha2-subtype non-selective agonist, dexmedetomidine (Dex; 50 nmol/kg s.c.), while the alpha2C-selective antagonists did not have significant effects. (veh = vehicle). (***$p<0.001$, compared to Dex + vehicle)

Figure 3 shows the effect of the alpha2C-selective antagonists compound K (3 micromol/kg) and compound L (3 micromol/kg), the non-selective antagonist atipamezole (10 micromol/kg) and the reference antidepressants desipramine (10 micromol/kg) and fluoxetine (10 micromol/kg) in the forced swimming test in rats. All compounds, except atipamezole, increased activity (***$p<0.001$, compared to vehicle).

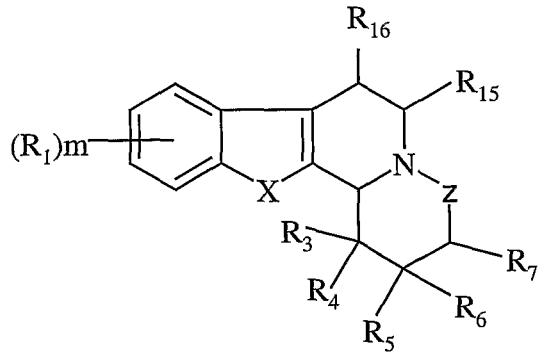
Figures 4a and 4b show the effect of compounds K and L on the startle reflex and its prepulse inhibition in rats. (Veh = vehicle). Asterisks as in Figure 1; comparisons were performed between PCP (phencyclidine) + vehicle and PCP + compounds K and L.

Figures 5a and 5b show the effect of the non-selective antagonist atipamezole (ati) on the startle reflex and its prepulse inhibition in rats in the prescence of

phencyclidine (PCP); (veh = vehicle). Asterisks as in Figure 1, compared to the vehicle + PCP –group.

DETAILED DESCRIPTION OF THE INVENTION

One embodiment of the present invention covers the use of compounds of formula I,



I

wherein,

X is CR_2R_2', O, S or NR_2;

Z is $-CHR_8-(CH_2)n-$ or a single bond;

R_1 is hydroxy, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, halogen, halo(C_1-C_6)alkyl, (C_1-C_6)alkoxy-CO-, CN, NO_2, NH_2, mono- or di(C_1-C_6)alkylamino or carboxyl;

R_2 and R_2' are independently H, hydroxy or (C_1-C_6)alkyl or R_2 and R_2' form, together with the carbon ring atoms to which they are attached, a carbonyl group;

R_3 is H, hydroxy, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)alkoxy(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkoxy(C_1-C_6)alkyl, (C_3-C_7)cycloalkyl, (C_3-C_7)cycloalkyl(C_1-C_6)alkyl, aryl, aryl(C_1-C_6)alkyl, aryloxy, aryl(C_1-C_6)alkoxy, aryloxy(C_1-C_6)alkyl, aryl(C_1-C_6)alkoxy(C_1-C_6)alkyl, halo(C_1-C_6)alkyl, NH_2, amino(C_1-C_6)alkyl, mono- or di(C_1-C_6)alkylamino,mono- or di(C_1-C_6)alkylamino(C_1-C_6)alkyl, (C_1-C_6)alkyl-CO-, (C_1-C_6)alkyl-CO-O-, (C_1-C_6)alkyl-CO-O-(C_1-C_6)alkyl, (C_1-C_6)alkoxy-CO-, (C_1-C_6)alkoxy-CO-(C_1-C_6)alkyl, (C_1-C_6)alkoxy-CO-(C_1-C_6)alkoxy(C_1-C_6)alkyl, carbamoyl, mono- or di(C_1-C_6)alkylcarbamoyl, carboxyl or (C_1-C_6)alkyl-S-(C_1-C_6)alkyl, wherein the said (C_3-C_7)cycloalkyl or aryl is unsubstituted or substituted with 1 or 2 substituents each independently being hydroxy, (C_1-C_6)alkyl, halogen, (C_1-C_6)alkoxy, NH_2, CN or

NO_2, or one of R_3 or R_4 and R_6 together form a bond between the ring atoms to which they are attached;

R_4 is H, hydroxy, (C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxy or (C_1-C_6)alkoxy(C_1-C_6)alkyl;

R_5 is H, hydroxy, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)alkoxy(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkoxy(C_1-C_6)alkyl, (C_3-C_7)cycloalkyl, (C_3-C_7)cycloalkyl(C_1-C_6)alkyl, aryl, aryl(C_1-C_6)alkyl, aryloxy, aryl(C_1-C_6)alkoxy, aryloxy(C_1-C_6)alkyl, aryl(C_1-C_6)alkoxy(C_1-C_6)alkyl, halo(C_1-C_6)alkyl, (C_1-C_6)alkyl-CO-, (C_1-C_6)alkyl-CO-O-, (C_1-C_6)alkyl-CO-O-(C_1-C_6)alkyl, (C_1-C_6)alkoxy-CO-, (C_1-C_6)alkoxy-CO-(C_1-C_6)alkyl, (C_1-C_6)alkoxy-CO-(C_1-C_6)alkoxy(C_1-C_6)alkyl, carbamoyl, mono- or di(C_1-C_6)alkylcarbamoyl, carboxyl or (C_1-C_6)alkyl-S-(C_1-C_6)alkyl, wherein the said (C_3-C_7)cycloalkyl or aryl is unsubstituted or substituted with 1 or 2 substituents each independently being hydroxy, (C_1-C_6)alkyl, halogen, (C_1-C_6)alkoxy, NH_2, CN or NO_2, or R_4 and R_5 form, together with the carbon ring atoms to which they are attached, a condensed five to seven membered saturated carbocyclic ring unsubstituted or substituted with 1 to 3 substituent(s) R_9 each independently being hydroxy, (C_1-C_6)alkyl, halogen, NH_2, NO_2, (C_3-C_7)cycloalkyl, hydroxy(C_1-C_6)alkyl, halo(C_1-C_6)alkyl, amino(C_1-C_6)alkyl, mono- or di(C_1-C_6)alkylamino, mono- or di(C_1-C_6)alkylamino(C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)alkoxy(C_1-C_6)alkyl, carboxyl, (C_1-C_6)alkyl-CO-, (C_1-C_6)alkyl-CO-O-, (C_1-C_6)alkoxy-CO-, (C_1-C_6)alkoxy-CO-(C_1-C_6)alkyl, carbamoyl mono- or di(C_1-C_6)alkylcarbamoyl or oxo;

R_6 is H, hydroxy, (C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxy or (C_1-C_6)alkoxy(C_1-C_6)alkyl or R_6 forms a bond between the ring atom to which it is attached and the ring atom to which R_7 is attached;

R_7 is H, hydroxy, (C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxy or (C_1-C_6)alkoxy(C_1-C_6)alkyl;

R_8 is H,hydroxy, (C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxy or (C_1-C_6)alkoxy(C_1-C_6)alkyl or, only when n is 0, R_7 and R_8 form, together with the carbon ring atoms to which they are attached, a condensed five to seven membered saturated carbocyclic ring unsubstituted or substituted with 1 to 3 substituent(s) R_{10} each independently being hydroxy, (C_1-C_6)alkyl, halogen, NH_2, NO_2, (C_3-C_7)cycloalkyl, hydroxy(C_1-C_6)alkyl, halo(C_1-C_6)alkyl, amino(C_1-C_6)alkyl, mono- or di(C_1-C_6)alkylamino, mono- or di(C_1-C_6)alkylamino(C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-

C_6)alkoxy(C_1-C_6)alkyl, carboxyl, (C_1-C_6)alkyl-CO-, (C_1-C_6)alkyl-CO-O-, (C_1-C_6)alkoxy-CO-, (C_1-C_6)alkoxy-CO-(C_1-C_6)alkyl, carbamoyl, mono- or di(C_1-C_6)alkylcarbamoyl or oxo;

R_{15} is H, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxy(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkoxy(C_1-C_6)alkyl, halo(C_1-C_6)alkyl, amino(C_1-C_6)alkyl, mono- or di(C_1-C_6)alkylamino(C_1-C_6)alkyl, (C_1-C_6)alkyl-CO-, (C_1-C_6)alkyl-CO-O-(C_1-C_6)alkyl, (C_1-C_6)alkoxy-CO-, (C_1-C_6)alkoxy-CO-(C_1-C_6)alkyl, (C_1-C_6)alkoxy-CO-(C_1-C_6)alkoxy(C_1-C_6)alkyl, carbamoyl, mono- or di(C_1-C_6)alkylcarbamoyl or carboxyl;

R_{16} is H or (C_1-C_6)alkyl;

R_7 and R_8 are attached to the carbon ring atoms, which are adjacent;

m is 0 to 2; and

n is 0 or 1,

or a pharmaceutically acceptable salt or ester thereof, with the proviso, that when X is O, m is 0, n is 0, R_3, R_4, R_7, R_8, R_{15} and R_{16} are hydrogen, and one of R_5 or R_6 is hydrogen, then the other R_5 or R_6 is not hydroxy(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkoxy(C_1-C_6)alkyl, (C_1-C_6)alkyl-CO-, (C_1-C_6)alkoxy-CO- or (C_1-C_6)alkoxy-CO-(C_1-C_6)alkyl, for the manufacture of a medicament for the treatment of diseases or conditions where alpha2 antagonists are indicated to be effective.

In a possible subgroup of the compounds of formula I X is NR_2.

In another possible subgroup of the compounds of formula I m is 0, n is 0, R_2 is H, R_3 is H, hydroxy, (C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxy(C_1-C_6)alkyl, (C_3-C_7)cycloalkyl, halo(C_1-C_6)alkyl, (C_1-C_6)alkyl-CO-, (C_1-C_6)alkyl-CO-O-(C_1-C_6)alkyl, (C_1-C_6)alkoxy-CO- or (C_1-C_6)alkoxy-CO-(C_1-C_6)alkyl, R_4 is H, hydroxy, (C_1-C_6)alkyl or hydroxy(C_1-C_6)alkyl, R_5 is H, hydroxy, (C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxy or (C_1-C_6)alkyl-CO-, R_6 is H or (C_1-C_6)alkyl and R_7 is H, (C_1-C_6)alkyl or hydroxy(C_1-C_6)alkyl.

In another possible subgroup of the compounds of formula I R_3 is H or (C_1-C_6)alkyl and R_4 is hydroxy or hydroxy(C_1-C_6)alkyl.

In another possible subgroup of the compounds of formula I R_4 and R_5 form, together with the carbon ring atoms to which they are attached, a condensed six membered saturated carbocyclic ring.

In another possible subgroup of the compounds of formula I R_4 and R_6 together form a bond between the ring atoms to which they are attached or R_6 forms a bond between the ring atom to which it is attached and the ring atom to which R_7 is attached.

In a further possible subgroup of the compounds of formula I the compound is 1α-ethyl-1,2,3,4,6,7,12,12bβ-octahydro-indolo[2,3-*a*]quinolizin-1-ol, (1β-ethyl-1,2,3,4,6,7,12,12bα-octahydro-indolo[2,3-*a*]quinolizin-1-yl)-methanol, 1α-Methyl-1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-*a*]quinolizin-1-ol, (1α-Methyl-1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-*a*]quinolizin-1-yl)-methanol, 1,2,3,4,4aβ,5,6,7,8,13,13bβ,13cα-dodecahydro-6a,13-diaza-indeno-[1,2-*c*]phenanthrene, 1,2,3,4,4aβ,5,6,7,8,13,13bβ,13cβ-dodecahydro-6a,13-diaza-indeno[1,2-*c*]phenanthrene or 3,4,4aβ,5,6,7,8,13,13bβ,13cα-decahydro-2H-6a,13-diaza-indeno[1,2-*c*]phenanthren-1-one.

In another possible subgroup of the compounds of formula I X is CR_2R_2'.

In a further possible subgroup of the compounds of formula I X is S.

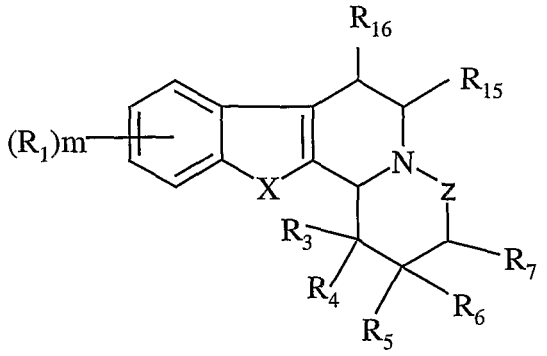
In yet another possible subgroup of the compounds of formula I X is O.

When X is O, one possible subgroup of the compounds of formula I includes R_5 and R_6 as defined in the description of the use of the compounds of formula I above.

Another possible subgroup of the compounds of formula I when X is O is where R_5 is H, hydroxy, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_1-C_6)alkoxy, (C_1-C_6)alkoxy(C_1-C_6)alkyl, (C_3-C_7)cycloalkyl, (C_3-C_7)cycloalkyl(C_1-C_6)alkyl, aryl, aryl(C_1-C_6)alkyl, aryloxy, aryl(C_1-C_6)alkoxy, aryloxy(C_1-C_6)alkyl, aryl(C_1-C_6)alkoxy(C_1-C_6)alkyl, halo(C_1-C_6)alkyl, (C_1-C_6)alkyl-CO-O-, (C_1-C_6)alkyl-CO-O-(C_1-C_6)alkyl, (C_1-C_6)alkoxy-CO-(C_1-C_6)alkoxy(C_1-C_6)alkyl, carbamoyl, mono- or

di(C_1-C_6)alkylcarbamoyl, carboxyl or (C_1-C_6)alkyl-S-(C_1-C_6)alkyl and R_6 is H, hydroxy, (C_1-C_6)alkyl, (C_1-C_6)alkoxy or (C_1-C_6)alkoxy(C_1-C_6)alkyl.

Another embodiment of the invention provides new compounds of formula IA:



IA

wherein,

X is CR_2R_2', O or S;

Z, R_1, R_2, R_2', R_3-R_{10}, R_{15} and R_{16}, m and n are as defined in claim 1,

or a pharmaceutically acceptable salt or ester thereof, with the provisos, that

a) when X is O, m is 0 and n is 0, then R_3-R_8 are not all simultaneously hydrogen;

b) when X is O, m is 0, n is 0, R_3, R_4, R_7, R_8, R_{15} and R_{16} are hydrogen, and one of R_5 or R_6 is hydrogen, then the other R_5 or R_6 is not hydroxy(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkoxy(C_1-C_6)alkyl, (C_1-C_6)alkyl-CO-, (C_1-C_6)alkoxy-CO- or (C_1-C_6)alkoxy-CO-(C_1-C_6)alkyl.

c) the compound is not 1,2,3,4,5,10b-hexahydro-10-thia-3a-aza-cyclopenta[a]fluorene; 1,3,4,5,6,11b-hexahydro-2H-11-thia-4a-aza-benzo[a]fluorene; 1-(1,3,4,5,6,11b-hexahydro-2H-11-thia-4a-aza-benzo[a]fluoren-1-yl)-ethanone or 1,3,4,5,6,11b-hexahydro-2H-11-thia-4a-aza-benzo[a]fluorene-1-carboxylic acid methyl ester; for example

wherein X is CR_2R_2'; or

wherein X is O; or

wherein X is S; or

wherein R_3 is hydroxy, (C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxy(C_1-C_6)alkyl, (C_1-C_6)alkoxy-CO- or (C_1-C_6)alkyl-CO-O-(C_1-C_6)alkyl and R_4 is H, (C_1-C_6)alkyl or hydroxy(C_1-C_6)alkyl; or

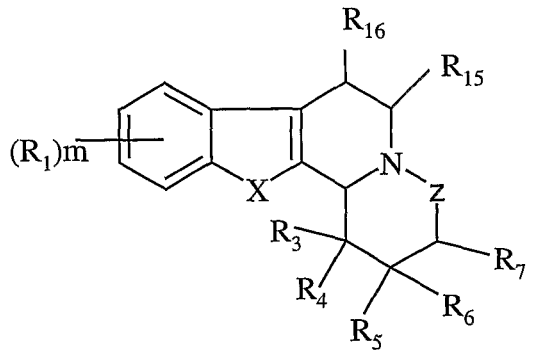
wherein R_3 is hydroxy, hydroxy(C_1-C_6)alkyl or (C_1-C_6)alkoxy(C_1-C_6)alkyl and R_4 is (C_1-C_6)alkyl; or

wherein R_4 and R_5 form, together with the carbon ring atoms to which they are attached, a condensed six membered saturated carbocyclic ring; or

wherein the compound is 1α-Methyl-1,3,4,5,6,11b-hexahydro-2H-11-oxa-4a-aza-benzo[a]fluoren-1-ol, (1α-Methyl-1,3,4,5,6,11bβ-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluoren-1-yl)-methanol, (-)-(1α-Methyl-1,3,4,5,6,11bβ-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluoren-1-yl)-methanol, (+)-(1α-Methyl-1,3,4,5,6,11bβ-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluoren-1-yl)-methanol, 1α-Isopropyl-1,3,4,5,6,11b-Hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluoren-1-ol, 1α-Ethyl-1,3,4,5,6,11bβ-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluoren-1-ol, (1α-Ethyl-1,3,4,5,6,11bβ-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluoren-1-yl)-methanol, 5,6,7,7aβ,8,9,10,11,11aβ,11bα-Decahydro-12-oxa-6a-aza-indeno[1,2-*a*]fluorene, 1-Methyl-1α,3,4,6,11bβ-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluorene, (1-Hydroxymethyl-1,3,4,5,6,11b-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluoren-1-yl]-methanol, 1-Methoxymethyl-1α-methyl-1,3,4,5,6,11bβ-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluorene, (-)-1-Methoxymethyl-1α-methyl-1,3,4,5,6,11bβ-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluorene, (+)-1-Methoxymethyl-1α-methyl-1,3,4,5,6,11bβ-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluorene, 2,3,4,4aβ,5,6,7,8,13bβ,13cβ-Decahydro-1H-13-oxa-6a-aza-indeno[1,2-*c*]phenanthrene, 2,3,4,4aβ,5,6,7,8,13bα,13cβ-Decahydro-1H-13-oxa-6a-aza-indeno[1,2-*c*]phenanthrene, 1α-Methyl-1,3,4,5,6,11bα-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluorene-1-carboxylic acid ethyl ester, 1-Ethoxymethyl-1α-methyl-1,3,4,5,6,11bβ-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluorene, (1α-Methyl-1,3,4,5,6,11bα-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluoren-1-yl)-methanol, (-)-(1α-Methyl-1,3,4,5,6,11bα-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluoren-1-yl)-methanol, (+)-(1α-Methyl-1,3,4,5,6,11bα-hexahydro-2H-11-oxa-4a-aza-

benzo[*a*]fluoren-1-yl)-methanol, 1α–Ethyl-1,3,4,5,6,11bα-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluorene-1-carboxylic methyl ester, 1-Methoxymethyl-1α-methyl-1,3,4,5,6,11bα-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluorene, (-)-1-Methoxymethyl-1α-methyl-1,3,4,5,6,11bα-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluorene, (+)-1-Methoxymethyl-1α-methyl-1,3,4,5,6,11bα-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluorene, (1α-Ethyl-1,3,4,5,6,11bα-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluorene-1-yl)-methanol, acetic acid 1α-Methyl-1,3,4,5,6,11bβ-hexahydro-2H-11-oxa-4a-aza-benzo[a]fluoren-1-ylmethyl ester or (1α-Methyl-1,2,3,4,6,7,12,12bα-octahydroindeno[2,1-*a*]quinolizin-1-yl)-methanol.

Another embodiment of the invention provides new compounds of formula IB:



IB

wherein,

X is NR_2;

R_2 is $(C_1\text{-}C_6)$alkyl;

Z, R_1, R_3-R_{10}, R_{15}, R_{16}, m and n are as defined in claim 1,

or a pharmaceutically acceptable salt and ester thereof, with the provisos, that

a) when m is 0 or R_1 is methoxy and R_4 is H or ethyl, then R_3 is not methoxy-CO;

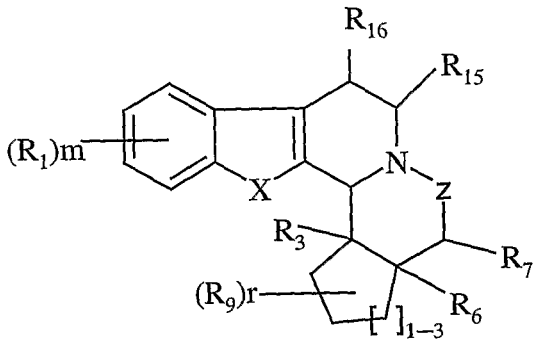
b) the compound is not 13-Methyl-1,2,3,4,4a,5,6,7,8,13,13b,13c-dodecahydro-6a,13-diaza-indeno[1,2-*c*]phenanthrene; 12-Methyl-1,2,3,4,6,7,12,12b-octahydro-indolo[2,3-*a*]quinolizine; 1-Ethyl-12-methyl-1,2,3,4,6,7,12,12b-octahydro-indolo[2,3-*a*]quinolizine; 2,3-Diethyl-12-methyl-1,2,3,4,6,7,12,12b-octahydro-indolo[2,3-*a*]quinolizine;

12-Methyl-1,2,3,4,6,7,12,12b-octahydro-indolo[2,3-*a*]quinolizin-1-ol; 2-(1-Ethyl-12-methyl-1,2,3,4,6,7,12,12b-octahydro-indolo[2,3-*a*]quinolizin-1-yl)-ethanol; 11-Methyl-2,3,5,6,11,11b-hexahydro-1H-indolizino[8,7-*b*]indole; (11-Methyl-2,3,5,6,11,11b-hexahydro-1H-indolizino[8,7-*b*]indol-1-yl)-methanol; (1,11-Diethyl-2,3,5,6,11,11b-hexahydro-1H-indolizino[8,7-*b*]indol-1-yl)-methanol or 3-(1-ethyl-12-methyl-1,2,3,4,6,7,12,12b-octahydro-indolo[2,3-*a*]quinolizin-1-yl)-propionic acid methyl ester; for example

wherein R_3 is hydroxy, (C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl or (C_1-C_6)alkoxy(C_1-C_6)alkyl and R_4 is H, (C_1-C_6)alkyl or hydroxy(C_1-C_6)alkyl; or

wherein the compound is 1α-Ethyl-12-methyl-1,2,3,4,6,7,12bβ-octahydro-indolo[2,3-*a*]quinolizin-1-ol or 1α-Ethyl-12-ethyl-1,2,3,4,6,7,12bβ-octahydro-indolo[2,3-*a*]quinolizin-1-ol.

