Novel 19-norsteroids substituted in position 11β, preparation process and intermediates, application as medicines and pharmaceutical compositions containing them

The present invention concerns 19-nor steroid compounds, substituted in position 11 β, their preparation process and intermediates, their application as medicines and the pharmaceutical compositions containing them.

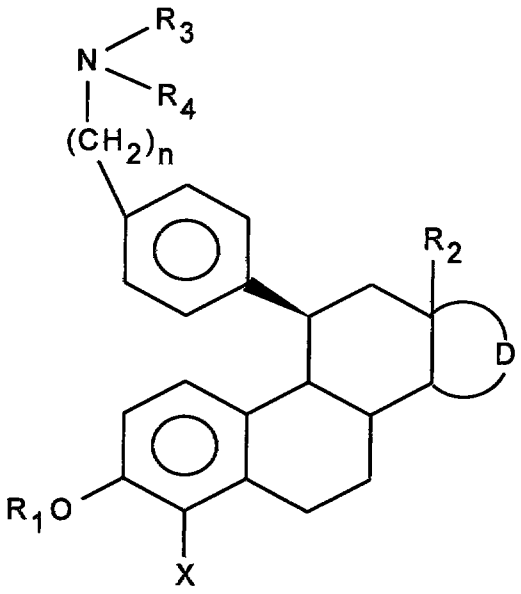
Osteoporosis is a pathology that is characterised by a quantitative and qualitative reduction of the bone tissue, sufficient to lead to vertebral or peripheral fractures, in a spontaneous manner or with minimum traumatism. Although this ailment is of multifactorial origin, it is the menopause that, in women, constitutes the dominating factor of bone loss or osteopenia.

This osteopenia shows itself by rarefaction and modification of the structure of spongy bone which has the consequence of accentuating skeletal fragility and the risk of fracture. The bone loss strongly accentuates after the menopause because of the suppression of ovarian function and reaches 3 to 5% per year to slow down after the age of 65 years.

In a therapeutic objective, postmenopausal hormonal deficiency can be compensated by hormone replacement therapy where oestrogen plays a major role in preserving the bone reserves. But long term oestrogen therapy is sometimes accompanied by undesirable effects on the genital organs (endometrial hyperplasia, mammary tumours), this constitutes a major drawback and limits its application.

It is thus advisable to find other compounds than oestradiol with a dissociated oestrogen activity, namely oestrogen activity at bone level, whilst having little or no endometrial hyperplasia activity, nor the activity of proliferating mammary tumours.

The invention thus has as its object the compounds of general formula (I):



(I)

in which:

R_1 represents a hydrogen atom, a $(CH_2)_m$-Ar, (CO)-Ar, $(CH_2)_m$-Alk or (CO)-Alk radical,

R_2 represents a radical derived from a saturated or unsaturated, linear or branched hydrocarbide containing from 1 to 6 carbon atoms

D represents the residue of a pentagonal or hexagonal ring optionally substituted and optionally unsaturated,

X represents a halogen or hydrogen atom, n is equal to 3, 4 or 5,

either identical or different R_3 and R_4 representing a hydrogen atom, a $(CH_2)_m$-AR, $(CH_2)_m$-Het or $(CH_2)_m$-Alk group,

or R_3 and R_4 together with the nitrogen atom to which they are linked form an aromatic or non aromatic, saturated or unsaturated mono or polyclique heterocycle, with 3 to 15 bonds optionally containing from 1 to 3 additional heteroatoms chosen from amongst non substituted or substituted oxygen, sulphur and nitrogen,

Ar representing a carbocyclic aryl group containing from 6 to 18 atoms of carbon, Het representing a saturated or unsaturated aromatic or non aromatic heterocycle, comprising from 1 to 9 carbon atoms and from 1 to 5

heteroatoms chosen from amongst oxygen nitrogen or sulphur atoms, Alk representing a radical derived from a non aromatic, linear, branched or cyclique, saturated or unsaturated hydrocarbide and comprising from 1 to 12 carbon atoms, the Ar radicals Het or Alk can be substituted or non substituted, m represents 0, 1, 2 or 3, as well as their addition salts with the bases or the acids.

By halogen is meant: iodine, bromine, chlorine or fluorine.

By $(CH_2)_m$ is meant the following values: single bond in the event that m is equal to 0, CH_2, $(CH_2)_2$ and $(CH_2)_3$.

By the term Ar representing the carbocyclic aryl group containing from 6 to 18 carbon atoms, is meant an aromatic cyclic hydrocarbide derivative such as the phenyl, naphtyl, phenanthrenyl radical or even a condensed bicyclic or tricyclic hydrocarbide derivative comprising a benzene ring like indanyl, indenyl, dihydronaphtyl, tetrahydronaphtyl or fluorenyl. The coupling is made at the benzene ring. It preferably concerns phenyl.

By the term (Het) representing an aromatic or non aromatic, saturated or unsaturated heterocycle, comprising from 1 to 9 carbon atoms and from 1 to 5 heteroatoms chosen from amongst oxygen, nitrogen and sulphur atoms these are notably designated:

- Heterocyclic monocyclic radicals, for example thienyl, furyl, pyrannyl, pyrrolyl, imadazoyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, thiazolyl, oxazolyl, furazannyl, pyrrolinyl, imidazolinyl, pyrazolinyl, thiazollinyl, triazolyl, tetrazolyl,
- the heterocyclic condensed rings, for example benzofurannyl, benzothienyl, benzimidazoyl, benzothiazolyl, naphto [2,3-b] thienyl, thianthrenyl, isobenzofurannyl, chromenyl, xanthenyl, phenoxathiinyl, indolizinyl, isoindolyl, 3H-indolyl, indolyl, indazolyl, purinyl, quinolizinyl, isoquinolyl, quinolyl, phtalazinyl, naphtyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, pteridinyl, carbazolyl, beta-carbolinyl, acridinyl, phenazinyl, phenothiazinyl,

phenoxazinyl, indolinyl, isoindolinyl, imidazopyridyl, imidazopyrimidinyl radicals or even condensed polycyclic systems, made up of monocyclic heterocyclics like those defined above like for example furo [2,3-b] pyrrol or thieno [2,3-b] furan,

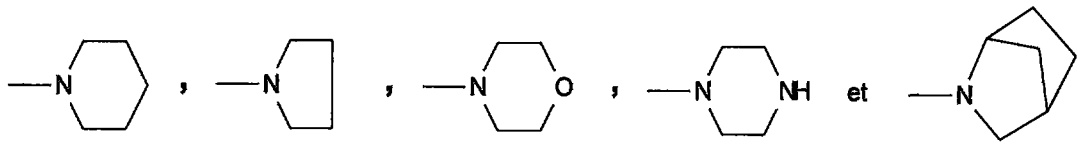
-or saturated heterocycles such as pyrrolidine, piperidine and morpholine.

By the term (Alk) representing a radical derived from a saturated or unsaturated, branched or cyclic, linear, non aromatic hydrocarbide, are designated, in the case of acyclic hydrocarbides alkyl radicals such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, n-pentyl, n-hexyl, 2-methyl pentyl, 2, 3-dimethyl butyl, n-heptyl, 2-methylhexyl, 2,2-dimethylpentyl, 3, 3-dimethylpentyl, 3-ethylpentyl, n-octyl, 2, 2-dimethylhexyl, 3,3-dimethylhexyl, 3-methyl-3-ethylpentyl, nonyl, 2, 4-dimethylheptyl or n-decyl, radical alkenyls such as vinyl, propenyl, isopropenyl, allyl, 2-methylallyl, butenyl or isobutenyl, or alkynyl radicals such as ethynyl, propynyl,propargyl, butynyl or isobutynyl, and in the case of cyclic radicals, the cycloalkyl radicals, such as cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

Preferably methyl and ethyl radicals are used.