Another embodiment of the invention provides new compounds of formula IC:



IC

wherein,

X is NR_2;

R_2 is H;

Z is $-CHR_8-(CH_2)n-$ or a single bond;

n is 0;

R_1, R_3, R_6-R_9, R_{15}, R_{16} and m are as defined in claim 1;

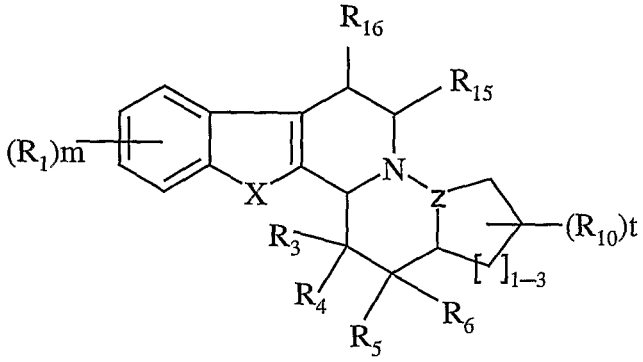
r is 0 to 3;

or a pharmaceutically acceptable salt and ester thereof, with the provisos, that the compound is not 1,2,3,4,4a,5,6,7,8,13,13b,13c-dodecahydro-6a,13-diaza-indeno[1,2-*c*]phenanthrene; 5,7,7a,8,9,10,11,11a,11b,12-decahydro-6H-6a,12-diaza-indeno[1,2-*a*]fluorene; 10-methyl-5,7,7a,8,9,10,11,11a,11b,12-decahydro-6H-6a,12-diaza-indeno[1,2-*a*]fluorene; 3-methoxy-5,7,7a,8,9,10,11,11a,11b,12-decahydro-6H-6a,12-diaza-indeno[1,2-*a*]fluorene; 3-hydroxy-1,2,3,4,4a,5,6,7,8,13,13b,13c-dodecahydro-6a,13-diaza-indeno[1,2-*c*]phenanthrene-4-carboxylic acid methyl ester; methyl-3-ethyl-1,2,3a,4,6,7,12b,12c-octahydro-3H,12H-indolo[2,3-*g*]cyclopent[*a*]indolizine-2-carboxylate; methyl-1,2,3a,4,6,7,12b,12c-octahydro-3H,12H-indolo[2,3-*g*]cyclopent[*a*]indolizine-2-carboxylate; 12c-ethyl-1,3a,4,6,7,12b,12c-octahydro-cyclopent[1,2]indolizino[8,7-*b*]indol-3(2H)-one or 6-methyl-5,7,7a,8,9,10,11,11a,11b,12-decahydro-6H-6a,12-diaza-indeno[1,2-*a*]fluorene; for example

wherein r is 0 or 1 and R_3 is H, hydroxy, (C_1-C_6)alkyl or hydroxy(C_1-C_6)alkyl; or

wherein the compound is 2,3,4,4aβ,5,6,7,8,13,13bβ-decahydro-1H-6a,13-diaza-indeno[1,2-*c*]phenanthren-13cβ-ol, (-)-2,3,4,4aβ,5,6,7,8,13,13bβ-decahydro-1H-6a,13-diaza-indeno[1,2-*c*]phenanthren-13cβ-ol, (+)-2,3,4,4aβ,5,6,7,8,13,13bβ-decahydro-1H-6a,13-diaza-indeno[1,2-*c*]phenanthren-13cβ-ol, (2,3,4,4aβ,5,6,7,8,13,13bβ-Decahydro-1H-6a,13-diaza-indeno[1,2-*c*]phenanthrenyl)-13cβ-methanol, 5,6,7,7a,11,11b,12-Decahydro-6a,12-diaza-indeno[1,2-*a*]fluoren-11a-ol, 3,4,4aβ,5,6,7,8,13,13bβ,13cα-decahydro-2H-6a,13-diaza-indeno[1,2-*c*]phenanthren-1-one, 1,2,3,4,5,6,7,8,13,13b-decahydro-6a,13-diaza-indeno[1,2-*c*]phenanthrene, acetic acid 1α,2,3,4,4aβ,5,6,7,8,13,13bβ,13cα-dodecahydro-6a,13-diaza-indeno[1,2-*c*]phenanthren-1-yl ester or acetic acid 1β,2,3,4,4aβ,5,6,7,8,13,13bβ,13cα-dodecahydro-6a,13-diaza-indeno[1,2-*c*]phenanthren-1-yl ester.

Another embodiment of the invention provides new compounds of formula ID:



ID

wherein,

X is NR_2;

R_2 is H;

Z is $-CHR_8-(CH_2)n-$;

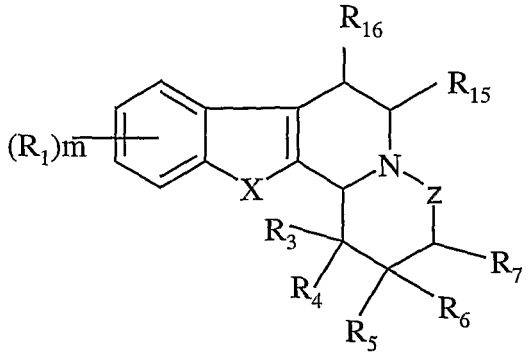
n is 0;

R_1, R_3-R_{10} R_{15}, R_{16} and m are as defined in claim 1;

t is 0 to 3;

or a pharmaceutically acceptable salt and ester thereof, with the provisos, that the compound is not 1,2,3,4,4a,5,6,11,11b,12,13,13a-dodecahydro-4b,11-diaza-indeno[2,1-*a*]phenanthrene; 1,2,3,4,4a,5,6,11,11b,12-decahydro-4b,11-diaza-indeno[2,1-*a*]phenanthrene; 9-methoxy-1,2,3,4,4a,5,6,11,11b,12-decahydro-4b,11-diaza-indeno[2,1-*a*]phenanthrene or 1-hydroxy-1,2,3,4,4a,5,6,11,11b,12,13,13a-dodecahydro-4b,11-diaza-indeno[2,1-*a*]phenanthrene-2-carboxylic acid methyl ester.

Another embodiment of the invention provides new compounds of formula IE:



IE

wherein,

X is NR_2;

R_2 is H;

Z, R_1, R_3-R_{10}, R_{15}, R_{16} and m are as defined in claim 1;

n is 1,

or a pharmaceutically acceptable salt and ester thereof, with the proviso, that the compound is not 2,3,4,5,7,8,13,13b-octahydro-1H-azepino[1',2':1,2]pyrido[3,4-b]indole-2-ethyl-2-methanol; 2,3,4,5,7,8,13,13b-octahydro-1H-azepino[1',2':1,2]pyrido[3,4-*b*]indole-4-ethyl-2-methanol; 2,3,4,5,7,8,13,13b-octahydro-2,3-diethyl-1H-azepino[1',2':1,2]pyrido[3,4-*b*]indole; 2,3,4,5,7,8,13,13b-octahydro-1H-azepino[1',2':1,2]pyrido[3,4-*b*]indole-2-methanol; 2,3,4,5,7,8,13,13b-octahydro-1H-azepino[1',2':1,2]pyrido[3,4-*b*]indole-3-hydroxy-2-methanol; 2,3,4,5,7,8,13,13b-octahydro-1H-azepino[1',2':1,2]pyrido[3,4-*b*]indole-4-ethyl-4-hydroxy-2-methanol; acetic acid 2,3,4,5,7,8,13,13b-octahydro-1H-azepino[1',2':1,2]pyrido[3,4-*b*]indol-2-ylmethyl ester; 2,3,4,5,7,8,13,13b-octahydro-1H-azepino[1',2':1,2]pyrido[3,4-*b*]indole-2-[(phenylmethoxy)methyl] or 2,3,4,5,7,8,13,13b-octahydro-1H-azepino[1',2':1,2]pyrido[3,4-*b*]indole-4-ethyl-2-[(phenylmethoxy)methyl]; for example

wherein the compound is 2,3,4,5,7,8,13,13b-Octahydro-1H-azepino[1',2':1,2]pyrido[3,4-*b*]indole.

Another embodiment of the invention provides new compounds which are 2β-Methoxy-1,2,3,4,6,7,12,12bα-octahydro-indolo[2,3-*a*]quinolizine, 2α-methoxy-1,2,3,4,6,7,12,12bα-octahydro-indolo[2,3-*a*]quinolizine, 1α-Ethyl-2α-methyl-1,2,3,4,6,7,12,12bβ-octahydro-indolo[2,3-*a*]quinolizin-1-ol, 1α-Isopropyl-1,2,3,4,6,7,12,12bβ-octahydro-indolo[2,3-*a*]quinolizin-1-ol, (-)-1α-isopropyl-1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-*a*]quinolizin-1-ol, (+)-1α-isopropyl-1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-*a*]quinolizin-1-ol, 1β-Isopropyl-1,2,3,4,6,7,12,12bβ-octahydro-indolo[2,3-*a*]quinolizine, (1α-Isopropyl-1,2,3,4,6,7,12,12bβ-octahydro-indolo[2,3-*a*]quinolizin-1-yl)-methanol, (1α- *n*-Propyl-1,2,3,4,6,7,12,12bβ-octahydro-indolo[2,3-*a*]quinolizin-1-yl)-methanol, 2-(1α,2,3,4,6,7,12,12bβ-Octahydro-indolo[2,3-*a*]quinolizin-1-yl)-butan-2-ol, 1-(1,2α,3,4,6,7,12,12bα-Octahydro-indolo[2,3-*a*]quinolizin-2-yl)-propan-1-ol, 2-

(1α,2,3,4,6,7,12,12bβ-Octahydro-indolo[2,3-*a*]quinolizin-1-yl)-propan-2-ol, 1-*s*-Butyl-1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-*a*]quinolizin-1-ol, 1-Cyclohexyl-1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-*a*]quinolizin-1-ol, 9-Fluoro-1α-isopropyl-1,2,3,4,6,7,12,12bβ-octahydro-indolo[2,3-*a*]quinolizin-1-ol, (1α-Methyl-1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-*a*]quinolizin-1-yl)-methanol, (-)-(1α-Methyl-1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-*a*]quinolizin-1-yl)-methanol, (+)-(1α-Methyl-1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-*a*]quinolizin-1-yl)-methanol, (1α-Ethyl-1,4,6,7,12,12bβ-hexahydroindolo[2,3-*a*]quinolizin-1-yl)-methanol, 3β,4α-Dimethyl-1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-*a*]quinolizine, (1,2α,3,4,6,7,12,12bα-Octahydroindolo[2,3-*a*]quinolizin-2-yl)-propan-2-ol, (1,2α,3,4,6,7,12,12bβ-Octahydroindolo[2,3-*a*]quinolizin-2-yl)-propan-2-ol, (2α-Ethyl-1,2,3,4,6,7,12,12bα-octahydroindolo[2,3-*a*]quinolizin-2-yl)-methanol, (2α-Ethyl-1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-*a*]quinolizin-2-yl)-methanol, (1-α̃Ethyl-1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-a]quinolizin-1-ylmethoxy)-acetic acid ethyl ester, 1-(2α-ethyl-1,2,3,4,6,7,12,12bα-octahydro-indolo[2,3-*a*]quinolizin-2-yl)-ethanone, 1-(2α-ethyl-1,2,3,4,6,7,12,12bα-octahydro-indolo[2,3-*a*]quinolizin-2-yl)-ethanol, 2-(2α-ethyl-1,2,3,4,6,7,12,12bα-octahydro-indolo[2,3-*a*]quinolizin-2-yl)-propan-2-ol, 2-(3-ethyl-1,2α,3α,4,6,7,12,12bα-octahydro-indolo[2,3-*a*]quinolizin-2-yl)-propan-2-ol, (3-ethyl-2-methyl-1α,2β,3β,4,6,7,12,12bβ-octahydro-indolo[2,3-*a*]quinolizin-1-yl)-methanol, 3-ethyl-1,2-dimethyl-1α,2β,3β,4,6,7,12,12bβ-octahydro-indolo[2,3-*a*]quinolizine, 1,2-dimethyl-1,2,3,4,6,7,12,12bβ-octahydro-indolo[2,3-*a*]quinolizin-1β-ol, (1-ethyl-2-methyl-1β,2β,3β,4,6,7,12,12bα-octahydro-indolo[2,3-*a*]quinolizin-3-yl)-methanol or 1-β-Hydroxymethyl-1-methyl-1,2,3,4,6,7,12,12bβ-octahydro-indolo[2,3-*a*]quinolizine-6β-carboxylic acid methyl ester.

The terms employed herein have the following meanings:

The term "halo" or "halogen", as employed herein as such or as part of another group, refers to chlorine, bromine, fluorine or iodine.

The term "carboxyl", as employed herein, refers to a –COOH group.

The term "oxo", as employed herein, refers to an =O group.

The term "(C_1-C_6)alkyl", as employed herein as such or as part of another group, refers to a straight or branched carbon chain having 1 to 6 carbon atoms. Representative examples of (C_1-C_6)alkyl include, but are not limited to, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, *tert*-butyl, *n*-pentyl, isopentyl, neopentyl, *n*-hexyl, and the like.

The term "(C_2-C_6)alkenyl", as employed herein as such or as part of another group, refers to a straight or branched chain radical having 2 to 6 carbon atoms, and containing (a) double bond(s).

The term "(C_3-C_7)cycloalkyl", as employed herein as such or as part of another group, refers to a saturated cyclic hydrocarbon group containing 3 to 7 carbons. Representative examples of cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like.

The term "(C_3-C_7)cycloalkyl(C_1-C_6)alkyl", as employed herein refers to a (C_3-C_7)cycloalkyl group, as defined herein, appended to the parent molecular moiety through a (C_1-C_6)alkyl group, as defined herein.

The term "aryl", as employed herein as such or as part of another group, refers to a monocyclic or bicyclic aromatic group containing 6 to 12 carbon atoms. Representative examples of aryl include, but are not limited to, phenyl, naphthyl, and the like.

The term "aryl(C_1-C_6)alkyl", as employed herein as such or as part of another group, refers to an aryl group, as defined herein, appended to the parent molecular moiety through an (C_1-C_6)alkyl group, as defined herein.

The term "aryloxy", as employed herein as such or as part of another group, refers to an aryl group, as defined herein, appended to the parent molecular moiety through an -O- group.

The term "aryl(C_1-C_6)alkoxy", as employed herein as such or as part of another group, refers to an aryl group, as defined herein, appended to the parent molecular moiety through an (C_1-C_6)alkoxy group, as defined herein.

The term "aryloxy(C_1-C_6)alkyl, as employed herein, refers to an aryloxy group, as defined herein, appended to the parent molecular moiety through an (C_1-C_6)alkyl group, as defined herein.

The term "aryl(C_1-C_6)alkoxy(C_1-C_6)alkyl, as employed herein, refers to an aryl(C_1-C_6)alkoxy group, as defined herein, appended to the parent molecular moiety through an (C_1-C_6)alkyl group, as defined herein.

The term "hydroxy", as employed herein as such or as part of another group, refers to an –OH group.

The term "hydroxy(C_1-C_6)alkyl", as employed herein as such or as part of another group, refers to at least one hydroxy group, as defined herein, appended to the parent molecular moiety through a (C_1-C_6)alkyl group, as defined herein. Representative examples of hydroxy(C_1-C_6)alkyl include, but are not limited to, hydroxymethyl, 2-hydroxyethyl, 1-hydroxyethyl, 3-hydroxypropyl, 1-hydroxypropyl, 1-methyl-1-hydroxyethyl, 1-methyl-1-hydroxypropyl, and the like.

The term "halo(C_1-C_6)alkyl", as employed herein, refers to one or more halogen, as defined herein, appended to the parent molecular moiety through a (C_1-C_6)alkyl group, as defined herein. Representative examples of halo(C_1-C_6)alkyl include, but are not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, 2-chloroethyl, 3-bromopropyl, and the like.

The term "amino", as employed herein as such or as part of another group, refers to a $–NH_2$ group.

The term "amino(C_1-C_6)alkyl", as employed herein, refers to an amino group, as defined herein, appended to the parent molecular moiety through a (C_1-C_6)alkyl group, as defined herein. Representative examples of amino(C_1-C_6)alkyl include, but are not limited to, aminomethyl, 2-aminoethyl, 1-aminoethyl, 3-aminopropyl, 2-aminopropyl, 4-aminobutyl, 1-methyl-1-aminoethyl, and the like.

The term "mono- or di(C_1-C_6)alkylamino", as employed herein as such or as part of another group, refers to one or two (C_1-C_6)alkyl group(s), as defined herein, appended to the parent molecular moiety through an amino group, as defined herein. Representative examples of mono- or di(C_1-C_6)alkylamino include, but are not

limited to methylamino, ethylamino, propylamino, butylamino, dimethylamino, diethylamino, *N*-ethyl-*N*-methylamino, and the like.

The term "mono- or di(C_1-C_6)alkylamino(C_1-C_6)alkyl", as employed herein, refers to a mono- or di(C_1-C_6)alkylamino group, as defined herein, appended to the parent molecular moiety through a (C_1-C_6)alkyl group, as defined herein. Representative examples of mono- or di(C_1-C_6)alkylamino(C_1-C_6)alkyl include, but are not limited to, *N*,*N*-dimethylaminomethyl, *N*,*N*-diethylaminomethyl, *N*-methylaminoethyl, *N*-methylaminopropyl, *N*-ethyl-*N*-methylaminomethyl, and the like.

The term "(C_1-C_6)alkoxy", as employed herein as such or as part of another group, refers to a (C_1-C_6)alkyl, as defined herein, appended to the parent molecular moiety through an -O- group. Representative examples of (C_1-C_6)alkoxy include, but are not limited to methoxy, ethoxy, propoxy, butoxy, isobutoxy, *sec*-butoxy, *tert*-butoxy, and the like.

The term "(C_1-C_6)alkoxy(C_1-C_6)alkyl", as employed herein as such or as part of another group, refers to at least one (C_1-C_6)alkoxy group, as defined herein, appended to the parent molecular moiety through an (C_1-C_6)alkyl group, as defined herein. Representative examples of (C_1-C_6)alkoxy(C_1-C_6)alkyl include, but are not limited to methoxymethyl, ethoxymethyl, 2-methoxyethyl, 2-ethoxyethyl, 3,3-dimethoxypropyl, 2,4-dimethoxybutyl and the like.

The term "hydroxy(C_1-C_6)alkoxy", as employed herein as such or as part of another group, refers to a hydroxy group, as defined herein, appended to the parent molecular moiety through an (C_1-C_6)alkoxy group, as defined herein.

The term "hydroxy(C_1-C_6)alkoxy(C_1-C_6)alkyl, as employed herein, refers to a hydroxy(C_1-C_6)alkoxy group, as defined herein, appended to the parent molecular moiety through an (C_1-C_6)alkyl group, as defined herein.

The term "carbamoyl", as employed herein as such or as part of another group, refers to a -$CONH_2$ group.

The term "mono- or di(C_1-C_6)-alkylcarbamoyl", as employed herein, refers to one or two (C_1-C_6)alkyl group(s), as defined herein, appended to the parent

molecular moiety through a -HNCO- or -NCO- group. Representative examples of mono- or di(C_1-C_6)-alkylcarbamoyl include, but are not limited to *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N*-propylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl and the like.

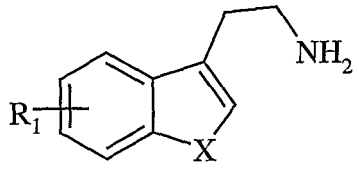
The compounds of formula I and IA, IB, IC, ID and IE, as well as the pharmaceutically acceptable salts and esters thereof, are referred to below as the compounds of the invention, unless otherwise indicated.

The invention includes within its scope all the possible stereoisomers of the compounds, including geometric isomers, e.g. *Z* and *E* isomers (*cis* and *trans* isomers), and optical isomers, e.g. diastereomers and enantiomers. Furthemore, the invention includes in its scope both the individual isomers and any mixtures thereof, e.g. racemic mixtures. The individual isomers may be obtained using the corresponding isomeric forms of the starting material or they may be separated after the preparation of the end compound according to conventional separation methods. For the separation of optical isomers, e.g. enantiomers, from the mixture thereof the conventional resolution methods, e.g. fractional crystallisation, may be used.

Pharmaceutically acceptable salts, e.g. acid addition salts with both organic and inorganic acids are well known in the field of pharmaceuticals. Non-limiting examples of these salts include chlorides, bromides, sulfates, nitrates, phosphates, sulfonates, formates, tartrates, maleates, citrates, benzoates, salicylates and ascorbates. Pharmaceutically acceptable esters, when applicable, may be prepared by known methods using pharmaceutically acceptable acids that are conventional in the field of pharmaceuticals and that retain the pharmacological properties of the free form. Non-limiting examples of those esters include esters of aliphatic or aromatic alcohols, e.g. methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *sec*-butyl and *tert*-butyl esters.

The compounds of the invention can be prepared analogously or according to the methods known in the literature using suitable starting materials. The starting materials of formulae II, III and IV are commercially available or can be prepared via a variety of known synthetic routes known in the literature.

For example, the starting materials used are arylalkylamines of formula (II)

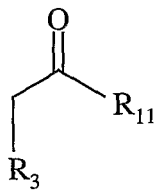


(II)

wherein R1 is as defined above and X is NH, O, CH2 or S.

When X is O, the amines of formula (II) can be prepared, for example, according to the process disclosed in the U.S. Patent Specification No. 4,710,504. When X is CH_2, the compounds of formula (II) can be prepared as described in *J. Med. Chem.* 10 (1967) 856-859. When X is S, the compounds of formula (II) can be prepared by decarboxylation of the corresponding 3-(thianaphten-3-yl)-L-alanine.

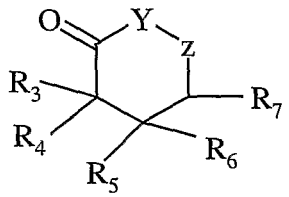
Other starting materials used are compounds of formula (III)



(III)

wherein R_3 is as defined above and R_{11} is OH or halogen.

Furthermore, the starting materials used are compounds of formula (IV)

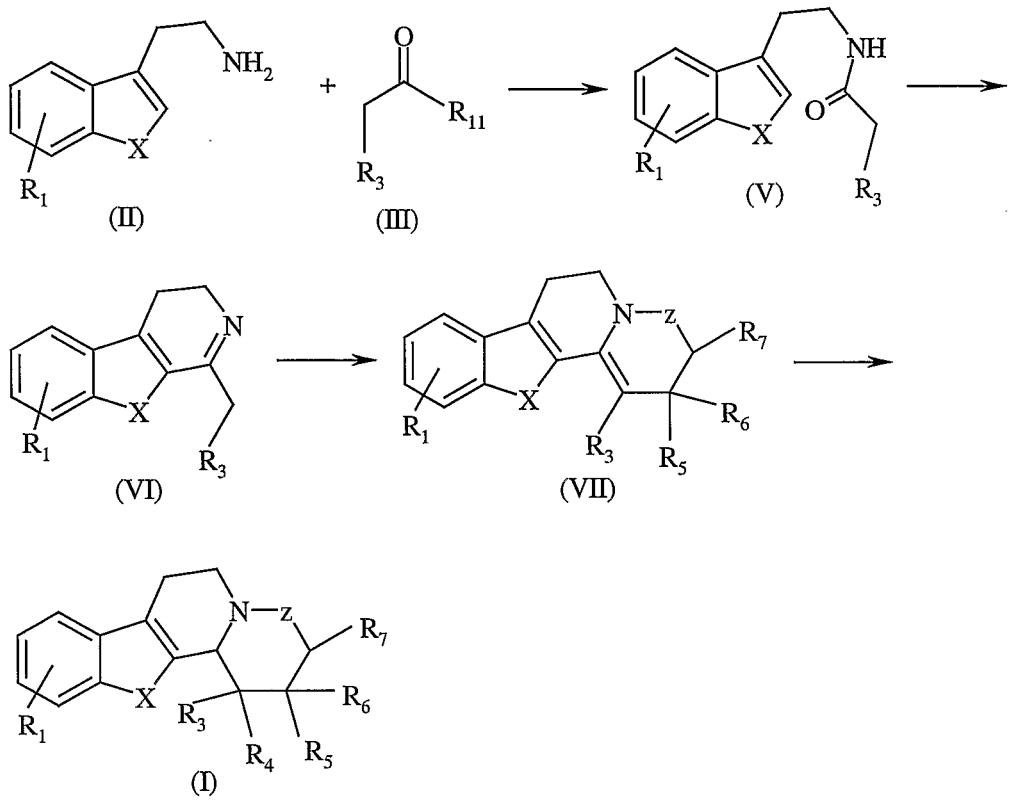


(IV)

wherein R_3-R_7 and Z are as defined above and Y is O or NH. Compounds of formula (IV) can be prepared according to the methods described in *Tetrahedron* 33 (1977) 1803-1808. Analogously, the corresponding acid chlorides can be used instead of lactones (Y=O). When R_3 and R_5 form a ring, compounds of formula (IV) are obtained by the partial reduction of their corresponding anhydrides.

In general, the compounds of formula (I), wherein X is NH, O or S, can be prepared e.g. analogously or according to the following reaction scheme 1:

Scheme 1



wherein R_1, R_3-R_7 and Z are as defined above.

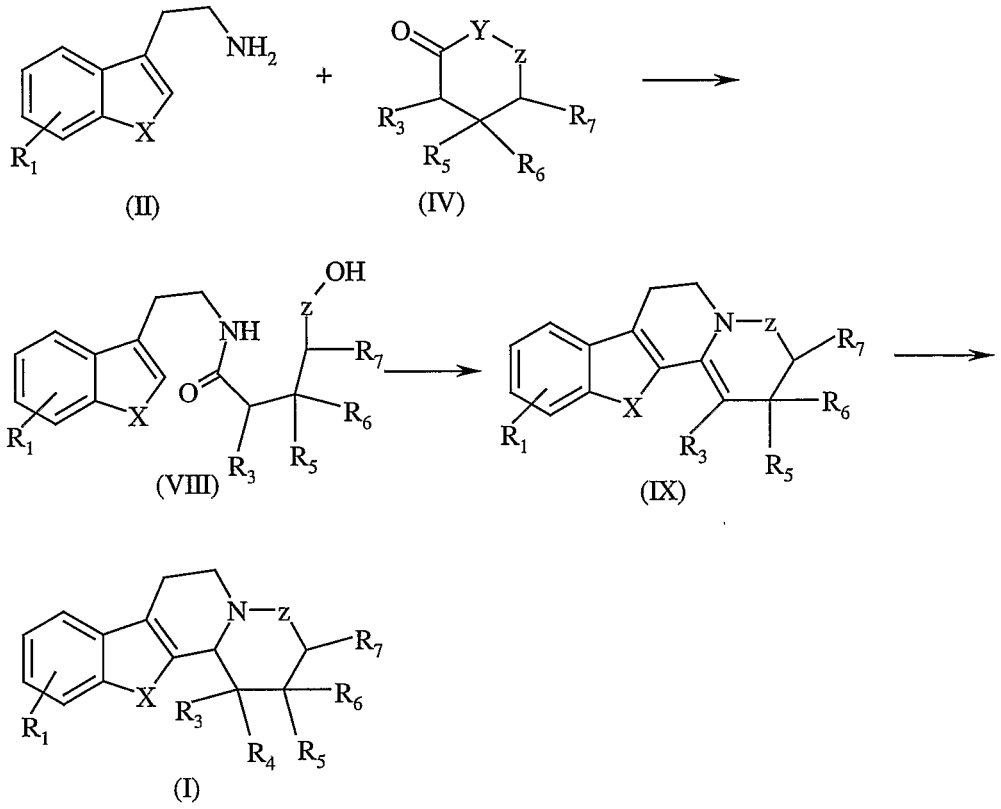
According to the reaction route of scheme I, alkylation of amines (II) with compounds of formula (III) gives amides (V) which are converted into enamines (VII) *via* beta carbolines (V) by Bischler-Napieralski reaction followed by ring D formation by allowing compounds of formula (VI) to react with 1,3-dihaloalkanes under basic conditions as described in *Gazz. Chim. Ital.* 111 (1981) 257-267. In the last step, compounds of formula (I) are obtained

1) by oxidation of enamines (VII) using potassium iodide, iodide and air or

2) by reaction of enamines (VII) with formaldehyde in presence of Hünig base at 60°C.

Another route for preparing compounds of formula (I), wherein X is NR_2, O, CH_2 or S, is illustrated in scheme 2

Scheme 2

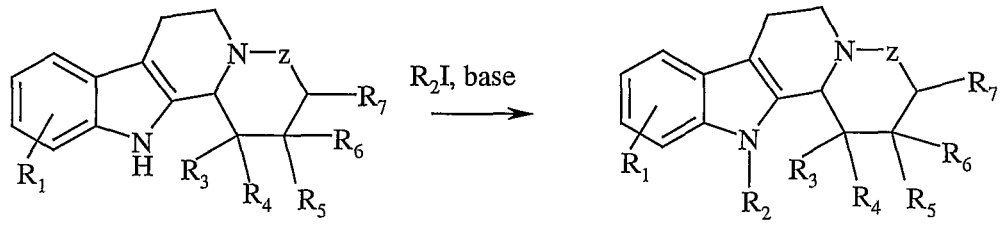


wherein X is NR_2, O, CH_2 or S, R_1-R_7 and Z are as defined above.

In scheme 2 arylalkylamines of formula (II), wherein X is NH, O, CH_2, or S, are reacted with compounds of formula (IV), or the corresponding acid chloride, to give amides (VIII) as described in *Tetrahedron* **33** (1977) 1803-1808. The Bischler-Napieralski cyclization of the intermediates (VIII) leads to enamines (IX) which are converted into compounds of formula (I).

The compounds of formula (I), wherein X is NH, can be alkylated with alkylhalides in the presence of a suitable base at room temperature (*Heterocycles* 27 (1988) 1179-1190) according to following scheme 3:

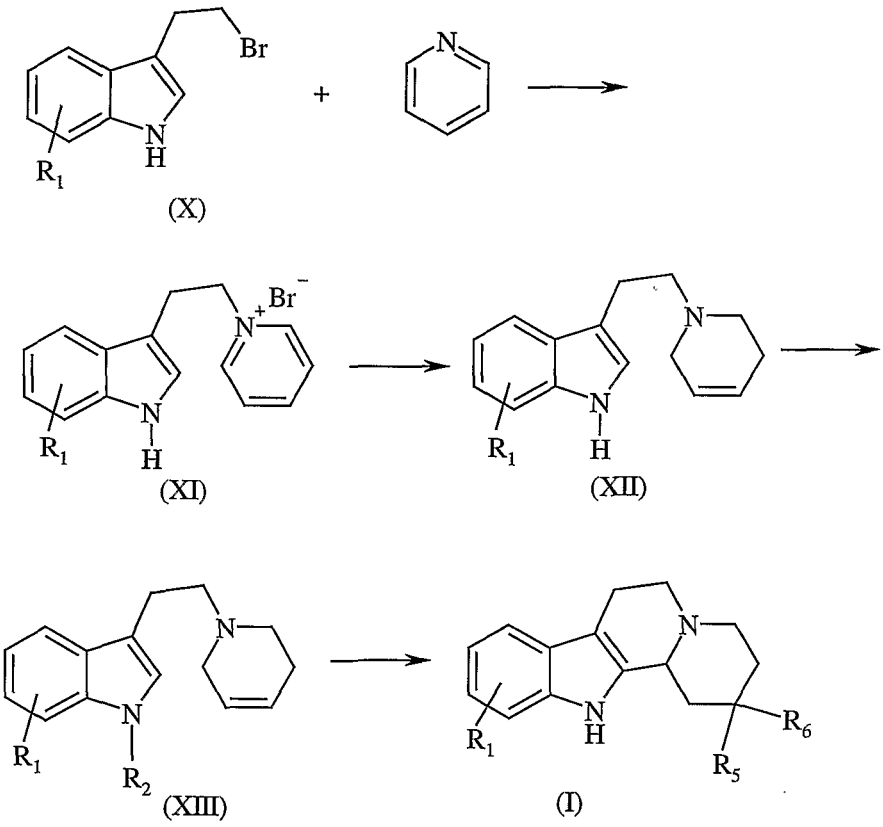
Scheme 3



wherein R_1-R_7 and Z are as defined above.

A further method for preparing compounds of formula (I) is illustrated in scheme 4:

Scheme 4



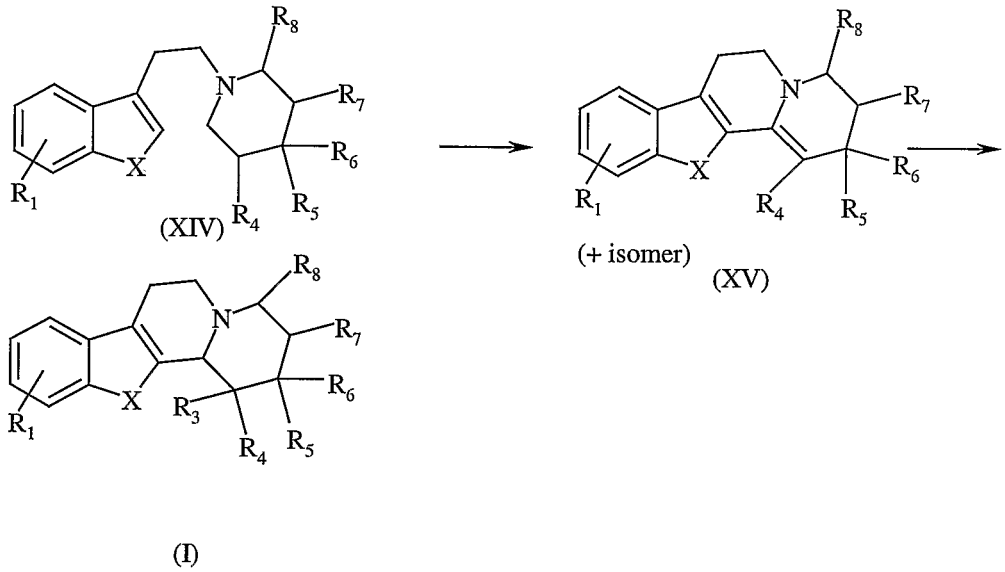
wherein R_2 is BOC and R_1, R_5 and R_6 are as defined above.

In scheme 4 pyridine is alkylated with tryptophyl bromides (X) to give pyridinium salts (XI) whose partial reduction gives compounds of formula (XII).

Protection of compounds of formula (XII) using di-*t*-butyl dicarbonate under basic conditions gives compounds of formula (XIII). The Polonovski-Potier reaction of the obtained intermediates and their cyclisation using MeOH/HCl yield the compounds of formula (I).

A further process for the preparation of compounds of formula (I), wherein X is O, S or NH, R_1 and R_3–R_8 are as defined above, is shown in the following scheme 5:

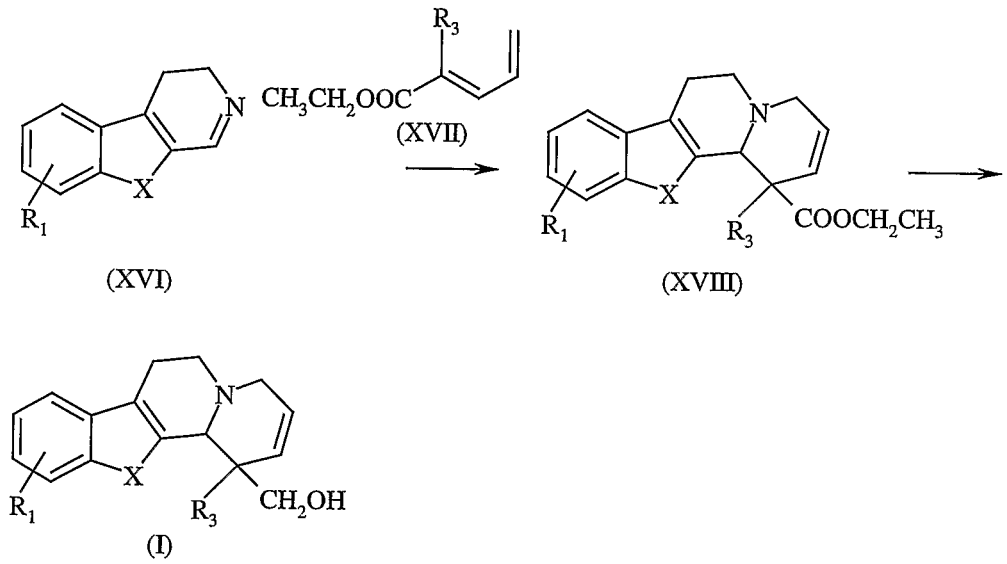
Scheme 5



In scheme 5 oxidative cyclization of derivative (XIV) with mercuric acetate according to the method described in *Heterocycles* **32** (1991) 489-497 gives enamine (XV). This intermediate can be oxidized or treated with formaldehyde as in scheme 1 or reduced with sodium borohydride to give compounds of formula (I).

A further method for preparing compounds of formula (I), wherein R_6 and R_7 form a bond, is illustrated in scheme 6:

Scheme 6

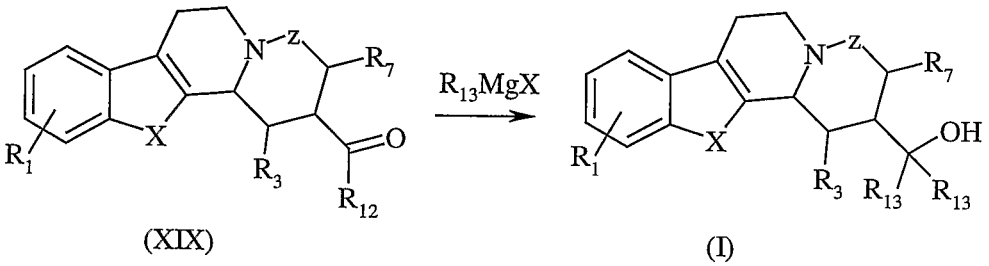


wherein X is NH and R_3 is lower alkyl.

Applying the method described in *J. Org. Chem.* **52** (1987) 353-356, the hetero-Diels-Alder reaction of 3,4-dihydro-β-carboline (XVI) with diene ester (XVII), prepared by the Wittig reaction as described in *Can. J. Chem.* **65** (1987) 670-682, gives compounds of formula (XVIII), which are then reduced to alcohols of formula (I).

A further method for preparing compounds of formula (I) is illustrated in scheme 7.

Scheme 7

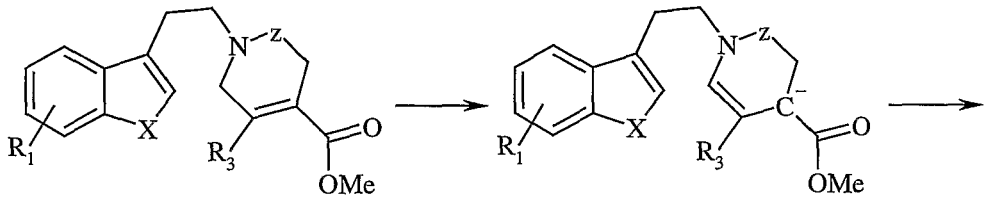


wherein X, R_1, R_3, R_7 and z are as defined above. R_{12} can be H or OCH_3 and R_{13} can be an alkyl or aryl group.

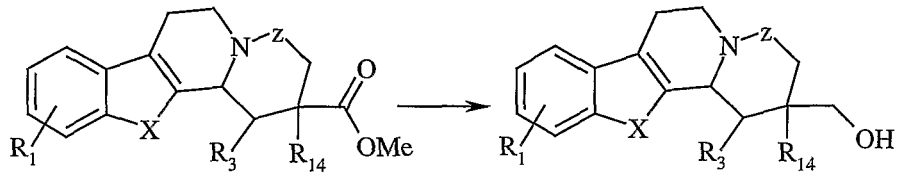
In scheme 7, compounds of formula (XIX), when R_{12} is H, are prepared as described in *J. Chem. Soc., Chem. Commun.* (1995) 2317-2318, and compounds of formula (XIX), when R_{12} is OCH_3, are prepared as described in *J. Chem. Soc. (C)* (1971) 736-743. Compounds of formula (XIX) are reacted with Grignard reagents to give compounds of formula (I). When R_{12} in formula (XIX) is H, the other R_{13} group in formula (I) is also H.

A new method to prepare certain compounds of formula (I) is shown in scheme 8.

Scheme 8



(XX) (XXI)



(XXII) (I)

wherein X, R_1, R_3 and z are as defined above. R_{14} is a lower alkyl group.

In scheme 8 tetrahydropyridine (XX), prepared according to the method described in *J. Chem. Soc. (C)* (1971) 736-743, is deprotonated with a strong base to give anion (XXI). This anion is alkylated and subsequently cyclized with acid to give compounds of formula (XXII). Reduction of (XXII) with $LiAlH_4$ then affords compounds of formula (I).

The resolution of the racemic compounds of formula (I) can be performed, for example, by converting compounds of formula (I) into their diastereoisomers salt mixture by reaction with an optically active acid such as D-tartaric acid, dibenzoyl-D-tartaric acid, etc and by separation of the diastereoisomers by crystallization.

It is obvious to a skilled person that, in the above reactions, any starting material or intermediate can be protected, if necessary, in manner well known in the chemical field. Any protected functionality is subsequently deprotected in a usual manner.

It should be noted that the above described synthetic routes are meant to illustrate the preparation of the compounds of the invention and the preparation is by no means limited thereto, i.e. other synthetic methods which are within the general knowledge of a skilled person are also possible.

The compounds of the invention may be converted, if desired, into their pharmaceutically acceptable salt or ester form using methods well known in the art.