By CO-Alk is preferably meant $COCH_3$ and COEt, by CO-Ar is preferably meant the benzoyl radical, when m is different to zero, $(CH_2)_m$-Ar will preferably be the benzyl group.

When R_3 and R_4 together with the nitrogen atom to which they are linked form a heterocycle, they are notably mono or bicyclic heterocycles optionally containing another heteroatom chosen from amongst oxygen and nitrogen such as the following unsaturated heterocycles: pyrrolyl, imidazolyl, indolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, thiazolyl, oxazoyl, furazolinyl, pyrazolinyl, thiazolinyl, or more particularly, the following saturated heterocycles:



When the different Alk, Ar, Het groups as well as the residue of a pentagonal or hexagonal ring cited earlier are substituted, they could notably be so by the following radicals: halogen, namely fluorine, chlorine, bromine or iodine, alkoxy such as methoxy, ethoxy, propyloxy, isopropyloxy, butyloxy, alkylthio such as methylthio, ethylthio, propylthio, isopropylthio, butylthio, amino, alkylamino such as methylamino or ethylamino, dialkylamino such as dimethylamino, diethylamino, methylethylamino, each of these dialkylamino radicals being optionally in oxidised form, aminoalkyl such as aminoethyl or aminoethyl, dialkylaminoalkyl such as dimethylamino methyl or ethyl, dialkylaminoalkyloxy such as dimethylamino ethyloxy, optionally acylated hydroxyl, acyl such as acetyl, propionyl, butyryl, benzoyl, free carboxy, esterified like alkoxy carbonyl for example methoxy carbonyl or ethoxy carbonyl, cyano, trifluoromethyl, aryl such as phenyl, aralkyl such as benzyl, alkyl, alkenyl or alkynyl these radicals being themselves optionally substituted by the halogen, alkyl, alkoxy, alkylthio, amino, alkylamino or dialkylamino radicals indicated above.

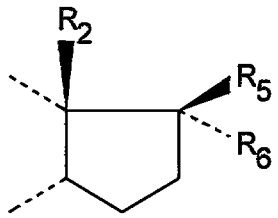
Of course, the expression "substituted" indicates that one or several identical or different substitutes, can be present. As an example, when the alkyl group is a methyl radical substituted by one or several halogen atoms, it can notably be CH_2Cl, CH_2F, CHF_2 and CF_3.

In the case of (Het), the substitutes can be at the level of NH or of a carbon atom.

Of course the values of R_1, R_2, R_3, and R_4, are independent from each other.

The invention naturally extends to the salts of the compounds of formula (I), like for example the salts formed with mineral or organic acids on the amine. It can thus concern chlorohydric, bromhydric, nitric, sulfuric, phosphoric, acetic, formic, propionic, benzoic, maleic, fumaric, succinic, tartric, citric, oxalic, glyoxylic, aspartic, alcane sulfonic acids such as methane or ethane, sulfonic, arylsulfonic acids, like the sulfonic and arylcarboxylic benzene or paratoluene acids. When the compounds of formula (I) include an acid function, the invention extends to the optionally substituted salts of alkaline, earthy alkaline or ammonium metals.

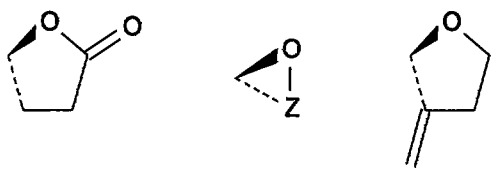
The invention more particularly has as its object the compounds of general formula (I) as described above, in which (D) represents the residue of a pentagonal ring of formula:



in which R_2 retains the same signification as before,

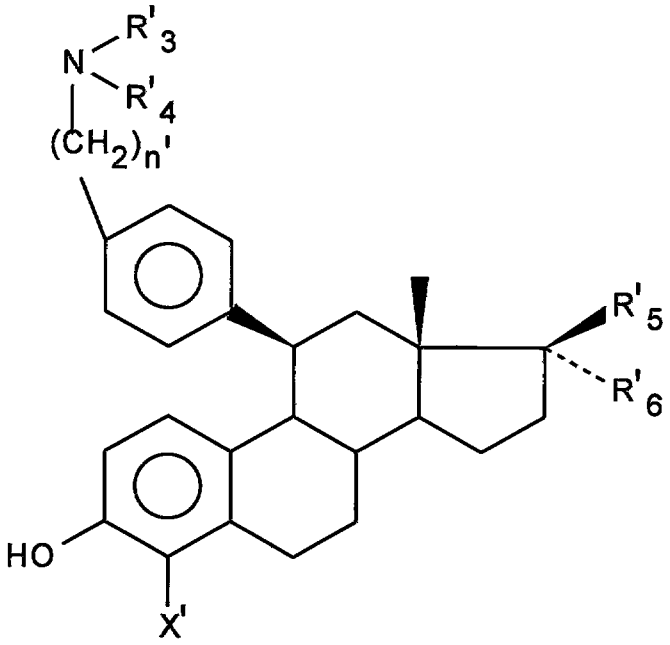
either R_5 represents an OH, O-$(CH_2)_m$-Alk, O-(CO)-Alk, O-$(CH_2)_m$-Ar,O-(CO)-Ar,O-$(CH_2)_m$–Het, O-(CO)-Het and R_6 represents a hydrogen atom, an alkyl, alkenyl or alkynyl radical containing from 1 to 6 substituted or non substituted carbon atoms, m, Alk, Ar and Het as previously described,

or R_5 and R_6 together with the carbon atom which carries them form in one of the following rings:



in which z represents a $-(CH_2)_1-$ or $-CH=CH-(CH_2)_{1'}$ group, 1 being an integer between 1 and 4 and 1' being an integer equal to 1 or 2,
either R_5 and R_6 together form an oxo group, as well as their addition salts with the acids or the bases.

The invention has more particularly as its object the compounds of formula (I) as previously described corresponding to general formula (I'):



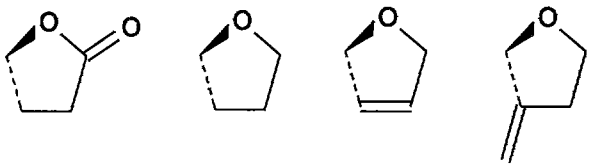
(I')

in which:
X represents a chlorine, bromine or hydrogen atom, n' is equal to 3,
or identical or different R'_3 and R'_4 represent an alkyl radical containing from 1 to 6 carbon atoms
or R'_3 and R'_4 together, with the atom of nitrogen to which they are linked, form a saturated mono or polyclic residue with 3 to 15 bonds optionally containing an additional heteroatom chosen from amongst oxygen, sulphur and nitrogen,
R'_5 and R'_6 have the same signification as R_5 and R_6,
as well as their addition salts with the acids and the bases.

The invention has more particularly as its object the compounds of formula (I) as previously described corresponding to general formula (I') in which:

either R'_5 represents an OH radical and R'_6 a hydrogen atom, an alkyl, alkenyl or alkynyl radical containing from 1 to 6 substituted or non substituted carbon atoms,

or R'_5 and R'_6 together with the carbon atom which carries them form one of the following rings:



or R'_5 and R'_6 together form an oxo group, as well as their addition salts with the acids or the bases.

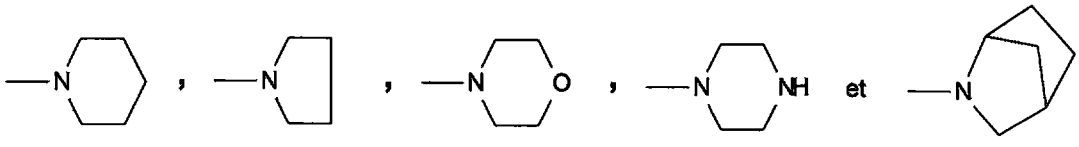
The invention has more particularly as its object the compounds of formula (I) corresponding to general formula (I') as previously described in which:

X' represents a chlorine or hydrogen atom,

n' is equal to 3,

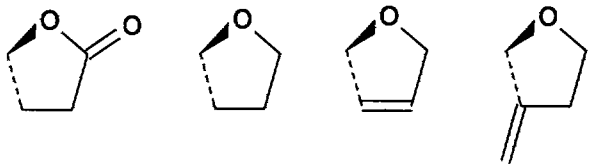
either identical or different R'_3 and R'_4 represent an alkyl radical containing from 1 to 6 carbon atoms

or R'_3 and R'_4 together with the nitrogen atom form the following saturated heterocycles:



and either R'_5 represents an OH radical and R'_6 represents a hydrogen atom, an alkyl, alkenyl or alkynyl radical containing from 1 to 6 carbon atoms, substituted or not,

or R'_5 and R'_6 together with the carbon atom which carries them form one of the following rings:



or R'_5 and R'_6 together form an oxo group,

as well as their addition salts with the acids or the bases.

The invention has more particularly as its object either the compounds of general formula (I) as previously described in which X=H, or the compounds of general formula (I) as previously described in which X=Cl or Br, and more particularly Cl.

The invention has very particularly as its object the compounds of formula (I) as well as their addition salts with the acids whose names are the following:

3-hydroxy-11 β -[4-[3-(1-piperidinyl)propyl]phenyl]-estra-1. 3. 5(10)-trien-17-one,

3-hydroxy-11β-[4-[3-(1-pyrrolidinyl)propyl]phenyl]-estra-1.3.5(10)-trien-17-one,

3-hydroxy-11β-[4-[3-dimethylamino)propyl]phenyl]-estra-1.3.5(10)-trien-17-one,

4-chloro-3-hydroxy-11β-[4-[3-(1-piperidinyl)propyl]phenyl]-estra-1.3.5(10)-trien-17-one

4-chloro-3-hydroxy-11β-[4-[3-(1-pyrrolidinyl)propyl]phenyl]-estra-1.3.5(10)-trien-17-one

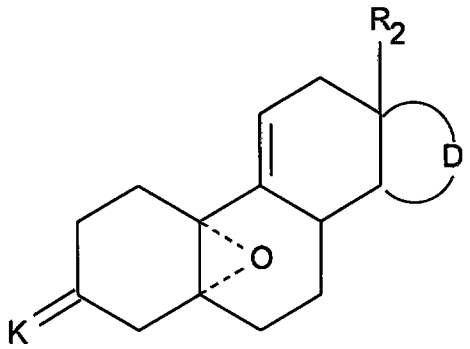
4-chloro-3-hydroxy-11β-[4-[3-(diethylamino)propyl]phenyl]-estra-1.3.5(10)-trien-17-one

11β-[4-[3-(1-pyrrolidinyl)propyl]phenyl]-estra-1.3.5(10)-trien-3.17β-diol,

11β-[4-(3-dimethylamino)propyl)phenyl]-estra-1.3.5(10)-trien-3.17β-diol

11β-[4-(3-(1-piperidinyl)propyl)phenyl]-estra-1.3.5(10)-trien-3.17β-diol
4-chloro-11β-[4-[3-(1-pyrrolidinyl)propyl]phenyl]-estra-1.3.5(10)-trien-3.17β-diol
4-chloro-11β-[4-[3-(1-piperidinyl)propyl]phenyl]-estra-1.3.5(10)-trien-3.17β-diol
4-chloro-11β-[4-[3-(diethylamino)propyl]phenyl]-estra-1.3.5(10)-trien-3.17β-diol,
17α-methyl-11β-[4-[3-(1-piperidinyl)propyl]phenyl]-estra-1.3.5(10)-trien-3.17β-diol,
4-chloro-17α-methyl-11β-[4-[3-(1-piperidinyl)propyl]phenyl]-estra-1.3.5(10)-trien-3.17β-[diol
11β-[4-[3-(1-piperidinyl)propyl]phenyl]-17α-(trifluoromethyl)-estra-1.3.5(10)-trien-3.17β-diol]
(17R) 11β-[4-(3-dimethylamino)propyl)phenyl]-spiro-(estra-1.3.5(10)-trien-17.2'(5'H)-furan)-3-ol
(17R) 4'.5'-dihydro-11β-[4-(3-dimethylamino)propyl) phenyl]-spiro-(estra-1.3.5(10)-trien-17.2'(3'H)-furan)-3-ol.