The present invention will be explained in more detail by the following examples. The examples are meant only for illustrating purposes and do not limit the scope of the invention defined in claims.

EXAMPLE 1

1-Propyl-4,9-dihydro-3H-β-carboline

8.00 g (50.0 mmol) of tryptamine was dissolved in 150 ml of ethyl acetate and 4.80 ml (52.0 mmol) of *n*-butyric acid was slowly added. After standing for 4 h at 0°C, the reaction mixture was filtered to give 12.30 g (49.5 mmol) of tryptamine butyrate, which was melted. The melt was heated at 200°C and kept for 30 min at that temperature. Water formed was removed using a Dean-Stark apparatus. The melt after cooling was mixed with 120 ml of toluene, 23.5 ml (257.7 mmol) of freshly distilled phosphorus oxychloride was added and the reaction mixture was refluxed for 4 h. The solution was evaporated in vacuum and the dark oil was mixed with 20% solution of acetic acid (3 x 50 ml). The solid was filtered off and the aqueous solution was made alkaline with 25% ammonium hydroxide under cooling and extracted with dichloromethane (3 x 50 ml). The combined organic phases were dried over sodium sulfate, the drying agent was filtered off and the filtrate was evaporated to give the title compound, which was purified by column chromatography (silica gel, dichloromethane/methanol, 95:5).

NMR: 1.00 (t, 3H), 1.75 (m, 2H), 2.66 (t, 2H), 2.87 (t, 2H), 3.90 (t, 2H), 7.00-7.62 (m, 4H), 8.94 (br s, 1H).

MS: 212 (28%), 211 (12%), 197 (25%), 184 (100%), 169 (13%).

EXAMPLE 2

1-Isobutyl-4,9-dihydro-3H-β-carboline

The procedure of example 1 was repeated, except that isovaleric acid was used instead of *n*-butyric acid.

NMR: 0.98 (d, 6H), 2.16 (m, 1H), 2.54 (d, 2H), 2.86 (t, 2H), 3.89 (t, 2H), 7.00-7.62 (m, 4H), 8.60 (br s, 1H).

MS: 226 (16%), 211 (18%), 184 (100%), 169 (13%).

EXAMPLE 3

1-Butyl-4,9-dihydro-3H-β-carboline

The procedure of example 1 was repeated, except that *n*-valeric acid was used instead of *n*-butyric acid.

NMR: 1.00 (t, 3H), 7.00-7.62 (m, 4H), 8.64 (br s, 1H).

MS: 226 (18%), 211 (18%), 184 (100%), 169 (14%).

EXAMPLE 4

1-(2-Methyl-butyl)-4,9-dihydro-3H-β-carboline

The procedure of example 1 was repeated, except that 3-methylvaleric acid was used instead of *n*-butyric acid.

NMR: 0.84 (t, 3H), 0.87 (d, 3H), 7.05-7.60 (m, 4H), 12.2 (br s, 1H).

MS: 240 (9%), 225 (10%), 211 (10%), 185 (13%), 184 (100%), 183 (14%), 155 (24%).

EXAMPLE 5

1-Cyclohexylmethyl-4,9-dihydro-3H-β-carboline

The procedure of example 1 was repeated, except that cyclohexylacetic acid was used instead of *n*-butyric acid.

NMR: 1.0-1.9 (m, 11H), 2.56 (d, 2H), 2.85 (m, 2H), 3.88 (m, 2H), 7.14-7.63 (m, 4H), 8.55 (br s, 1H).

MS: 266 (8%), 185 (15%), 184 (100%), 183 (12%), 155 (17%).

EXAMPLE 6

1β-Isopropyl-1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-*a*]quinolizine

2.56 g (11.5 mmol) of 4,9-Dihydro-1-isobutyl-3-*H*-pyrido[3,4-*b*]indole (example 2), 2 ml of *N*-ethyldiisopropylamine, and 1.35 ml (13.8 mmol) of 1-bromo-3-chloropropane were dissolved in 50 ml of acetonitrile. The mixture was refluxed under argon for 8 h. After evaporation of the solvent, 20 ml of methanol and 1.3 g (34.5 mmol) of sodium borohydride were added. The reaction mixture was stirred for 1 h at room temperature and 20 ml of water was then added. The reaction mixture was extracted with dichloromethane (3 x 50 ml). The combined organic phases were dried over sodium sulfate, the drying agent was filtered off and the filtrate was evaporated to give the title compound, which was purified by column chromatography (silica gel, dichloromethane/methanol, 95:5).

NMR: 1.02 (br s, 6H), 7.11 (t, 1H), 7.18 (t, 1H), 7.35 (d, 1H), 7.48 (d, 1H), 7.85 (br s, 1H).

MS: 267 (100%), 253 (20%), 197 (35%), 170 (30%), 169 (30%).

EXAMPLE 7

2-(1α,2,3,4,6,7,12,12bβ-Octahydroindolo[2,3-*a*]quinolizin-1-yl)-butan-2-ol

To a solution of 190 mg (0.7 mmol) of 1-(1,2,3,4,6,7,12,12b-octahydro-indolo[2,3-*a*]quinolizin-1-yl)-ethanone (*Tetrahedron Lett.* **30** (1989) 719-722) in 5 ml of dichloromethane at –60° C was added 0.11 ml (0.8 mmol) of ethylmagnesium bromide (1.0 *M*). The reaction mixture was stirred 30 min at that temperature and 2 h at room temperature. Water (10 ml) was then added and the reaction mixture was extracted with dichloromethane (3 x 50 ml). The combined organic phases were dried over sodium sulfate, the drying agent was filtered off and the filtrate was evaporated to give the title compound, which was purified by column chromatography (silica gel, dichloromethane/methanol, 95:5).

NMR: 0.97 (t, 3H), 1.30 (s, 3H), 4.69 (br s, 1H), 7.00-7.50 (m, 4H), 8.36 (br s, 1H).

MS: 297 (100%), 281 (30%), 269 (35%), 225 (28%), 197 (45%), 170 (35%), 169 (34%).

EXAMPLE 8

2-(1α,2,3,4,6,7,12,12bβ-Octahydroindolo[2,3-*a*]quinolizin-1-yl)-propan-2-ol

The procedure of example 7 was repeated, except that methylmagnesium bromide (excess) was used instead of ethylmagnesium bromide.

NMR: 1.37 (s, 3H), 1.42 (s, 3H), 4.73 (br s, 1H), 7.00-7.50 (m, 4H), 8.18 (br s, 1H).

MS: 283 (100%), 267 (42%), 225 (33%), 197 (60%), 170 (50%), 169 (50%).

EXAMPLE 9

1α-Isopropyl-1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-*a*]quinolizin-1-ol (Compound A)

5.13 g (23.0 mmol) of 4,9-Dihydro-1-isobutyl-3-*H*-pyrido[3,4-*b*]indole, 4 ml of *N*-ethyldiisopropylamine, and 2.7 ml (27.6 mmol) of 1-bromo-3-chloropropane were dissolved in 100 ml of acetonitrile. The mixture was refluxed under argon for 8 h. The dark solution was concentrated to an oil, which was treated with 20% sodium hydroxide. After 10 min stirring, the solution was extracted with dichloromethane (3 x 50 ml). The combined organic phases were dried over sodium sulfate, the drying agent was filtered off and the filtrate was evaporated to give the corresponding enamine, which was dissolved in 100 ml of acetonitrile. 7.0 g (27.6 mmol) of iodine and 4.6 g (27.6 mmol) of potassium iodide were added. The reaction mixture was stirred in the dark under air for 3 h. After evaporation of the solvent, 50 ml of methanol and, with cooling, 2.6 g (69 mmol) of sodium borohydride were added. The reaction mixture was stirred for 1 h at room temperature and 20 ml of water was then added. The reaction mixture was extracted with dichloromethane (3 x 50 ml). The combined organic phases were dried over sodium sulfate, the drying agent was filtered off and the filtrate was evaporated to give the title compound, which was purified by column chromatography (silica gel, dichloromethane/methanol, 95:5).

NMR: 0.47 (d, 3H), 0.90 (d, 3H), 3.48 (br s, 1H), 7.00-7.50 (m, 4H), 8.92 (br s, 1H).

MS: 284 (14%), 239 (13%), 171 (100%), 170 (16%), 169 (33%).

EXAMPLE 10

1α-Ethyl-2α-methyl-1,2,3,4,6,7,12,12bβ-octahydro-indolo[2,3-*a*]quinolizin-1-ol (Compound B)

The procedure of example 9 was repeated, except that 4,9-dihydro-1-propyl-3-*H*-pyrido[3,4-*b*]indole was used instead of 4,9-dihydro-1-isobutyl-3-*H*-pyrido[3,4-*b*]indole and 1,3-dibromobutane was used instead of 1-bromo-3-chloropropane.

NMR: 0.69 (t, 3H), 1.00 (d, 3H), 3.20 (br s, 1H), 7.00-7.60 (m, 4H), 9.04 (br s, 1H).

MS: 284 (5%), 267 (15%), 225 (100%), 210 (15%), 195 (15%), 182 (72%), 171 (41%), 170 (22%), 169 (32%).

EXAMPLE 11

9-Fluoro-1α-isopropyl-1,2,3,4,6,7,12,12bβ-octahydro-indolo[2,3-*a*]quinolizin-1-ol

The procedure of example 9 was repeated, except that 6-fluoro-1-isobutyl-4,9-dihydro-3*H*-pyrido[3,4-*b*]indole (prepared from 5-fluorotryptamine as described in example 2) was used instead 4,9-dihydro-1-isobutyl-3*H*-pyrido[3,4-*b*]indole.

NMR: 0.45 (d, 3H), 0.89 (d, 3H), 3.32 (s, 1H), 6.8-7.25 (m, 3H), 8.94 (br s, 1H).

MS: 302 (26%), 203 (13%), 189 (100%), 161 (26%).

EXAMPLE 12

1-*s*-Butyl-1,2,3,4,6,7,12,12bβ-octahydro-indolo[2,3-*a*]quinolizin-1-ol (mixture of isomers) (Compound C)

The procedure of example 9 was repeated, except that 1-(2-methylbutyl)-4,9-dihydro-3*H*-pyrido[3,4-*b*]indole was used instead of 4,9-dihydro-1-isobutyl-3*H*-pyrido[3,4-*b*]indole.

NMR: 0.48 (d, 3H, major isomer), 0.69 (t, 3H, minor isomer), 0.82 (t, 3H, major isomer), 0.92 (d, 3H, minor isomer), 3.30 (s, 1H), 7.0-7.5 (m, 4H), 8.88 (br s, 1H, minor isomer), 8.93 (br s, 1H, major isomer).

MS: 298 (23%), 172 (24%), 171 (100%), 170 (15%), 169 (23%), 143 (29%).

EXAMPLE 13

1-Cyclohexyl-1,2,3,4,6,7,12,12bβ-octahydro-indolo[2,3-*a*]quinolizin-1-ol

The procedure of example 9 was repeated, except that 1-cyclohexylmethyl-4,9-dihydro-3*H*-pyrido[3,4-*b*]indole was used instead 4,9-dihydro-1-isobutyl-3*H*-pyrido[3,4-*b*]indole.

NMR: 3.35 (br s, 1H), 7.02-7.55 (m, 4H), 8.98 (br s, 1H).

MS: 324 (21%), 172 (12%), 171 (100%), 170 (10%), 169 (15%), 143 (22%).

EXAMPLE 14

(1α-Isopropyl-1,2,3,4,6,7,12,12bβ-octahydro-indolo[2,3-*a*]quinolizin-1-yl)-methanol

The procedure of example 9 was repeated, except that instead of oxidation using iodine and potassium iodide, the enamine obtained was treated with 40 % aqueous formaldehyde and the reaction mixture was heated to reflux for 3 h and the solvent was evaporated. The residue was diluted with ethyl acetate and washed with brine. The organic phase was dried over sodium sulfate, the drying agent was filtered off and the filtrate was evaporated to give the title compound, which was purified by column chromatography (silica gel, dichloromethane/methanol, 98:2).

NMR: 0.58 (br s, 3H), 0.82 (d, 3H), 3.07 (br s, 1H), 3.62 (d, 1H), 4.13 (d, 1H), 7.00-7.50 (m, 4H), 9.41 (br s, 1H).

MS: 298 (100%), 297 (55%), 281 (60%), 170 (75%), 169 (52%).

EXAMPLE 15

(1α- *n*-Propyl-1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-*a*]quinolizin-1-yl)-methanol

The procedure of example 14 was repeated, except that 4,9-dihydro-1-butyl-3-*H*-pyrido[3,4-*b*]indole was used instead of 4,9-dihydro-1-isobutyl-3-*H*-pyrido[3,4-*b*]indole.

NMR: 0.81 (t, 3H), 3.34 (br s, 1H), 3.65 (d, 1H), 3.82 (d, 1H), 7.00-7.50 (m, 4H), 10.07 (br s, 1H).

MS: 298 (100%), 297 (65%), 281 (67%), 170 (75%), 169 (52%).

EXAMPLE 16

(1α-Methyl-1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-*a*]quinolizin-1-yl)-methanol

The procedure of example 14 was repeated, except that 1-ethyl-4,9-dihydro-3*H*-pyrido[3,4-*b*]indole was used instead 4,9-dihydro-1-isobutyl-3*H*-pyrido[3,4-*b*]indole.

NMR: 0.91 (s, 3H), 3.37 (br s, 1H), 3.70 (d, 1H), 3.76 (d, 1H), 7.0-7.6 (m, 4H), 9.78 (br s, 1H).

MS: 270 (97%), 269 (100%), 253 (53%), 197 (48%), 170 (68%), 169 (62%).

EXAMPLE 17

(1α-Ethyl-1,4,6,7,12,12bβ-hexahydroindolo[2,3-*a*]quinolizin-1-yl)-methanol

A mixture of 0.34 g (2.0 mmol) of 3,4-dihydro-β-carboline and 0.39 g (2.5 mmol) of ethyl 2-ethylpenta-2,4-dienoate in 5 ml of chlorobenzene was refluxed for 16 h. The solvent was evaporated and the residue was subjected to column chromatography (silica gel, dichloromethane/methanol, 99:1) to give the ester intermediate. This product was reduced in the usual manner with lithium aluminum hydride in dry tetrahydrofuran to afford the title compound.

NMR: 0.82 (t, 3H), 3.69 (d, 1H), 3.70 (br s, 1H), 3.90 (d, 1H), 5.42 (ddd, 1H), 5.97 (ddd, 1H), 7.0-7.5 (m, 4H), 10.02 (br s, 1H).

MS: 282 (31%), 171 (14%), 170 (100%), 169 (52%).

EXAMPLE 18

2β-Methoxy-1,2,3,4,6,7,12,12bα-octahydro-indolo[2,3-*a*]quinolizine

and

2α-Methoxy-1,2,3,4,6,7,12,12bα-octahydro-indolo[2,3-*a*]quinolizine

(Compound D)

1.16 g (14.7 mmol) of pyridine and 3.0 g (13.4 mmol) of tryptophyl bromide were dissolved in 15 ml of dry diethyl ether. The reaction mixture was heated with stirring at 60°C until complete evaporation of the solvent. The mixture was then heated at 100°C for 2 h to give the corresponding pyridinium bromide salt. This was dissolved in 100 ml of methanol and 1.52 g (40.1 mmol) of sodium borohydride was added in portions with cooling. The reaction mixture was stirred at room temperature

for 4 h, followed by addition of 20 ml of water. The reaction mixture was extracted with dichloromethane (3 x 30 ml). The combined organic phases were dried over sodium sulfate, the drying agent was filtered off and the filtrate was evaporated. The residue was dissolved in 100 ml of dry dichloromethane and 2.91 g (13.3 mmol) of di-*t*-butyl dicarbonate and 0.149 g (1.2 mmol) of 4-(dimethylamino)pyridine were added. The reaction mixture was stirred for 2 h at room temperature under argon. The solvent was evaporated and the residue purified by column chromatography (silica gel, dichloromethane/methanol, 98:2). The obtained viscous oil was dissolved in 40 ml of dichloromethane and 2.54 g (13.3 mmol) of *m*CPBA was added. The solution was stirred for 2 h at 0°C, after which the solvent was evaporated and the crude product was purified by column chromatography (silica gel, dichloromethane/methanol, 98:2) to yield the Boc N_b-oxide.

To a stirred solution of 0.59 g (1.7 mmol) of Boc N_b-oxide in 15 ml of dichloromethane at 0°C was slowly added 3.0 ml of trifluoroacetic anhydride. The cooling bath was removed and stirring was continued for 2 h at rt, after which the solvent was evaporated. Methanol saturated with hydrogen chloride gas (20 ml) was added and the mixture was refluxed for 2 h. Alkaline work-up and purification by column chromatography (silica gel, dichloromethane/methanol, 98:2) yielded two ethers.

2β-Methoxy-1,2,3,4,6,7,12,12bα-octahydro-indolo[2,3-*a*]quinolizine:

NMR: 1.54 (ddd, 1H), 3.24 (dd, 1H), 3.38 (dddd, 1H), 3.43 (s, 3H), 7.00-7.50 (m, 4H), 7.77 (br s, 1H).

MS: 256 (100%), 255 (86%), 255 (59%), 197 (35%), 169 (30%).

2α-Methoxy-1,2,3,4,6,7,12,12bα-octahydro-indolo[2,3-*a*]quinolizine:

NMR: 3.41 (s, 3H), 3.67 (br s, 1H), 3.68 (br d, 1H), 7.00-7.50 (m, 4H), 7.72 (br s, 1H).

MS: 256 (100%), 255 (75%), 255 (70%), 223 (45%), 197 (40%), 170 (45%), 169 (65%).

EXAMPLE 19

1-(1,2α,3,4,6,7,12,12bα-Octahydroindolo[2,3-*a*]quinolizin-2-yl)-propan-1-ol

To a solution of 0.086 g (0.3 mmol) of 1,2,3,4,6,7,12,12b-octahydro-indolo[2,3-*a*]quinolizine-2-carbaldehyde (*J. Chem. Soc. Chem. Commun.* **22** (1995)

2317-2318) in 2 ml of dichloromethane at –60°C was added 0.22 ml (1.7 mmol) of 1M ethylmagnesium bromide. The reaction mixture was stirred for 4 h under argon. Work-up with aqueous sodium hydroxide, followed by extraction with dichloromethane, and purification by column chromatography (silica gel, dichloromethane/methanol, 98:2) gave the title compound.

NMR: 1.02 (t, 3H), 1.93 (br d, 1H), 2.30 (br d, 1H), 6.80-7.40 (m, 4H).

MS: 284 (95%), 283 (100%), 225 (80%), 169 (36%).

EXAMPLE 20

(1,2α,3,4,6,7,12,12bα-Octahydroindolo[2,3-*a*]quinolizin-2-yl)-propan-2-ol

To a solution of 88 mg (0.31 mmol) of 1,2α,3,4,6,7,12,12bα-octahydroindolo[2,3-*a*]-quinolizine-2-carboxylic acid methyl ester in 3 ml of dry tetrahydrofuran was added dropwise 1 ml (3.0 mmol) of a solution of methylmagnesium chloride (3 M in tetrahydrofuran). The resulting solution was then refluxed for 90 min. The mixture was then worked-up as in example 7 to give the crude alcohol, which was purified by column chromatography (silica gel, dichloromethane/methanol, 95:5) to give the title compound.

NMR: 1.20 (s, 3H), 1.25 (s, 3H), 3.28 (br d, 1H), 7.0-7.5 (m, 4H).

MS: 284 (86%), 283 (65%), 225 (100%).

EXAMPLE 21

(1,2α,3,4,6,7,12,12bβ-Octahydroindolo[2,3-*a*]quinolizin-2-yl)-propan-2-ol

As in example 20, 64 mg (0.23 mmol) of 1,2α,3,4,6,7,12,12bβ-octahydroindolo[2,3-*a*]-quinolizine-2-carboxylic acid methyl ester in 3 ml of dry tetrahydrofuran and 0.7 ml (2.1 mmol) of a solution of methylmagnesium chloride (3 M in tetrahydrofuran) were refluxed for 90 min. Work-up as above gave, after column chromatography (silica gel, dichloromethane/methanol, 90:10), the title compound.

NMR: 1.17 (s, 3H), 1.18 (s, 3H), 4.57 (br s, 1H), 7.0-7.5 (m, 4H), 8.65 (br s, 1H).

MS: 284 (58%), 283 (53%), 225 (100%).

EXAMPLE 22

(2α-Ethyl-1,2,3,4,6,7,12,12bα-octahydroindolo[2,3-*a*]quinolizin-2-yl)-methanol

To a stirred solution of 0.36 g (3.6 mmol) of diisopropylamine in 4 ml of dry tetrahydrofuran at -50°C was added 2.0 ml (3.6 mmol) of n-butyllithium (1.8 M in hexanes). The mixture was allowed to warm up to -30°C (15 min), after which it was cooled to -70°C. At this temperature, 0.64 g (3.6 mmol) of hexamethylphosphoramide was added. Stirring was continued for 30 min at this temperature, after which 0.42 g (1.48 mmol) of methyl 1-[2-(3-indolyl)ethyl]-1,2,5,6-tetrahydropyridine-4-carboxylate in 7 ml of tetrahydrofuran was added. After stirring for 20 min at -70°C, the mixture was allowed to warm up to -40°C (15 min). At this temperature, 0.3 g (3.6 mmol) of ethyl iodide was added and stirring was continued for 1 h. The cooling bath was then removed and, after additional 15 min, the mixture was quenched with 5% ammonia. The aqueous layer was extracted with dichloromethane (3 x 20 ml) and the combined organic layers were washed with water. Drying over sodium sulfate, filtration and evaporation of the solvent gave the crude enamine, which was dissolved in 50 ml of methanol saturated with hydrogen chloride and the resulting solution was stirred for 16 h at room temperature. The solvent was evaporated and the residue was treated with aqueous sodium hydrogen carbonate. After normal extraction procedures (dichloromethane), the solvent was evaporated to give the crude product, which was subjected to column chromatography (silica gel, dichloromethane/methanol, 98:2) to afford the intermediate ester, 2α-ethyl-1,2,3,4,6,7,12,12bα-octahydroindolo[2,3-*a*]quinolizine-2-carboxylic acid methyl ester. This compound was then treated with lithium aluminum hydride in dry tetrahydrofuran in the usual manner to give, after column chromatography (silica gel, dichloromethane/methanol, 95:5), the title alcohol.

NMR: 0.90 (t, 3H), 3.29 (d, 1H), 3.43 (d, 1H), 3.52 (br d, 1H), 7.0-7.5 (m, 4H).

MS: 284 (100%), 283 (98%), 253 (33%), 197 (37%), 170 (33%), 169 (40%), 156 (34%).

EXAMPLE 23

(2α-Ethyl-1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-*a*]quinolizin-2-yl)-methanol

A solution of 51 mg (0.16 mmol) of the ester intermediate obtained in example 22 (2α-ethyl-1,2,3,4,6,7,12,12bα-octahydroindolo[2,3-*a*]quinolizine-2-carboxylic acid methyl ester) in 4 ml of trifluoroacetic acid was refluxed under argon for 16 h. The acid was evaporated and the residue treated with aqueous sodium hydrogen carbonate. After normal extraction procedures (dichloromethane) a crude mixture (20:80) of the two diastereomers, 2α-ethyl-1,2,3,4,6,7,12,12bα-octahydroindolo[2,3-*a*]quinolizine-2-carboxylic acid methyl ester and 2α-ethyl-1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-*a*]quinolizine-2-carboxylic acid methyl ester, was obtained. The latter isomer was separated by column chromatography (silica gel, dichloromethane/methanol, 99:1) and it was then reduced in the usual way with lithium aluminum hydride in dry tetrahydrofuran. Purification as above then gave the title alcohol.

NMR: 0.87 (t, 3H), 3.51 (d, 1H), 3.78 (d, 1H), 7.0-7.5 (m, 4H).

MS: 284 (95%), 283 (100%), 253 (30%), 197 (30%), 170 (17%), 169 (23%), 156 (19%).

EXAMPLE 24

1-(2α-Ethyl-1,2,3,4,6,7,12,12bα-octahydroindolo[2,3-*a*]quinolizin-2-yl)-ethanone and

2-(2α-Ethyl-1,2,3,4,6,7,12,12bα-octahydroindolo[2,3-*a*]quinolizin-2-yl)-propan-2-ol

As in example 20, 230 mg (0.74 mmol) of the ester intermediate obtained in example 22 (2α-ethyl-1,2,3,4,6,7,12,12bα-octahydroindolo[2,3-*a*]quinolizine-2-carboxylic acid methyl ester) in dry tetrahydrofuran (9 ml) and 3.7 ml (11.1 mmol) of methylmagnesium chloride (3M in tetrahydrofuran) were refluxed overnight. Usual work-up gave, after column chromatography (silica gel, dichloromethane/methanol, 98:2 – 95:5), a 5:1 mixture of two compounds.

1-(2α-Ethyl-1,2,3,4,6,7,12,12bα-octahydroindolo[2,3-*a*]quinolizin-2-yl)-ethanone:

NMR: 0.82 (t, 3H), 2.14 (s, 3H), 3.44 (br d, 1H), 7.05-7.50 (m, 4H), 8.05 (br s, 1H).

MS: 296 (83%), 295 (62%), 253 (100%), 184 (95%).

2-(2α-Ethyl-1,2,3,4,6,7,12,12bα-octahydroindolo[2,3-*a*]quinolizin-2-yl)-propan-2-ol:

NMR: 1.05 (t, 3H), 1.24 (s, 6H), 3.42 (br d, 1H), 7.05-7.50 (m, 4H), 7.88 (br s, 1H).

MS: 312 (48%), 311 (37%), 253 (100%).

EXAMPLE 25

1-(2α-Ethyl-1,2,3,4,6,7,12,12bα-octahydroindolo[2,3-*a*]quinolizin-2-yl)-ethanol

The ketone obtained in the above reaction was reduced with sodium borohydride in methanol in the usual manner to give the title alcohol as an inseparable mixture of diastereomers.

NMR: 0.95 (t, 3H, minor), 1.18 (t, 3H, major), 3.61 (q, 1H, minor), 3.67 (q, 1H, major).

MS: 298 (100%), 297 (64%), 253 (87%).

EXAMPLE 26

2,3,4,5,7,8,13,13b-Octahydro-1H-azepino[1',2':1,2]pyrido[3,4-*b*]indole (Compound E)

To a solution of 0.20 g (1.2 mmol) of tryptamine in 5.0 ml of xylene was added 0.14 g (1.2 mmol) of ε-caprolactam. The mixture was refluxed for 7 h. After evaporation of the solvent, the residue was dissolved in 5.0 ml of toluene, 0.65 ml of freshly distilled phosphorus oxychloride was added and the reaction mixture was refluxed for 9 h. The solution was evaporated in vacuum and the residue was mixed with a 20% solution of acetic acid (3 x 10 ml). The solid was filtered off and the aqueous solution was made alkaline (pH 11) with 25% ammonium hydroxide under cooling and extracted with dichloromethane (3 x 20 ml). To the combined organic layers was added 6.0 ml of 4 M sodium hydroxide and this mixture was refluxed for 1 h. The organic phase was dried over sodium sulfate, the drying agent was filtered off and the filtrate was concentrated to give an oil, which was dissolved in 30 ml of methanol. To the cold solution was added 0.2 g (5.6 mmol) of sodium borohydride.

The mixture was stirred at room temperature for 1 h. Water was slowly added and the reaction mixture was extracted with dichloromethane (3 x 20 ml). The combined organic phases were dried over sodium sulfate, the drying agent was filtered off and the solvent evaporated to give the title compound, which was purified by column chromatography (silica gel, dichloromethane/methanol, 95:5).

NMR: 4.03 (br d, 1H), 7.11-7.46 (m, 4H), 8.05 (br s, 1H).

MS: 240 (52%), 239 (100%), 198 (10%), 170 (24%).

EXAMPLE 27

1α-Ethyl-12-methyl-1,2,3,4,6,7,12bβ-octahydroindolo[2,3-*a*]quinolizin-1-ol

To a solution of 0.05 g (0.1 mmoles) of 1α-ethyl-1β-hydroxy-1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-*a*]quinolizine and 0.05 g (0.9 mmoles) of KOH in 1.0 ml of acetone was added 0.02 ml (0.3 mmoles) of iodomethane. The reaction mixture was stirred at rt for 1 h. Water was slowly added and the reaction mixture was extracted with dichloromethane (3 x 20 ml). The combined organic phases were dried over sodium sulfate, the drying agent was filtered off and the filtrate was evaporated to give the title compound, which was purified by column chromatography (silica gel, dichloromethane/methanol, 95:5).

NMR: 0.71 (t, 3H), 1.01 (m, 2H), 3.59 (br s, 1H), 3.72 (s, 3H), 7.00-7.50 (m, 4H).

MS: 284 (21%), 283 (100%), 185 (60%), 170 (10%).

EXAMPLE 28

1α-Ethyl-12-ethyl-1,2,3,4,6,7,12bβ-octahydro-indolo[2,3-*a*]quinolizin-1-ol

The procedure of example 27 was repeated, except that iodoethane was used instead of iodomethane.

NMR: 0.71 (t, 3H), 1.00 (m, 2H), 1.07 (t, 3H), 3.60 (s, 1H), 4.20 (m, 1H), 4.64 (m, 1H), 7.00-7.50 (m, 4H).

MS: 298 (29%), 297 (19%), 199 (100%), 171 (33%).

EXAMPLE 29

1α-Methyl-1,3,4,5,6,11b-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluoren-1-ol

To a solution of 0.48 g (3.0 mmol) of 2-(3-benzo[b]furanyl)ethylamine in 5.0 ml of xylene was added 0.34 g (3.0 mmol) of α-methyl-δ-valerolactone. The mixture was refluxed for 7.5 h. After evaporation of the solvent the residue was dissolved in 6.0 ml of toluene, 0.72 ml of freshly distilled phosphorus oxychloride was added and the reaction mixture was refluxed for 11 h. The solution was evaporated in vacuum and the obtained oil was mixed with a 20% solution of acetic acid (3 x 20 ml). The solid was filtered off and the aqueous solution was made alkaline (pH 11) with 25% ammonium hydroxide under cooling and extracted with dichloromethane (3 x 20 ml). To the combined organic phases was added 12.5 ml of 4 M sodium hydroxide and this mixture was refluxed for 1 h. The organic phase was dried over sodium sulfate, the drying agent was filtered off and the filtrate was concentrated to give the corresponding enamine, which was oxidised as described in example 9.

NMR: 1.18 (s, 3H), 3.25 (br d, 1H), 7.10-7.50 (m, 4H).

MS: 257 (25%), 242 (10%), 172 (100%).

EXAMPLE 30

(1α-Methyl-1,3,4,5,6,11bβ-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluoren-1-yl)-methanol

The procedure of example 29 was repeated, except that to the formed enamine, 40 % aqueous formaldehyde was slowly added. The reaction mixture was refluxed for 3.5 h and the solvent was evaporated. The residue was diluted with ethyl acetate and washed with brine. The organic phase was dried over sodium sulfate, the drying agent was filtered off and the filtrate was evaporated to give the title compound, which was purified by column chromatography (silica gel, (dichloromethane/methanol, 98:2).

NMR: 0.89 (s, 3H), 3.40 (br s, 1H), 3.62 (d, 1H), 4.29 (d, 1H), 7.10-7.50 (m, 4H).

MS: 271 (69%), 270 (100%), 198 (45%), 171 (52%), 170 (60%).

EXAMPLE 31

1α-Isopropyl-1,3,4,5,6,11b-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluoren-1-ol

The procedure of example 9 was repeated, except that 2-(3-benzo[b]furanyl)ethylamine was used instead of tryptamine.

NMR: 1.00 (m, 6H), 7.25 (m, 2H), 7.44 (m, 2H),

MS: 285 (23%), 242 (10%), 198 (10%), 186 (23%), 172 (100%).

EXAMPLE 32

1α-Ethyl-1,3,4,5,6,11bβ-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluoren-1-ol

The procedure of example 29 was repeated, except that α-ethyl-δ-valerolactone was used instead of α-methyl-δ-valerolactone.

NMR: 0.73 (t, 3H), 3.22 (br s, 1H), 7.00-7.30 (m, 2H), 7.40-7.55 (m, 2H).

MS: 271 (15%), 186 (18%), 173 (11%), 172 (100%), 170 (28%).

EXAMPLE 33

(1α-Ethyl-1,3,4,5,6,11bβ-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluoren-1-yl)-methanol

The procedure of example 30 was repeated, except that α-ethyl-δ-valerolactone was used instead of α-methyl-δ-valerolactone.

NMR: 0.62 (t, 3H), 3.48 (br s, 1H), 3.52 (d, 1H), 4.06 (d, 1H), 7.00-7.30 (m, 2H), 7.40-7.55 (m, 2H).

MS: 285 (56%), 284 (100%), 268 (19%), 198 (36%), 172 (20%), 171 (44%), 170 (54%).

EXAMPLE 34

5,6,7,7a,11,11b,12-Decahydro-6a,12-diaza-indeno[1,2-*a*]fluoren-11a-ol

The procedure of example 29 was repeated, except that instead of 2-(3-benzo[*b*]furanyl)ethylamine and α-methyl-δ-valerolactone, tryptamine and hexahydroisobenzofuran-1-one were used.

NMR: 4.45 (br d, 1H), 7.00-7.60 (m, 4H), 9.11 (br s, 1H).

MS: 296 (8%), 143 (100%), 130 (81%).

EXAMPLE 35

1,2,3,4,4a,5,6,7,8,13-Decahydro-6a,13-diaza-indeno[1,2-*c*]phenanthrene

To a solution of 0.356 g (1.26 mmol) of *N*-[2-(3-indolyl)ethyl)]decahydroisoquinoline in 20 ml of ethanol was added a solution of 1.6 g of mercuric acetate and 1.88 g of ethylenediaminetetra-acetic acid disodium salt dihydrate in 40 ml of water and the resulting mixture was refluxed for 3 h. The cooled mixture was made basic with dilute ammoniumhydroxide (pH 11) and then extracted with dichloromethane (3 x 30 ml). The combined organic layers were dried over sodium sulfate, filtered and the solvent evaporated to give the crude enamine (mixture of regioisomers), which was directly used in the next step (see example 36). The pure enamine could be obtained by column chromatography (silica gel, dichloromethane/methanol/ triethylamine, 98:1:1).

EXAMPLE 36

2,3,4,4aβ,5,6,7,8,13,13bβ-Decahydro-1H-6a,13-diaza-indeno[1,2-*c*]phenanthren-13cβ-ol (Compound F)

As in example 9, 0.42 g (1.51 mmol) of the crude enamine from example 35 was treated with 0.21 g of potassium iodide and 0.32 g of iodine in 30 ml of acetonitrile. After reduction with 0.29 g of sodium borohydride in 30 ml of methanol, the crude product was purified by column chromatography (silica, dichloromethane/methanol, 99:1) to afford the pure alcohol.

NMR: 3.18 (br s, 1H), 7.0-7.55 (m, 4H), 9.18 (br s, 1H).

MS: 296 (25%), 295 (10%), 185 (15%), 171 (100%).

EXAMPLE 37

(2,3,4,4aβ,5,6,7,8,13,13bβ-Decahydro-1H-6a,13-diaza-indeno[1,2-*c*]phenanthrenyl)-13cβ-methanol

A solution of 150 mg (1.51 mmol) of the above pure enamine (from example 35), 2 ml of 36% aqueous formaldehyde and 0.2 ml *N*-ethyldiisopropylamine in 10 ml of acetonitrile was refluxed for 3 h. After work-up the crude product was purified by column chromatography (silica gel, dichloromethane/methanol, 98:2) to afford the pure alcohol.

NMR: 3.29 (br s, 1H), 3.98 (d, 1H), 4.17 (d, 1H), 7.0-7.5 (m, 4H), 10.05 (br s, 1H).

MS: 310 (88%), 309 (100%), 293 (34%), 197 (67%), 184 (35%), 170 (90%), 169 (77%).

EXAMPLE 38

3β,4α-Dimethyl-1,2,3,4,6,7,12,12bβ-octahydro-indolo[2,3-*a*]quinolizine

To a solution of 0.422 g (1.65 mmol) of *N*-[2'-(3'-indolyl)ethyl)]-2,3-dimethylpiperidine in 25 ml of ethanol was added 2.1 g of mercuric acetate and 2.46 g of ethylenediaminetetraacetic acid disodium salt dihydrate in 50 ml of water and the resulting mixture was refluxed for 3 h. The cooled mixture was made basic with dilute ammoniumhydroxide and then extracted with dichloromethane. Drying over sodium sulfate, filtration and evaporation of the solvent gave the crude enamine, which was dissolved in 30 ml methanol and cooled with an ice bath. A few drops of acetic acid were added followed by 0.322 g of sodium borohydride in portions. After stirring for 1.5 h, the mixture was worked up in the usual manner to give the crude product, which was purified by column chromatography (silica gel, dichloromethane/methanol (98.5:1.5).

NMR: 0.89 (d, 3H), 0.96 (d, 3H), 3.76 (br d, 1H), 7.0-7.5 (m, 4H), 7.71 (br s, 1H).

MS: 254 (95%), 253 (100%), 239 (30%), 170 (31%), 169 (36%).

EXAMPLE 39

(1α-Ethyl-1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-a]quinolizin-1-ylmethoxy)-acetic acid ethyl ester

A solution of 0.02 g (0.07 mmol) of (1β-ethyl-1,2,3,4,6,7,12,12bα-octahydro-indolo[2,3-*a*]quinolizin-1-yl)-methanol (*Gazz. Chim. Ital.* **111** (1981) 257-267) in *N*,*N*-dimethylformamide-toluene (1 ml, 1:1) was added to 6.8 mg (0.28 mmol) of sodium hydride, previously washed with heptane. The reaction mixture was stirred at rt for 1 h and then ethyl bromoacetate (0.009 ml, 0.084 mmol) in toluene (1 ml) was added dropwise. The stirring was continued for 3 h at rt. Water was slowly added and the reaction mixture was extracted with dichloromethane (3 x 20 ml). The combined organic phases were dried over sodium sulfate, the drying agent was filtered off and the filtrate was evaporated to give the title compound, which was purified by column chromatography (silica gel, dichloromethane/ methanol, 5:5).

NMR: 0.61 (t, 3H), 1.28 (t,3H), 3.49 (s, 1H), 4.25 (d, 1H), 4.30 (q, 2H), 4.55 (d, 1H), 6.93 (t, 1H), 7.03 (t, 1H), 7.35 (d, 1H), 7.38 (d, 1H), 10.64(s, 1H).

MS: 370 (40%), 369 (30%), 283 (12%), 267 (100%), 197 (12%), 170 (12%), 169 (16%)

EXAMPLE 40

5,6,7,7aβ,8,9,10,11,11aβ,11bα-Decahydro-12-oxa-6a-aza-indeno[1,2-a]fluorene

To a solution of 0.70 g (0.43 mmol) of 2-(3-benzo[*b*]furanyl)ethylamine in 30 ml of chlorobenzene was added 0.13 g (0.87 mmol) of *cis*-1,2-cyclohexanedicarboxylic anhydride. The mixture was irradiated in a microwave oven (1000 W, T=130°C) for 30 min. Chlorobenzene was replaced by ethanol (5 ml) and 82.7 mg (2.18 mmol) of sodium borohydride was added. The mixture was stirred at rt for 18 h, after which water was added and the product was isolated in the usual manner. Trifluoroacetic acid (0.12 ml, 1.53 mmol) in dichloromethane (10 ml) was added and the reaction mixture was stirred for 2 h at rt. Alkaline work-up (4 M sodium hydroxide), gave the amide intermediate, which was dissolved in diethyl ether (15 ml), 0.1 g (2.63 mmol) of lithium aluminum hydride was added and the reaction mixture was refluxed for 1.5 h. Water was slowly added under cooling. After normal extraction procedures, the crude product was purified by column chromatography (silica gel, dichloromethane/methanol, 90:10).

NMR: 1.77 (m, 2H), 2.07 (m, 1H), 2.29 (m, 1H), 2.48 (m, 1H), 3.04 (m, 1H), 3.20 (m, 1H), 4.13 (s, 1H), 7.18–7.50 (m, 4H).

MS: 267 (46%), 266 (100%), 185 (52%), 170 (12%).

EXAMPLE 41

1-Methyl-1α,3,4,6,11bβ-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluorene (Compound G)

The procedure of example 26 was repeated, except that α-methyl-δ-valerolactone and 2-(3-benzo[b]furanyl)ethylamine were used instead of ε-caprolactam and tryptamine, respectively.

NMR: 0.88 (d, 3H), 3.34 (br s, 1H), 7.19-7.43 (m, 4H).

MS: 241 (40%), 240 (50%), 226 (100%), 198 (10%), 170 (68%), 170 (24%).

EXAMPLE 42

(1-Hydroxymethyl-1,3,4,5,6,11b-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluoren-1-yl]-methanol

The procedure of example 41 was repeated, except that δ-valerolactone was used instead of α-methyl-δ-valerolactone, and the obtained enamine was treated with formaldehyde as in example 14.

NMR: 3.30 (d, 1H), 3.76 (d, 1H), 3.79 (d, 1H), 3.82 (s, 1H), 4.31 (d, 1H), 7.18-7.50 (m, 4H).

MS: 287 (56%), 286 (60%), 270 (40%), 256 (100%), 198 (34%), 172 (26%), 170 (54%).

EXAMPLE 43

1-Methoxymethyl-1α-methyl-1,3,4,5,6,11bβ-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluorene

A solution of 173.1 mg (0.64 mmol) of the alcohol described in example 30 in 5 ml of tetrahydrofuran was added to 153.0 mg (6.38 mmol) of sodium hydride, previously washed with heptane. The reaction mixture was stirred at 35°C for 1 h followed by dropwise addition of a solution of 0.04 ml (0.64 mmol) of iodomethane in tetrahydrofuran (5 ml). The stirring was continued for 1h. Water was slowly added and the reaction mixture was extracted with dichloromethane (3 x 20 ml). The combined organic phases were dried over sodium sulfate, the drying agent was filtered off and the filtrate was evaporated to give the title compound, which was purified by column chromatography (silica gel, dichloromethane/methanol, 90:10).

NMR: 0.74 (s, 3H), 3.29 (s, 3H), 3.36 (d, 1H), 3.89 (d, 1H), 7.20-7.52 (m, 4H).

MS: 285 (80%), 284 (100%), 270 (20%), 254 (98%), 198 (35%), 171 (82%), 170 (70%).

EXAMPLE 44

2,3,4,4aβ,5,6,7,8,13bβ,13cβ-Decahydro-1H-13-oxa-6a-aza-indeno[1,2-*c*]phenanthrene and **2,3,4,4aβ,5,6,7,8,13bα,13cβ-decahydro-1H-13-oxa-6a-aza-indeno[1,2-*c*]phenanthrene**

The procedure of example 41 was repeated, except that *cis*-octahydro-isochromen-1-one was used instead of α-methyl-δ-valerolactone. The two isomers were separated by column chromatography (silica gel, ethyl acetate/heptane, 70:30).

2,3,4,4aβ,5,6,7,8,13bβ,13cβ-Decahydro-1H-13-oxa-6a-aza-indeno[1,2-*c*]phenanthrene:

NMR: 3.28 (s, 1H), 7.17-7.53 (m, 4H).

MS: 281 (40%), 280 (100%), 238 (15%), 198 (12%), 170 (24%).

2,3,4,4aβ,5,6,7,8,13bα,13cβ-decahydro-1H-13-oxa-6a-aza-indeno[1,2-*c*]phenanthrene:

NMR: 2.75 (d, 1H), 7.15-7.43 (m, 4H).

MS: 281 (38%), 280 (100%), 198 (16%), 170 (30%).

EXAMPLE 45

1α-Methyl-1,3,4,5,6,11bα-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluorene-1-carboxylic acid ethyl ester

To a mixture of 0.375 g (2.33 mmol) of 2-(3-benzo[b]furanyl)ethylamine and triethylamine (0.97 ml, 7.0 mmol) in dichloromethane (3 ml) was added 0.56 g (2.33 mmol) 5-chloro-2-ethoxycarbonyl-2-methylvaleroyl chloride (prepared according to the process described for the corresponding 2-ethyl derivative in *J. Org. Chem.* **45** (1980) 32-34) in dichloromethane (4 ml). After stirring at rt for 45 min, water was added and the mixture was extracted with dichloromethane. Drying over sodium sulfate, filtration of the drying agent and evaporation of the solvent gave the crude amide, which was purified by column chromatography (ethyl acetate/heptane, 1:1). The pure amide (0.3 g, 0.82 mmol) was dissolved in toluene (3 ml) and 0.38 ml (4.1 mmol) of phosphorus oxychloride was added. The mixture was refluxed for 2 h, after which it was evaporated to dryness. The residue was dissolved methanol (3 ml) and 57 mg (1.5 mmol) of sodium borohydride was added in portions. After stirring at rt for 1 h, water was added and the mixture was extracted with ethyl acetate. Drying over sodium sulfate, followed by filtration and evaporation gave the crude ester which was purified by column chromatography (silica gel, ethyl acetate/heptane, 1:1).

NMR: 0.65 (t, 3H), 1.55 (s, 3H), 3.30 (br s, 1H), 7.16-7.50 (m, 4H).

MS: 313 (70%), 312 (100%), 284 (22%), 240 (32%), 198 (80%), 171 (35%), 170 (95%).

EXAMPLE 46

1-Ethoxymethyl-1α-methyl-1,3,4,5,6,11bβ-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluorene

The procedure of example 43 was repeated, except that iodoethane was used instead of iodomethane.

NMR: 0.74 (s, 3H), 1.17 (t, 3H), 3.37 (s, 1H), 3.38 (d, 1H), 3.54 (q, 2H), 3.96 (d, 1H), 7.10-7.60 (m, 4H).

MS: 299 (70%), 298 (92%), 270 (40%), 254 (100%), 198 (34%), 171 (86%), 170 (72%).

EXAMPLE 47

(1α-Methyl-1,3,4,5,6,11bα-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluoren-1-yl)-methanol

To a suspension of 0.31 g (8.23 mmol) of lithium aluminum hydride in dry tetrahydrofuran (10 ml), was added 0.86 g (2.74 mmol) of the ester described in example 45 in dry tetrahydrofuran (10 ml). The reaction mixture was refluxed for 1 h. Water was slowly added and the reaction mixture was extracted with ethyl acetate (3 x 20 ml). The combined organic phases were dried over sodium sulfate, filtered and the filtrate was evaporated to give the desired product, which was purified by column chromatography (silica gel, ethyl acetate/heptane, 50:50).

NMR: 1.30 (s, 3H), 2.98 (br s, 1H), 3.21 (d, 1H), 3.69 (d, 1H), 4.33 (s, 1H), 7.15-7.55 (m, 4H).

MS: 271 (52%), 270 (100%), 198 (34%), 172 (20%), 171 (44%), 170 (66%).

EXAMPLE 48

(1α-Methyl-1,2,3,4,6,7,12,12bα-octahydroindeno[2,1-a]quinolizin-1-yl)-methanol

The procedures described in examples 45 and 47 were repeated, except that 2-(3H-inden-1-yl)-ethylamine was used instead of 2-(3-benzo[b]furanyl)ethylamine.

NMR: 0.82 (s, 3H), 3.07 (br s, 1H), 3.23 (d, 1H), 3.39 (d, 1H), 3.52 (d, 1H), 3.70 (d, 1H), 7.05-7.35 (m, 4H).

MS: 269 (43%), 268 (100%), 252 (29%), 196 (36%), 168 (40%).

EXAMPLE 49

1α–Ethyl-1,3,4,5,6,11bα-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluorene-1-carboxylic methyl ester

The procedure of example 45 was repeated, except that 5-chloro-2-ethoxycarbonyl-2-ethylvaleroyl chloride was used instead of 5-chloro-2-ethoxycarbonyl-2-methylvaleroyl chloride.

NMR: 0 .90 (t, 3H), 6.90-7.58 (m, 4H).

MS: 327 (72%), 326 (100%), 312 (20%), 298 (20%), 254 (30%), 198 (54%), 172 (60%), 170 (90%).

EXAMPLE 50

1-Methoxymethyl-1α-methyl-1,3,4,,5,6,11bα-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluorene

The procedure of example 43 was repeated, except that the alcohol described in example 47 was used as the starting compound.

NMR: 1.44 (s, 3H), 2.99 (d, 1H), 3.15 (br s, 1H), 3.22 (s, 3H), 3.70 (d, 1H), 7.18-7.50 (m, 4H).

MS: 285 (84%), 284 (100%), 270 (14%), 254 (92%), 198 (34%), 171 (74%), 170 (50%).

EXAMPLE 51

(1α-Ethyl-1,3,4,5,6,11bα-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluorene-1-yl)-methanol

The procedure of example 47 was repeated, except that the ester described in example 49 was used as the starting compound.

NMR: 1.00 (t, 3H), 2.93 (m, 2H), 3.29 (s, 1H), 7.15-7.60 (m, 4H).

MS: 286 (90%), 285 (68%), 284 (100%), 268 (16%), 198 (22%), 171 (22%), 170 (36%).

EXAMPLE 52

1-β-Hydroxymethyl-1-methyl-1,2,3,4,6,7,12,12bβ-octahydro-indolo[2,3-*a*]quinolizine-6β-carboxylic acid methyl ester

The procedure of the preparation of (1β-ethyl-1,2,3,4,6,7,12,12bα-octahydro-indolo[2,3-*a*]quinolizin-1-yl)-methanol (*Gazz. Chim. Ital.* **111** (1981) 257-267) was repeated, except that L-tryptophan methyl ester was used instead of tryptamine.

NMR: 0.74 (s, 3H), 3.39 (s, 3H), 3.46 (d, 1H), 3.97 (d, 1H), 4.38 (br s, 1H), 7.00-7.50 (m, 4H), 8.90 (br s, 1H).

MS: 328 (26%), 327 (100%), 299 (38%), 268 (32%), 170 (10%), 169 (24%).

EXAMPLE 53

Resolution of 1α-isopropyl-1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-*a*]quinolizin-1-ol

A solution of 0.3 g (1.1 mmol) of (±)-1α-isopropyl-1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-*a*]quinolizin-1-ol and 0.16 g (1.1 mmol) of L-tartaric acid in 15 ml of acetone was refluxed for 30 min. On standing at room temperature overnight there was deposited of 200 mg of a solid. After two recrystallizations from methanol the collected L-tartrate salt was partitioned between dichloromethane and 10% sodium hydroxide solution, dried over sodium sulfate and evaporated to yield 116.6 mg of (-)-1α-isopropyl-1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-*a*]quinolizin-1-ol with $[\alpha]_D$= -64.5° (c, 0.011 in $CHCl_3$). The other enantiomer (+)-1α-isopropyl-1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-*a*]quinolizin-1-ol $[\alpha]_D$= +64.5° (c, 0.011 in $CHCl_3$) was isolated from the mother liquor in the same manner.

EXAMPLE 54

Resolution of (1α-methyl-1,3,4,5,6,11bβ-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluoren-1-yl)-methanol

The procedure of example 53 was repeated, except that (+)-diacetyl-L-tartaric anhydride and isopropanol were used instead of L-tartaric acid and acetone. Optical purities of the separated enantiomers were confirmed by chiral HPLC (column: DAICEL CHEMICAL INDUSTRIES, LTD CHIRACEL OJ, dimension 0.46 cm * 25 cm, flow: 0.5 ml/min, mobile phase: n-hexane (Merck Uvasol for Spectroscopy)/isopropanol (Rathburn, HPLC-grade) (100:20), UV detection at 272 nm, retention times: 8.8 min [(+)-(1α-methyl-1,3,4,5,6,11bβ-hexahydro-2H-11-oxa-

4a-aza-benzo[*a*]fluoren-1-yl)-methanol] and 11.1 min [(-)-(1α-methyl-1,3,4,5,6,11bβ-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluoren-1-yl)-methanol].

EXAMPLE 55

Resolution of (1α-methyl-1,3,4,5,6,11bα-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluoren-1-yl)-methanol

The procedure of example 53 was repeated, except that (-)-di-p-toluoyl-L-tartaric acid monohydrate and ethyl acetate were used instead of L-tartaric acid and acetone. Optical purities of the separated enantiomers were confirmed by chiral HPLC (column: DAICEL CHEMICAL INDUSTRIES, LTD CHIRACEL OJ, dimension 0.46 cm * 25 cm, flow: 0.8 ml/min, mobile phase: n-hexane (Merck Uvasol for Spectroscopy)/isopropanol (Rathburn, HPLC-grade) (180:20), UV detection at 254 nm, retention times: 7.8 min [(+)-(1α-methyl-1,3,4,5,6,11bα-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluoren-1-yl)-methanol] and 12.6 min [(-)-(1α-methyl-1,3,4,5,6,11bα-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluoren-1-yl)-methanol].

EXAMPLE 56

Enantiomers of 1-methoxymethyl-1α-methyl-1,3,4,5,6,11bβ-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluorene

The procedure of example 43 was repeated, except that pure enantiomers, (+)-(1α-methyl-1,3,4,5,6,11bβ-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluoren-1-yl)-methanol and (-)-(1α-methyl-1,3,4,5,6,11bβ-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluoren-1-yl)-methanol, respectively, from example 54 were used instead of the alcohol described in example 30. Optical purities of the products were confirmed by chiral HPLC (column: ROCKLAND TECHNOLOGIES, INS ULTRON ES-OVM, dimension 4.6 cm * 15 cm, flow: 0.8 ml/min, mobile phase: 0.04 M KH_2PO_4 (pH 4.6)/acetonitrile (Merck Lichrosolv Isocratic grade for liquid chromatography) (90:10), retention times 3.8 min [(-)-1-methoxymethyl-1α-methyl-1,3,4,5,6,11bβ-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluorene] and 5.8 min [(+)-1-methoxymethyl-1α-methyl-1,3,4,5,6,11bβ-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluorene].

EXAMPLE 57

Enantiomers of 1-methoxymethyl-1α-methyl-1,3,4,5,6,11bα-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluorene

The procedure of example 43 was repeated, except that pure enantiomers, (+)-(1α-methyl-1,3,4,5,6,11bα-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluoren-1-yl)-methanol and (-)-(1α-methyl-1,3,4,5,6,11bα-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluoren-1-yl)-methanol, respectively, from example 55 were used instead of the alcohol described in example 30. Optical purities of the products were confirmed by chiral HPLC (column: DAICEL CHEMICAL INDUSTRIES, LTD CHIRACEL OJ, dimension 0.46 cm * 25 cm, flow: 0.8 ml/min, mobile phase: n-hexane (Merck Uvasol for Spectroscopy), retention times 5.6 min [(+)-1-methoxymethyl-1α-methyl-1,3,4,5,6,11bα-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluorene] and 6.3 min [(-)-1-methoxymethyl-1α-methyl-1,3,4,5,6,11bα-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluorene].

The following known compounds can be prepared analogously or according to the methods known in the literature.

1α-Methyl-1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-*a*]quinolizin-1-ol (Compound H): The procedure of example 6 was repeated, except that 1-ethyl-4,9-dihydro-3*H*-pyrido[3,4-*b*]indole (*J. Chem. Soc., Perkin Trans I* (1977) 2109-2115) was used instead of 1-isobutyl-4,9-dihydro-3*H*-pyrido[3,4-*b*]indole.

1,2,3,4,4aβ,5,6,7,8,13,13bβ,13cβ-Dodecahydro-6a,13-diaza-indeno[1,2-*c*]phenanthrene and **1,2,3,4,4aβ,5,6,7,8,13,13bβ,13cα-dodecahydro-6a,13-diaza-indeno-[1,2-*c*]phenanthrene** and their **13b-epimers**: The pure enamine from example 35 was reduced with sodium borohydride in methanol (containing a few drops of acetic acid) to give the two isomers, which are then separated by chromatography. The corresponding 13b-epimers are prepared by acid-catalysed epimerization of their parent isomers.

2β-Methyl-1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-*a*]quinolizin-2-ol and **2α-methyl-1,2,3,4,6,7,12,12bβ-octahydro-indolo[2,3-*a*]quinolizin-2-ol** are

prepared following the procedures described in *J. Org. Chem.* **56** (1991) 2701-2712 and *Chem. Ber.* **106** (1973) 3106-3118. **1,2,3,4,6,7,12,12bβ-Octahydroindolo[2,3-*a*]quinolizin-1α-ol** and **1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-*a*]quinolizin-1β-ol** are prepared according to the procedure described in *Chem. Pharm. Bull.* **34** (1986) 3713-3721. **1,2,3,4,6,7,12,12b-Octahydroindolo[2,3-*a*]quinolizine** is prepared according to the method described in *J.Chem. Soc., Chem. Comm.,* (1972) 461. **1,4,6,7,12,12b-Hexahydroindolo[2,3-*a*]quinolizine** (Compound I) is prepared according to the method described in *Tetrahedron* **45** (1989) 3975-3992. **3,4,6,7,12,12b-Hexahydroindolo[2,3-*a*]quinolizine** and **1-ethyl- 3,4,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizine** are prepared according to the method described in *Bull. Soc. Chim. Fr.* **7-8** (1976) 1222. **1α-Ethyl-1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-*a*]quinolizine** and **1β-ethyl-1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-*a*]quinolizine** (Compound J) are prepared according to the method described in *Tetrahedron* **45** (1989) 7615-7630. **1α-Ethyl-1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-*a*]quinolizin-1-ol** (Compound K) and **(1β-ethyl-1,2,3,4,6,7,12,12bα-octahydroindolo[2,3-*a*]quinolizin-1-yl)-methanol** (Compound L) are prepared according to the method described in *Gazz. Chim. Ital.* **111** (1981) 257-267. **(1β-Ethyl-1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-*a*]quinolizin-1-yl)-methanol** (Compound M) is prepared according to the method described in *Indian J. Chem., Sect. B* **22** (1983) 531. **3-Ethyl-2-methyl-1,4,6,7,12,12b-hexahydro-indolo[2,3-*a*]quinolizine** (Compound N) and **3α-ethyl-2α-methyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine** are prepared according to the method described in *Tetrahedron* **46** (1990) 2633-2650. **2,3,5,6,7,11,11b-Hexahydro-1H-indolizino[8,7-*b*]indole** is prepared according to the method described in *J. Org. Chem.* **53** (1988) 4236. **(1β,2,3,4,6,7,12,12bα-Octahydroindolo[2,3-*a*]quinolizin-1-yl)-methanol** (Compound O) is prepared by reduction of the corresponding ester which synthesis is described in *Tetrahedron* **52** (1996) 9925. **1-(1α,2,3,4,6,7,12,12bβ-Octahydroindolo[2,3-*a*]quinolizin-1-yl)-ethanol** (Compound P) is prepared by reduction of its corresponding ketone which synthesis is described in *Tetrahedron Lett.* **30** (1989) 719. **1β-Propyl-1,2,3,4,6,7,12,12bβ-octahydro-indolo[2,3-*a*]quinolizine** is prepared according to the method described in *J. Org. Chem.* **34** (1969) 330. **1α-Ethyl-1β-methyl-**

1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-*a*]quinolizine is prepared according to the method described in *J. Chem. Res. (S)* (1995) 382. **2β-*Tert*-butyl-1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-*a*]quinolizine** and **2β-tert-butyl-1,2,3,4,6,7,12,12bα-octahydro-indolo[2,3-*a*]quinolizine** (Compound Q) are prepared according to the method described in *Tetrahedron* **45** (1989) 3975. **2-*tert*-Butyl-1,4,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizine** and **2-*tert*-butyl-3,4,6,7,12,12b-hexahydro-indolo[2,3-*a*]quinolizine** are prepared according to the method described in *Tetrahedron* **47** (1991) 2879-2894. **(-)-1α-Ethyl-1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-*a*]quinolizin-1-ol** and **(+)-1α-ethyl-1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-*a*]quinolizin-1-ol** are obtained by resolution of their racemic mixture (Compound K).

As already mentioned hereinbefore, the compounds of the present invention show interesting pharmacological properties, namely they exhibit affinity for alpha2 adrenoceptors. The said pharmacological activity of the compounds of the invention is demostrated with the pharmacological tests presented below.

EXPERIMENT I: **Radioligand binding to alpha2-adrenoceptors**

Examples of the alpha2-adrenoceptor binding affinities of the compounds including in the present invention are shown in the Table 1. Many of these compounds are high-affinity ligands for all the alpha2-receptors, but some of them display selectivity for the alpha2C-subtype.

Table 1. Calculated Ki values from radioligand binding assays using cells expressing human alpha2-adrenoceptor subtypes

Compound	Binding affinity (Ki; nM)		
	alpha2A	alpha2B	alpha2C
A	480	330	61
B	130	160	25
C	710	580	87
D	29	81	17
E	30	110	26
F	514	not measured	70
G	96	not measured	22
H	280	45	23
I	150	460	85
J	210	520	75
K	359	245	31
L	85	20	18
M	440	470	110
N	130	1110	46
O	380	270	110
P	290	410	90
Q	27	40	6,4

EXPERIMENT II: ***In vitro*** **antagonism on the alpha2-adrenoceptors**

The functional activities of two compounds (K and L) displaying alpha2C-selectivity in binding experiments were determined as the abilities of the compounds to inhibit the epinephrine-stimulated binding of ^{35}S-GTPγS to G proteins (Jasper, J.R. et al., *Biochem. Pharmacol.* **55(7)** (1998) 1035-44) in membranes of CHO cells stably transfected with the human alpha2-adrenoceptor subtypes. The antagonist potencies of compound K and compound L are presented in the Table 2. The results show that these compounds are selective antagonists for the alpha2C-subtypes.

Table 2. The mean antagonist potencies (K_B) of compound K and compound L on the human alpha2-adrenoceptor subtypes.

Compound	Antagonist potency (K_B; nM)		
	alpha2A	alpha2B	alpha2C
K	295	351	23
L	320	75	4,2

***In vivo* effects of alpha2C-selective compounds**

It is currently not well-known in the art what effects *in vivo* could be attributed to a selective alpha2C-antagonism. Based on available knowledge and our previous experience, we have selected two different behavioral models, namely *d*-amphetamine –stimulated locomotor activity model and the forced swimming test, in order to demonstrate specific alpha2C-antagonistic effects in the CNS of mice and rats *in vivo*. The selection of these methods is essentially based on published hypotheses on theoretical effects of alpha2C-antagonists; in the lack of suitable ligands, these hypotheses were based on studies employing mice with genetically altered alpha2C-adrenoceptor expression (Scheinin, M. et al., *Life Sci* **68(19-20)** (2001) 2277-85).

EXPERIMENT III: **D-amphetamine stimulated locomotor activity test**

Genetically modified mice having non-functional alpha2C-adrenoceptors (alpha2C-"knockout"; alpha 2C-KO) are more sensitive to the locomotor-enhancing effects of the psychostimulant d-amphetamine and, on the other-hand, over-expression of the alpha2C-adrenoceptor in mice (alpha2C-OE) leads to an opposite effect, i.e. to attenuation of the stimulant effect (Scheinin, M. et al., *Life Sci* **68(19-20)** (2001) 2277-85). Thus, it could be hypothesized that alpha2C-antagonist would potentiate the locomotor effects of d-amphetamine.

The above assumption was tested by administering groups of mice (n = 10-12/dose group) amphetamine (4 micromol/kg s.c.) either alone or together with the alpha2C-antagonists (3 micromol/kg s.c.) of this invention or with the alpha2-subtype non-selective potent alpha2-antagonist (1 micromol/kg s.c.) (Haapalinna, A. et al., *Naunyn-Schmiedeberg's Arch. Pharmacol.* **356** (1997) 570-582), and by subsequently measuring the locomotor activity of mice with an automated infrared photobeam system designed for activity studies (PAS CageRack, SanDiego Instruments, San Diego, CA., USA). As expected, both of the tested alpha2C-selective antagonists increased the activity of mice (Figure 1a+b), as was expected for alpha2C-antagonist. The subtype non-selective alpha2-antagonist also potentiated

the d-amphetamine effect. The tested compounds did not affect the baseline locomotor activity of mice (at doses between 0.1 – 10 mg/kg s.c.).

EXPERIMENT IV: **Antagonism of alpha2-agonist –induced sedation**

One of the prominent effects of non-selective alpha2-agonists in rodents is their ability to cause profound sedation. This effect, measured as locomotor inhibition by the alpha2-agonist dexmedetomidine was not modified in mice with genetically altered alpha2C-expression (Scheinin, M. et al., *Life Sci* **68(19-20)** (2001) 2277-85). On the other hand, alpha2-agonist did not have sedative effect in mice with genetically disrupted alpha2A-adrenoceptor (Hunter, J.C. et al., *British Journal of Pharmacology* **122(7)** (1997) 1339-44). Therefore, since the sedative effect of alpha2-agonists is generally attributed to the alpha2A-adrenoceptor, it is expected that alpha2C-antagonists would not modulate significantly the alpha2-agonist-induced sedation. This assumption was tested in experiment, where dexmedetomidine was administered to mice pre-treated with the alpha2C-antagonists compound K or compound L, or the subtype non-selective antagonist atipamezole (Haapalinna, A. et al., *Naunyn-Schmiedeberg's Arch. Pharmacol.* **356** (1997) 570-582). As expected, the alpha2C-antagonists did not have clear effects, whereas atipamezole effectively antagonised the effect of dexmedetomidine. This result demonstrates the lack of alpha2A-antagonism of the alpha2C-selective compounds of the present invention (Figure 2).

EXPERIMENT V: **Forced swimming test**

Forced swimming test (FST, i.e. Porsolt's test) is generally used in the pharmacological screening of new antidepressants. In this test, antidepressants increase the animals' activity compared to non-treated controls. Alpha2C-KO mice appeared to be more active, and alpha2C-OE mice were less active in FST (U.S. Patent No. 5,902,807 and Scheinin, M. et al., *Life Sci* **68(19-20)** (2001) 2277-85). Therefore, it was tested, whether a selective alfa2C-antagonist would have antidepressant-like activity (e.g. activity-increasing property) in the FST. The figure 3 shows how both of the alpha2C-compounds increased activity in this test as was expected based on studies on transgenic mice (Scheinin, M. et al., *Life Sci* **68(19-20)** (2001) 2277-85) and as reported with recently developed alpha2C-antagonist (WO

01/64645). Also the positive control substances desipramine and fluoxetine (clinically effective antidepressant agents) were active. The subtype non-selective alpha2-antagonist atipamezole did not possess antidepressant-like effect, as expected (WO 01/64645).

EXPERIMENT VI: **Prepulse inhibition of the startle reflex**

Prepulse-inhibition (PPI) of a startle response refers to the reduction in the startle response caused by a low intensity non-startling stimulus (the prepulse) which is presented shortly before the startle stimulus. PPI can be used as an operational measure of sensorimotor gating and appears to be present in all mammals, including rats and humans (Swerdlow, N.R. et al., *The archives of general psychiatry* **51** (1994) 139-154). Normally functioning PPI can be disrupted by psychostimulants, such as d-amphetamine or phencyclidine (PCP), and reversed by clinically effective antipsychotics.

In a previous study, alpha2C-KO mutation was associated with weakened PPI whereas alpha2C-OE demonstrated increased PPI. In other words, the genetically altered alpha2C-expression in mice was associated with changes in PPI in a way suggesting that an alpha2C-antagonist would decrease PPI (Scheinin, M. et al., *Life Sci* **68(19-20)** (2001) 2277-85). This hypothesis was tested with compounds K and L alone and against PCP –disruption of the PPI.

Groups of rats (n =10/group) were administered the alpha2C-antagonists 20 min before, and PCP or vehicle 10 min before measurement of the acoustic startle reactivity and PPI in a test system designed for startle studies (SR-LAB, San Diego Instruments, CA, USA). It was found that the alpha2C-antagonists were able to attenuate the PPI disruption caused by PCP (Figure 3). This was unexpected and opposite to the hypothesis based on transgenic studies. The non-selective alpha2-antagonist atipamezole produced different effects than was observed with the selective alpha2C-antagonists: atipamezole did not enhance PPI, but it increased the startle reflex per se (i.e. startle without prepulses)(Figure 4).

In conclusion, the results presented in this chapter show that those antagonists which are classified as alpha2C-selective according to *in vitro* experiments, appeared to function as alpha2C-selective antagonists also *in vivo* in a manner that was

predicted based on the available knowledge on alpha2C-antagonism. However, the finding that the alpha2C-antagonists did not decrease PPI, as predicted, but on the contrary, increased PPI, could be considered unexpected and this adds the novelty value of the now proposed usefulness of the compounds of the present invention.

The compounds according to the invention may be used to treat any disease or condition wherein alpha-2 antagonists are indicated to be effective. The compounds can also be used to reverse effects induced by alpha-2 agonists. Accordingly, the compounds of the invention may be useful in the treatment of various disorders of the central nervous system (CNS), i.e. different neurological, psychiatric and cognition disorders (such as depression, anxiety disorders, post traumatic stress disorder, schizophrenia, Parkinson's disease and other movement disorders). Furthermore, they may be used in the treatment of various peripheral disorders, e.g. diabetes, orthostatic hypotension, lipolytic disorders (such as obesity), Raynaud's disease or both male and female sexual dysfunctions.

The selective alpha-2C antagonists of the present invention may be used for the treatment of various disorders or conditions of CNS-system where alpha-2C antagonists are indicated to be beneficial, for example, to alleviate the symptoms of various mental disorders propagated by stress, Parkinson's disease, depression, negative symptoms of schizophrenia, attention deficit hyperactivity disorder, post-traumatic stress-disorder, and anxiety disorders.

In addition, due to the novel and previously unpublished findings of the effects of the present alpha2C-antagonists on the PCP –disrupted PPI, the alpha2C-selective compounds can also be used to treat disorders and conditions associated with sensorimotor gating deficits, particularly disorders and conditions wherein the sensorimotor gating deficits results in sensory flooding and cognitive fragmentation causing dysfunction in attention and perception. Such disorders and conditions include, but are not limited to, schizophrenia, obsessive compulsive disorder, Tourette's syndrome, blepharospasm and other focal dystonias, temporal lobe epilepsy with psychosis, drug-induced psychosis (for example, psychosis caused by chronic use of dopaminergic agents) (Braff, D.L. et al., *Psychopharmacology (Berl)* **156(2-3)** (2001) 234-258), Huntington's disease, Parkinson's disease, disorders

caused by fluctuation of the levels of sex hormones (such as premenstrual syndrome), and panic disorder.

Further, the symptoms which are usually associated with above-mentioned disorders or conditions include, but are not limited to, hallucination, delusion, parathymia, agitation, psychotic cognitive impairment (including deficits in thinking and speech), social withdrawal and withdrawal symptoms (including delirium) associated with cessation of cigarette smoking or alcohol or drug abuse. These symptoms may also be seen in animals in exceptional circumstances, for example, during withdrawal from masters or during transportation.

Due to their selectivity of action, the alpha-2C antagonists of the invention have less or no undesirable side-effects attributed to non-selective alpha2-antagonism, such as increases in blood pressure, heart rate, salival secretions, gastrointestinal secretion, anxiety, and startle reactivity per se (Ruffolo, R.R.J. et al., *Annu Rev Pharmacol Toxicol* **32** (1993) 243-279).

The compound of the invention can be administered for example enterally, topically or parenterally by means of any pharmaceutical formulation useful for said administration, and containing at least one active compound of formula I in pharmaceutically acceptable and effective amounts together with pharmaceutically acceptable diluents, carriers, and/or excipients known in the art. The manufacture of such pharmaceutical formulations is well known in the art.

The therapeutic dose to be given to a patient in need of treatment will vary depending on the compound being administered, the species, age and the sex of the subject being treated, the particular condition being treated, as well as the route and method of administration, and are easily determined by person skilled in the art. Accordingly, the typical dosage for oral administration is from 5 μg/kg to 100 mg/kg per day and that for parenteral administration from 0.5 μg/kg to 10 mg/kg for an adult mammal.

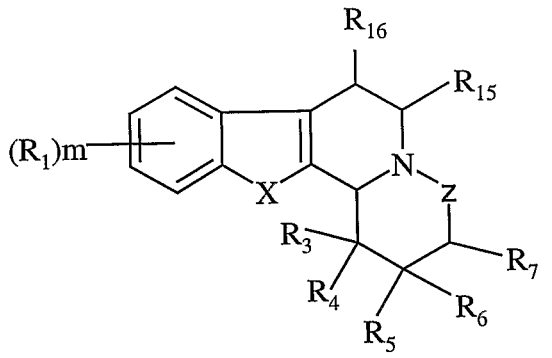
The present invention further provides a compound of the invention or an ester or salt thereof for use as alpha-2 antagonist. Furthermore, a method for the treatment of diseases or conditions where alpha-2 antagonists, e.g. alpha-2C antagonists, are indicated to be useful, e.g. a method for the treatment of diseases or

conditions of the central nervous system, is provided. In such a method a therapeutically effective amount of a compound of the invention is administered to a subject in need of such treatment. The use of the compounds of the invention for the manufacture of a medicament to be used for the above indications is also provided.

Those skilled in the art will appreciate that the embodiments described in this application could be modified without departing from the broad inventive concept. Those skilled in the art also understand that the invention is not limited to the particular disclosed embodiments, but is intended to also cover modifications to the embodiments that are within the spirit and scope of the invention.

CLAIMS

1. Use of a compound of formula I,



I

wherein,

X is CR_2R_2', O, S or NR_2;

Z is $-CHR_8-(CH_2)n-$ or a single bond;

R_1 is hydroxy, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, halogen, halo(C_1-C_6)alkyl, (C_1-C_6)alkoxy-CO-, CN, NO_2, NH_2, mono- or di(C_1-C_6)alkylamino or carboxyl;

R_2 and R_2' are independently H, hydroxy or (C_1-C_6)alkyl or R_2 and R_2' form, together with the carbon ring atoms to which they are attached, a carbonyl group;

R_3 is H, hydroxy, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)alkoxy(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkoxy(C_1-C_6)alkyl, (C_3-C_7)cycloalkyl, (C_3-C_7)cycloalkyl(C_1-C_6)alkyl, aryl, aryl(C_1-C_6)alkyl, aryloxy, aryl(C_1-C_6)alkoxy, aryloxy(C_1-C_6)alkyl, aryl(C_1-C_6)alkoxy(C_1-C_6)alkyl, halo(C_1-C_6)alkyl, NH_2, amino(C_1-C_6)alkyl, mono- or di(C_1-C_6)alkylamino,mono- or di(C_1-C_6)alkylamino(C_1-C_6)alkyl, (C_1-C_6)alkyl-CO-, (C_1-C_6)alkyl-CO-O-, (C_1-C_6)alkyl-CO-O-(C_1-C_6)alkyl, (C_1-C_6)alkoxy-CO-, (C_1-C_6)alkoxy-CO-(C_1-C_6)alkyl, (C_1-C_6)alkoxy-CO-(C_1-C_6)alkoxy(C_1-C_6)alkyl, carbamoyl, mono- or di(C_1-C_6)alkylcarbamoyl, carboxyl or (C_1-C_6)alkyl-S-(C_1-C_6)alkyl, wherein the said (C_3-C_7)cycloalkyl or aryl is unsubstituted or substituted with 1 or 2 substituents each independently being hydroxy, (C_1-C_6)alkyl, halogen, (C_1-C_6)alkoxy, NH_2, CN or NO_2, or one of R_3 or R_4 and R_6 together form a bond between the ring atoms to which they are attached;

R_4 is H, hydroxy, (C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxy or (C_1-C_6)alkoxy(C_1-C_6)alkyl;

R_5 is H, hydroxy, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)alkoxy(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkoxy(C_1-C_6)alkyl, (C_3-C_7)cycloalkyl, (C_3-C_7)cycloalkyl(C_1-C_6)alkyl, aryl, aryl(C_1-C_6)alkyl, aryloxy, aryl(C_1-C_6)alkoxy, aryloxy(C_1-C_6)alkyl, aryl(C_1-C_6)alkoxy(C_1-C_6)alkyl, halo(C_1-C_6)alkyl, (C_1-C_6)alkyl-CO-, (C_1-C_6)alkyl-CO-O-, (C_1-C_6)alkyl-CO-O-(C_1-C_6)alkyl, (C_1-C_6)alkoxy-CO-, (C_1-C_6)alkoxy-CO-(C_1-C_6)alkyl, (C_1-C_6)alkoxy-CO-(C_1-C_6)alkoxy(C_1-C_6)alkyl, carbamoyl, mono- or di(C_1-C_6)alkylcarbamoyl, carboxyl or (C_1-C_6)alkyl-S-(C_1-C_6)alkyl, wherein the said (C_3-C_7)cycloalkyl or aryl is unsubstituted or substituted with 1 or 2 substituents each independently being hydroxy, (C_1-C_6)alkyl, halogen, (C_1-C_6)alkoxy, NH_2, CN or NO_2, or R_4 and R_5 form, together with the carbon ring atoms to which they are attached, a condensed five to seven membered saturated carbocyclic ring unsubstituted or substituted with 1 to 3 substituent(s) R_9 each independently being hydroxy, (C_1-C_6)alkyl, halogen, NH_2, NO_2, (C_3-C_7)cycloalkyl, hydroxy(C_1-C_6)alkyl, halo(C_1-C_6)alkyl, amino(C_1-C_6)alkyl, mono- or di(C_1-C_6)alkylamino, mono- or di(C_1-C_6)alkylamino(C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)alkoxy(C_1-C_6)alkyl, carboxyl, (C_1-C_6)alkyl-CO-, (C_1-C_6)alkyl-CO-O-, (C_1-C_6)alkoxy-CO-, (C_1-C_6)alkoxy-CO-(C_1-C_6)alkyl, carbamoyl mono- or di(C_1-C_6)alkylcarbamoyl or oxo;

R_6 is H, hydroxy, (C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxy or (C_1-C_6)alkoxy(C_1-C_6)alkyl or R_6 forms a bond between the ring atom to which it is attached and the ring atom to which R_7 is attached;

R_7 is H, hydroxy, (C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxy or (C_1-C_6)alkoxy(C_1-C_6)alkyl;

R_8 is H,hydroxy, (C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxy or (C_1-C_6)alkoxy(C_1-C_6)alkyl or, only when n is 0, R_7 and R_8 form, together with the carbon ring atoms to which they are attached, a condensed five to seven membered saturated carbocyclic ring unsubstituted or substituted with 1 to 3 substituent(s) R_{10} each independently being hydroxy, (C_1-C_6)alkyl, halogen, NH_2, NO_2, (C_3-C_7)cycloalkyl, hydroxy(C_1-C_6)alkyl, halo(C_1-C_6)alkyl, amino(C_1-C_6)alkyl, mono- or di(C_1-C_6)alkylamino, mono- or di(C_1-C_6)alkylamino(C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)alkoxy(C_1-C_6)alkyl, carboxyl, (C_1-C_6)alkyl-CO-, (C_1-C_6)alkyl-CO-O-, (C_1-C_6)alkoxy-CO-, (C_1-C_6)alkoxy-CO-(C_1-C_6)alkyl, carbamoyl, mono- or di(C_1-C_6)alkylcarbamoyl or oxo;

R_{15} is H, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxy(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkoxy(C_1-C_6)alkyl, halo(C_1-C_6)alkyl, amino(C_1-C_6)alkyl, mono- or di(C_1-C_6)alkylamino(C_1-C_6)alkyl, (C_1-C_6)alkyl-CO-, (C_1-C_6)alkyl-CO-O-(C_1-C_6)alkyl, (C_1-C_6)alkoxy-CO-, (C_1-C_6)alkoxy-CO-(C_1-C_6)alkyl, (C_1-C_6)alkoxy-CO-(C_1-C_6)alkoxy(C_1-C_6)alkyl, carbamoyl, mono- or di(C_1-C_6)alkylcarbamoyl or carboxyl;

R_{16} is H or (C_1-C_6)alkyl;

R_7 and R_8 are attached to the carbon ring atoms, which are adjacent;

m is 0 to 2; and

n is 0 or 1,

or a pharmaceutically acceptable salt or ester thereof, with the proviso, that when X is O, m is 0, n is 0, R_3, R_4, R_7, R_8, R_{15} and R_{16} are hydrogen, and one of R_5 or R_6 is hydrogen, then the other R_5 or R_6 is not hydroxy(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkoxy(C_1-C_6)alkyl, (C_1-C_6)alkyl-CO-, (C_1-C_6)alkoxy-CO- or (C_1-C_6)alkoxy-CO-(C_1-C_6)alkyl,

for the manufacture of a medicament for the treatment of diseases or conditions where antagonists of alpha-2 adrenoceptors are indicated to be useful.

2. The use of a compound according to claim 1, wherein X is NR_2.

3. The use of a compound according to any one of claims 1 or 2, wherein m is 0, n is 0, R_2 is H, R_3 is H, hydroxy, (C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxy(C_1-C_6)alkyl, (C_3-C_7)cycloalkyl, halo(C_1-C_6)alkyl, (C_1-C_6)alkyl-CO-, (C_1-C_6)alkyl-CO-O-(C_1-C_6)alkyl, (C_1-C_6)alkoxy-CO- or (C_1-C_6)alkoxy-CO-(C_1-C_6)alkyl, R_4 is H, hydroxy, (C_1-C_6)alkyl or hydroxy(C_1-C_6)alkyl, R_5 is H, hydroxy, (C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxy or (C_1-C_6)alkyl-CO-, R_6 is H or (C_1-C_6)alkyl and R_7 is H, (C_1-C_6)alkyl or hydroxy(C_1-C_6)alkyl.

4. The use of a compound according to any one of claims 1 to 3, wherein R_3 is H or (C_1-C_6)alkyl and R_4 is hydroxy or hydroxy(C_1-C_6)alkyl.

5. The use of a compound according to any one of claims 1 or 2, wherein R_4 and R_5 form, together with the carbon ring atoms to which they are attached, a condensed six membered saturated carbocyclic ring.

6. The use of a compound according to any one of claims 1 or 2, wherein R_4 and R_6 together form a bond between the ring atoms to which they are attached or R_6 forms a bond between the ring atom to which it is attached and the ring atom to which R_7 is attached.

7. The use of a compound according to any one of claims 1 to 5, wherein the compound is 1α-ethyl-1,2,3,4,6,7,12,12bβ-octahydro-indolo[2,3-*a*]quinolizin-1-ol, (1β-ethyl-1,2,3,4,6,7,12,12bα-octahydro-indolo[2,3-*a*]quinolizin-1-yl)-methanol, 1α-Methyl-1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-*a*]quinolizin-1-ol, (1α-Methyl-1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-*a*]quinolizin-1-yl)-methanol, 1,2,3,4,4aβ,5,6,7,8,13,13bβ,13cα-dodecahydro-6a,13-diaza-indeno-[1,2-*c*]phenanthrene, 1,2,3,4,4aβ,5,6,7,8,13,13bβ,13cβ-dodecahydro-6a,13-diaza-indeno[1,2-*c*]phenanthrene or 3,4,4aβ,5,6,7,8,13,13bβ,13cα-decahydro-2H-6a,13-diaza-indeno[1,2-*c*]phenanthren-1-one.

8. The use of a compound according to claim 1, wherein X is CR_2R_2'.

9. The use of a compound according to claim 1, wherein X is O

10. The use of a compound according to claim 1, wherein X is S.

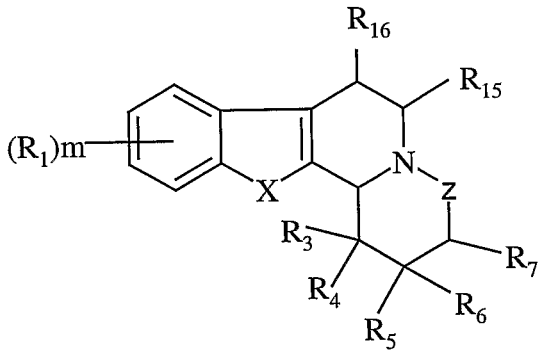
11. The use of a compound according to any one of claims 1 to 10, for the manufacture of a medicament for the treatment of a disorder of the central nervous system, diabetes, orthostatic hypotension, lipolytic disorders, Raynaud's disease or male and female sexual dysfunctions.

12. The use according to claim 11, wherein the disorder of the central nervous system is depression, anxiety disorders, post-traumatic stress disorder, schizophrenia, Parkinson's disease, or another movement disorder.

13. The use of a compound according to any one of claims 1 to 10 for the manufacture of a medicament for use as a selective alpha-2C antagonist.

14. The use according to claim 13 for the manufacture of a medicament for the treatment of mental disorders propagated by stress, Parkinson's disease, depression, negative symptoms of schizophrenia, attention deficit hyperactivity disorder, post-traumatic stress-disorder, or anxiety disorders.

15. A compound of formula IA



IA

wherein,

X is CR_2R_2', O or S;

Z, R_1, R_2, R_2', R_3-R_{10}, R_{15} and R_{16}, m and n are as defined in claim 1,

or a pharmaceutically acceptable salt or ester thereof, with the provisos, that

a) when X is O, m is 0 and n is 0, then R_3-R_8 are not all simultaneously hydrogen;

b) when X is O, m is 0, n is 0, R_3, R_4, R_7, R_8, R_{15} and R_{16} are hydrogen, and one of R_5 or R_6 is hydrogen, then the other R_5 or R_6 is not hydroxy(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkoxy(C_1-C_6)alkyl, (C_1-C_6)alkyl-CO-, (C_1-C_6)alkoxy-CO- or (C_1-C_6)alkoxy-CO-(C_1-C_6)alkyl.

c) the compound is not 1,2,3,4,5,10b-hexahydro-10-thia-3a-aza-cyclopenta[a]fluorene; 1,3,4,5,6,11b-hexahydro-2H-11-thia-4a-aza-benzo[a]fluorene; 1-(1,3,4,5,6,11b-hexahydro-2H-11-thia-4a-aza-benzo[a]fluoren-1-yl)-ethanone or 1,3,4,5,6,11b-hexahydro-2H-11-thia-4a-aza-benzo[a]fluorene-1-carboxylic acid methyl ester.

16. A compound according to claim 15, wherein X is CR_2R_2'.

17. A compound according to claim 15, wherein X is O.

18. A compound according to claim 15, wherein X is S.

19. A compound according to any one of claims 15 to 18, wherein R_3 is hydroxy, (C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxy(C_1-C_6)alkyl, (C_1-C_6)alkoxy-CO- or (C_1-C_6)alkyl-CO-O-(C_1-C_6)alkyl and R_4 is H, (C_1-C_6)alkyl or hydroxy(C_1-C_6)alkyl.

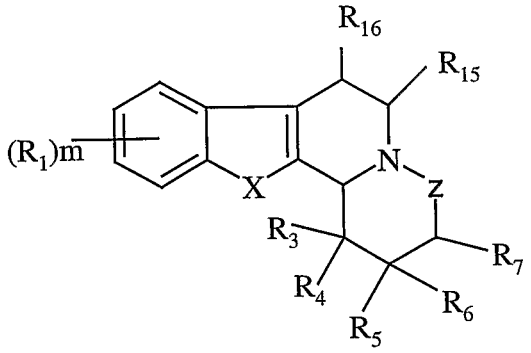
20. A compound according to any one of claims 15 to 19, wherein R_3 is hydroxy, hydroxy(C_1-C_6)alkyl or (C_1-C_6)alkoxy(C_1-C_6)alkyl and R_4 is (C_1-C_6)alkyl.

21. A compound according to any one of claims 15 to 18, wherein R_4 and R_5 form, together with the carbon ring atoms to which they are attached, a condensed six membered saturated carbocyclic ring.

22. A compound according to any one of claims 15 to 21, wherein the compound is 1α-Methyl-1,3,4,5,6,11b-hexahydro-2H-11-oxa-4a-aza-benzo[a]fluoren-1-ol, (1α-Methyl-1,3,4,5,6,11bβ-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluoren-1-yl)-methanol, (-)-(1α-Methyl-1,3,4,5,6,11bβ-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluoren-1-yl)-methanol, (+)-(1α-Methyl-1,3,4,5,6,11bβ-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluoren-1-yl)-methanol, 1α-Isopropyl-1,3,4,5,6,11b-Hexahydro-2H-11-oxa-4a-aza-benzo[a]fluoren-1-ol, 1α-Ethyl-1,3,4,5,6,11bβ-hexahydro-2H-11-oxa-4a-aza-benzo[a]fluoren-1-ol, (1α-Ethyl-1,3,4,5,6,11bβ-hexahydro-2H-11-oxa-4a-aza-benzo[a]fluoren-1-yl)-methanol, 5,6,7,7aβ,8,9,10,11,11aβ,11bα-Decahydro-12-oxa-6a-aza-indeno[1,2-a]fluorene, 1-Methyl-1α,3,4,6,11bβ-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluorene, (1-Hydroxymethyl-1,3,4,5,6,11b-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluoren-1-yl]-methanol, 1-Methoxymethyl-1α-methyl-1,3,4,5,6,11bβ-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluorene, (-)-1-Methoxymethyl-1α-methyl-1,3,4,5,6,11bβ-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluorene, (+)-1-Methoxymethyl-1α-methyl-1,3,4,5,6,11bβ-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluorene, 2,3,4,4aβ,5,6,7,8,13bβ,13cβ-Decahydro-1H-13-oxa-6a-aza-indeno[1,2-*c*]phenanthrene, 2,3,4,4aβ,5,6,7,8,13bα,13cβ-Decahydro-1H-

13-oxa-6a-aza-indeno[1,2-*c*]phenanthrene, 1α-Methyl-1,3,4,5,6,11bα-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluorene-1-carboxylic acid ethyl ester, 1-Ethoxymethyl-1α-methyl-1,3,4,5,6,11bβ-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluorene, (1α-Methyl-1,3,4,5,6,11bα-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluoren-1-yl)-methanol, (-)-(1α-Methyl-1,3,4,5,6,11bα-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluoren-1-yl)-methanol, (+)-(1α-Methyl-1,3,4,5,6,11bα-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluoren-1-yl)-methanol, 1α–Ethyl-1,3,4,5,6,11bα-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluorene-1-carboxylic methyl ester, 1-Methoxymethyl-1α-methyl-1,3,4,5,6,11bα-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluorene, (-)-1-Methoxymethyl-1α-methyl-1,3,4,5,6,11bα-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluorene, (+)-1-Methoxymethyl-1α-methyl-1,3,4,5,6,11bα-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluorene, (1α-Ethyl-1,3,4,5,6,11bα-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluorene-1-yl)-methanol, acetic acid 1α-Methyl-1,3,4,5,6,11bβ-hexahydro-2H-11-oxa-4a-aza-benzo[a]fluoren-1-ylmethyl ester or (1α-Methyl-1,2,3,4,6,7,12,12bα-octahydroindeno[2,1-*a*]quinolizin-1-yl)-methanol.

23. A compound of formula IB



IB

wherein,

X is NR_2;

R_2 is $(C_1\text{-}C_6)$alkyl;

Z, R_1, R_3-R_{10}, R_{15}, R_{16}, m and n are as defined in claim 1,

or a pharmaceutically acceptable salt and ester thereof, with the provisos, that

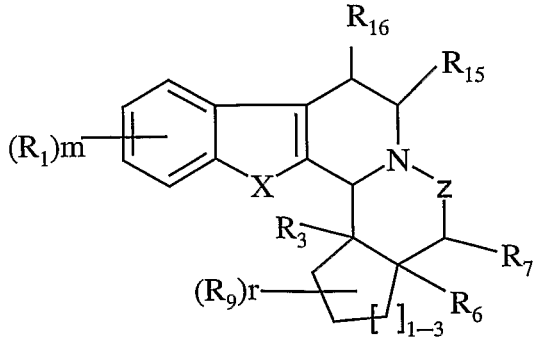
a) when m is 0 or R_1 is methoxy and R_4 is H or ethyl, then R_3 is not methoxy-CO;

b) the compound is not 13-Methyl-1,2,3,4,4a,5,6,7,8,13,13b,13c-dodecahydro-6a,13-diaza-indeno[1,2-*c*]phenanthrene; 12-Methyl-1,2,3,4,6,7,12,12b-octahydro-indolo[2,3-*a*]quinolizine; 1-Ethyl-12-methyl-1,2,3,4,6,7,12,12b-octahydro-indolo[2,3-*a*]quinolizine; 2,3-Diethyl-12-methyl-1,2,3,4,6,7,12,12b-octahydro-indolo[2,3-*a*]quinolizine; 12-Methyl-1,2,3,4,6,7,12,12b-octahydro-indolo[2,3-*a*]quinolizin-1-ol; 2-(1-Ethyl-12-methyl-1,2,3,4,6,7,12,12b-octahydro-indolo[2,3-*a*]quinolizin-1-yl)-ethanol; 11-Methyl-2,3,5,6,11,11b-hexahydro-1H-indolizino[8,7-*b*]indole; (11-Methyl-2,3,5,6,11,11b-hexahydro-1H-indolizino[8,7-*b*]indol-1-yl)-methanol, (1,11-Diethyl-2,3,5,6,11,11b-hexahydro-1H-indolizino[8,7-*b*]indol-1-yl)-methanol or 3-(1-ethyl-12-methyl-1,2,3,4,6,7,12,12b-octahydro-indolo[2,3-*a*]quinolizin-1-yl)-propionic acid methyl ester.

24. A compound according to claim 23, wherein R_3 is hydroxy, (C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl or (C_1-C_6)alkoxy(C_1-C_6)alkyl and R_4 is H, (C_1-C_6)alkyl or hydroxy(C_1-C_6)alkyl.

25. A compound according to any one of claims 23 or 24, wherein the compound is 1α-Ethyl-12-methyl-1,2,3,4,6,7,12bβ-octahydro-indolo[2,3-*a*]quinolizin-1-ol or 1α-Ethyl-12-ethyl-1,2,3,4,6,7,12bβ-octahydro-indolo[2,3-*a*]quinolizin-1-ol.

26. A compound of formula IC



IC

wherein,

X is NR_2;

R_2 is H;

Z is -CHR_8-(CH_2)n- or a single bond;

n is 0;

R_1, R_3, R_6-R_9, R_{15}, R_{16} and m are as defined in claim 1;

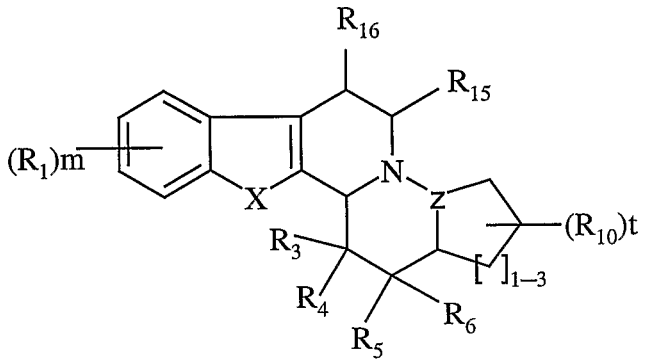
r is 0 to 3;

or a pharmaceutically acceptable salt and ester thereof, with the provisos, that the compound is not 1,2,3,4,4a,5,6,7,8,13,13b,13c-dodecahydro-6a,13-diaza-indeno[1,2-*c*]phenanthrene; 5,7,7a,8,9,10,11,11a,11b,12-decahydro-6H-6a,12-diaza-indeno[1,2-*a*]fluorene; 10-methyl-5,7,7a,8,9,10,11,11a,11b,12-decahydro-6H-6a,12-diaza-indeno[1,2-*a*]fluorene; 3-methoxy-5,7,7a,8,9,10,11,11a,11b,12-decahydro-6H-6a,12-diaza-indeno[1,2-*a*]fluorene; 3-hydroxy-1,2,3,4,4a,5,6,7,8,13,13b,13c-dodecahydro-6a,13-diaza-indeno[1,2-c]phenanthrene-4-carboxylic acid methyl ester; methyl-3-ethyl-1,2,3a,4,6,7,12b,12c-octahydro-3H,12H-indolo[2,3-*g*]cyclopent[a]indolizine-2-carboxylate; methyl-1,2,3a,4,6,7,12b,12c-octahydro-3H,12H-indolo[2,3-*g*]cyclopent[a]indolizine-2-carboxylate; 12c-ethyl-1,3a,4,6,7,12b,12c-octahydro-cyclopent[1,2]indolizino[8,7-b]indol-3(2H)-one or 6-methyl-5,7,7a,8,9,10,11,11a,11b,12-decahydro-6H-6a,12-diaza-indeno[1,2-*a*]fluorene.

27. A compound according to claim 26, wherein r is 0 or 1 and R_3 is H, hydroxy, $(C_1$-$C_6)$alkyl or hydroxy$(C_1$-$C_6)$alkyl.

28. A compound according to any one of claims 26 or 27, wherein the compound is 2,3,4,4aβ,5,6,7,8,13,13bβ-decahydro-1H-6a,13-diaza-indeno[1,2-*c*]phenanthren-13cβ-ol, (-)-2,3,4,4aβ,5,6,7,8,13,13bβ-decahydro-1H-6a,13-diaza-indeno[1,2-*c*]phenanthren-13cβ-ol, (+)-2,3,4,4aβ,5,6,7,8,13,13bβ-decahydro-1H-6a,13-diaza-indeno[1,2-*c*]phenanthren-13cβ-ol, (2,3,4,4aβ,5,6,7,8,13,13bβ-Decahydro-1H-6a,13-diaza-indeno[1,2-*c*]phenanthrenyl)-13cβ-methanol, 5,6,7,7a,11,11b,12-Decahydro-6a,12-diaza-indeno[1,2-*a*]fluoren-11a-ol, 3,4,4aβ,5,6,7,8,13,13bβ,13cα-decahydro-2H-6a,13-diaza-indeno[1,2-*c*]phenanthren-1-one, 1,2,3,4,5,6,7,8,13,13b-decahydro-6a,13-diaza-indeno[1,2-*c*]phenanthrene, acetic acid 1α,2,3,4,4aβ,5,6,7,8,13,13bβ,13cα-dodecahydro-6a,13-diaza-indeno[1,2-*c*]phenanthren-1-yl ester or acetic acid 1β,2,3,4,4aβ,5,6,7,8,13,13bβ,13cα-dodecahydro-6a,13-diaza-indeno[1,2-*c*]phenanthren-1-yl ester.

29. A compound of formula ID



ID

wherein,

X is NR_2;

R_2 is H;

Z is $-CHR_8-(CH_2)n-$;

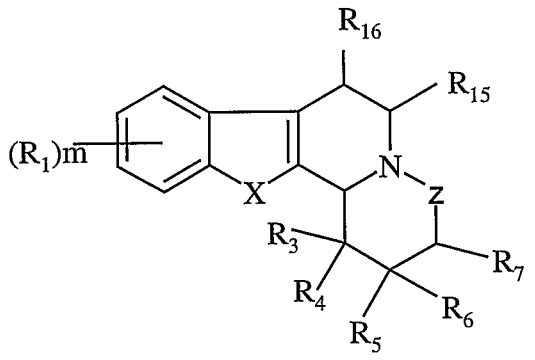
n is 0;

R_1, R_3-R_{10} R_{15}, R_{16} and m are as defined in claim 1;

t is 0 to 3;

or a pharmaceutically acceptable salt and ester thereof, with the provisos, that the compound is not 1,2,3,4,4a,5,6,11,11b,12,13,13a-dodecahydro-4b,11-diaza-indeno[2,1-*a*]phenanthrene; 1,2,3,4,4a,5,6,11,11b,12-decahydro-4b,11-diaza-indeno[2,1-*a*]phenanthrene; 9-methoxy-1,2,3,4,4a,5,6,11,11b,12-decahydro-4b,11-diaza-indeno[2,1-*a*]phenanthrene or 1-hydroxy-1,2,3,4,4a,5,6,11,11b,12,13,13a-dodecahydro-4b,11-diaza-indeno[2,1-*a*]phenanthrene-2-carboxylic acid methyl ester.

30. A compound of formula IE



IE

wherein,

X is NR_2;

R_2 is H;

Z, R_1, R_3-R_{10}, R_{15}, R_{16} and m are as defined in claim 1;

n is 1,

or a pharmaceutically acceptable salt and ester thereof, with the proviso, that the compound is not 2,3,4,5,7,8,13,13b-octahydro-1H-azepino[1',2':1,2]pyrido[3,4-b]indole-2-ethyl-2-methanol; 2,3,4,5,7,8,13,13b-octahydro-1H-azepino[1',2':1,2]pyrido[3,4-*b*]indole-4-ethyl-2-methanol; 2,3,4,5,7,8,13,13b-octahydro-2,3-diethyl-1H-azepino[1',2':1,2]pyrido[3,4-*b*]indole; 2,3,4,5,7,8,13,13b-octahydro-1H-azepino[1',2':1,2]pyrido[3,4-*b*]indole-2-methanol; 2,3,4,5,7,8,13,13b-octahydro-1H-azepino[1',2':1,2]pyrido[3,4-*b*]indole-3-hydroxy-2-methanol; 2,3,4,5,7,8,13,13b-octahydro-1H-azepino[1',2':1,2]pyrido[3,4-*b*]indole-4-ethyl-4-hydroxy-2-methanol; acetic acid 2,3,4,5,7,8,13,13b-octahydro-1H-azepino[1',2':1,2]pyrido[3,4-*b*]indol-2-ylmethyl ester; 2,3,4,5,7,8,13,13b-octahydro-1H-azepino[1',2':1,2]pyrido[3,4-*b*]indole-2-[(phenylmethoxy)methyl] or 2,3,4,5,7,8,13,13b-octahydro-1H-azepino[1',2':1,2]pyrido[3,4-*b*]indole-4-ethyl-2-[(phenylmethoxy)methyl].

31. A compound according to claim 30, wherein the compound is 2,3,4,5,7,8,13,13b-octahydro-1H-azepino[1',2':1,2]pyrido[3,4-*b*]indole.

32. A compound which is 2β-Methoxy-1,2,3,4,6,7,12,12bα-octahydro-indolo[2,3-*a*]quinolizine, 2α-methoxy-1,2,3,4,6,7,12,12bα-octahydro-indolo[2,3-

a]quinolizine, 1α-Ethyl-2α-methyl-1,2,3,4,6,7,12,12bβ-octahydro-indolo[2,3-*a*]quinolizin-1-ol, 1α-Isopropyl-1,2,3,4,6,7,12,12bβ-octahydro-indolo[2,3-*a*]quinolizin-1-ol, (-)-1α-isopropyl-1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-*a*]quinolizin-1-ol, (+)-1α-isopropyl-1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-*a*]quinolizin-1-ol, 1β-Isopropyl-1,2,3,4,6,7,12,12bβ-octahydro-indolo[2,3-*a*]quinolizine, (1α-Isopropyl-1,2,3,4,6,7,12,12bβ-octahydro-indolo[2,3-*a*]quinolizin-1-yl)-methanol, (1α- *n*-Propyl-1,2,3,4,6,7,12,12bβ-octahydro-indolo[2,3-*a*]quinolizin-1-yl)-methanol, 2-(1α,2,3,4,6,7,12,12bβ-Octahydro-indolo[2,3-*a*]quinolizin-1-yl)-butan-2-ol, 1-(1,2α,3,4,6,7,12,12bα-Octahydro-indolo[2,3-*a*]quinolizin-2-yl)-propan-1-ol, 2-(1α,2,3,4,6,7,12,12bβ-Octahydro-indolo[2,3-*a*]quinolizin-1-yl)-propan-2-ol, 1-*s*-Butyl-1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-*a*]quinolizin-1-ol, 1-Cyclohexyl-1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-*a*]quinolizin-1-ol, 9-Fluoro-1α-isopropyl-1,2,3,4,6,7,12,12bβ-octahydro-indolo[2,3-*a*]quinolizin-1-ol, (1α-Methyl-1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-*a*]quinolizin-1-yl)-methanol, (-)-(1α-Methyl-1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-*a*]quinolizin-1-yl)-methanol, (+)-(1α-Methyl-1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-*a*]quinolizin-1-yl)-methanol, (1α-Ethyl-1,4,6,7,12,12bβ-hexahydroindolo[2,3-*a*]quinolizin-1-yl)-methanol, 3β,4α-Dimethyl-1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-*a*]quinolizine, (1,2α,3,4,6,7,12,12bα-Octahydroindolo[2,3-*a*]quinolizin-2-yl)-propan-2-ol, (1,2α,3,4,6,7,12,12bβ-Octahydroindolo[2,3-*a*]quinolizin-2-yl)-propan-2-ol, (2α-Ethyl-1,2,3,4,6,7,12,12bα-octahydroindolo[2,3-*a*]quinolizin-2-yl)-methanol, (2α-Ethyl-1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-*a*]quinolizin-2-yl)-methanol, (1-α̃Ethyl-1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-a]quinolizin-1-ylmethoxy)-acetic acid ethyl ester, 1-(2α-ethyl-1,2,3,4,6,7,12,12bα-octahydro-indolo[2,3-*a*]quinolizin-2-yl)-ethanone, 1-(2α-ethyl-1,2,3,4,6,7,12,12bα-octahydro-indolo[2,3-*a*]quinolizin-2-yl)-ethanol, 2-(2α-ethyl-1,2,3,4,6,7,12,12bα-octahydro-indolo[2,3-*a*]quinolizin-2-yl)-propan-2-ol, 2-(3-ethyl-1,2α,3α,4,6,7,12,12bα-octahydro-indolo[2,3-*a*]quinolizin-2-yl)-propan-2-ol, (3-ethyl-2-methyl-1α,2β,3β,4,6,7,12,12bβ-octahydro-indolo[2,3-*a*]quinolizin-1-yl)-methanol, 3-ethyl-1,2-dimethyl-1α,2β,3β,4,6,7,12,12bβ-octahydro-indolo[2,3-*a*]quinolizine, 1,2-dimethyl-1,2,3,4,6,7,12,12bβ-octahydro-indolo[2,3-*a*]quinolizin-

1β-ol, (1-ethyl-2-methyl-1β,2β,3β,4,6,7,12,12bα-octahydro-indolo[2,3-*a*]quinolizin-3-yl)-methanol or 1-β-Hydroxymethyl-1-methyl-1,2,3,4,6,7,12,12bβ-octahydro-indolo[2,3-*a*]quinolizine-6β-carboxylic acid methyl ester.

33. A pharmaceutical composition comprising at least one compound according to any one of claims 15 to 32 and a pharmaceutically acceptable diluent, carrier and/or excipient.

34. A compound according to any one of claims 15 to 32 for use as a medicament.

35. A method for the treatment of a disease or condition where an antagonist of alpha-2 adrenoceptors is indicated to be useful, which comprises administering to a mammal in need of the treatment an effective amount of at least one compound according to claim 1.