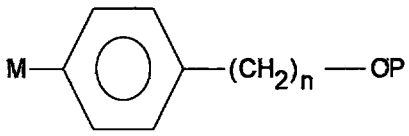
The invention equally has as its object a preparation process for the compounds of formula (I) as previously described in which a compound of formula (II) is submitted:



(II)

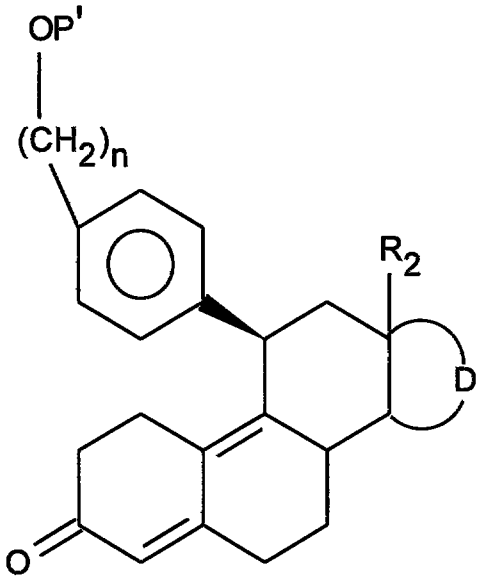
in which D and R_2 are as previously described and K represents a protector group of 3-ceto function, successive to the following reactions:

a) action of a formula (III) compound:



(III)

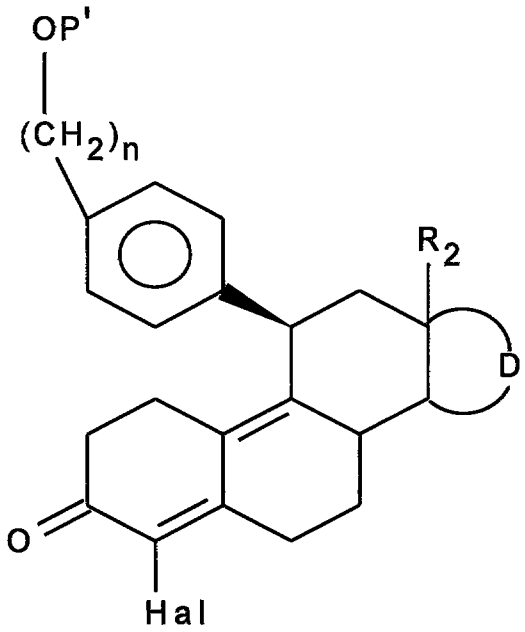
in which, M represents a metallic derivative, P represents an alcohol protector group and n is an integer equal to 3, 4 or 5, then optionally deprotection of one or several protected reagent functions, in order to obtain a formula (III_a) compound:



(III_a)

P' having the same values as P as well as hydrogen,

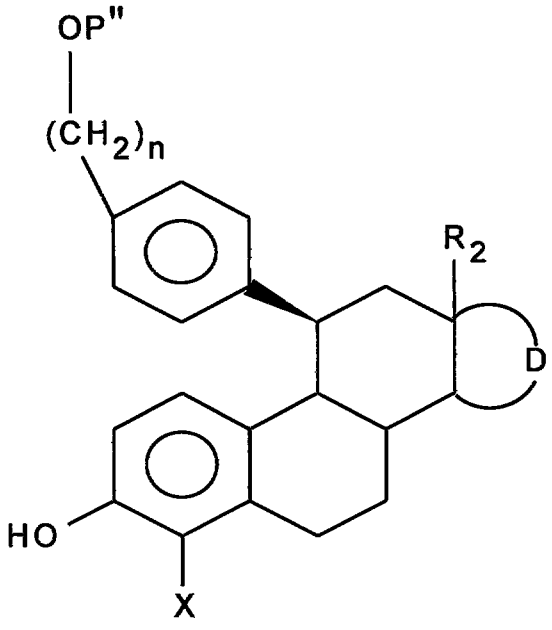
b) action, optionally, of a halogenation reagent, in order to obtain a formula (III_b) compound:



(III_b)

Hal representing a halogen atom,

c) after having optionally protected and/or activated the OH function, action of an aromatisation reagent of ring (A) on the formula (III_a) and (III_b) compounds, then action of a base to obtain the formula (IV) compound:

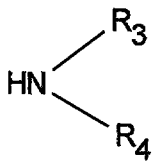


(IV)

P" having the same values as p' and able moreover to represent an activating group,

X being as previously described,

d) action of a formula (V) amine:



(V)

R_3 and R_4 being as previously defined, this compound optionally being in the form of a salt, in order to obtain certain compounds of formula (I), the compounds of formulas (III_a), (III_b), (IV) and (I) being submitted if desired or if necessary, in a suitable order, to one or several of the following reactions:

-protection/deprotection of the OH group(s),

-alkylation/acylation of the OH group(s),

-action of a reduction agent when D represents the residue of a pentagonal ring as previously described and R_5 and R_6 together form an oxo group,

-action of an organometallic or CF_3SIMe_3 on the compounds of formula (IV) or (I) with D representing the residue of a pentagonal ring as previously described and R_5 and R_6 together forming an oxo group,

-action of a lactonisation agent on the compounds of formula (IV) or (I) with D representing the residue of a pentagonal ring as previously described and R_5 and R_6 together forming an oxo group,

-action of a reduction agent of the double bond, when D represents the residue of a pentagonal ring as previously described and R_5 and R_6 together with the carbon that carries them, form an $O-(CH_2)_{1'}-CH=CH-$,

-action of a reduction agent, when D represents the residue of a pentagonal ring as previously described, and R_6 is an alkenyl or alkynyl radical containing from 2 to 6 carbon atoms,

-salification.

The action of a compound of formula (III) on the compound of formula (II) is preferably carried out in the presence of a copper salt such as copper chloride I.

The action of a halogenation reagent such as N-bromosuccinimide or N-chlorosuccinimide on the compounds of formula (III_a) is notably carried out in the presence of a dipolar aprotic solvent such as dimethylformamide.

The reaction of aromatisation followed by the reaction of saponification (basic action) is carried out according to standard methods such as are described in European patent 0097572. Preferably a compound of acetic anyhydride and acetyl bromide is used as aromatisation agent then a base such as soda in methanol as saponification agent.

By activation of the alcohol is meant the introduction notably of a mesylate, tosylate or triflate which makes it possible to facilitate the nucleophile substitution of the amine of formula (V) on the compounds of formula (IV). The formation of the mesylate, tosylate or triflate from compounds of formula (III_a) or (III_b) with P' representing hydrogen is carried out in the presence of a base such as triethylamine.

The substitution of alcohol with a halogen atom can equally be envisaged.

The protection and deprotection reactions are standard methods known to a specialist. A quite comprehensive review is found in the following work: Protective groups in organic synthesis T.W Greene, John Wiley & sons (1981).

The protector group P can represent an alkyl radical containing from 1 to 4 carbon atoms, a benzyl group, a tetrahydropyrannyl group, an $R_CR_DR_ESi$ group, in which identical or different R_C,R_D and R_E, independently from one another each represent an alkyl radical containing from 1 to 4 carbon atoms or a phenyl group. It particularly concerns the $Si(Me)_2Cme_3$ or $-Si(PH)_2CMe_3$ or $SiMe_3$ groups.

As an example, the deprotection reactions of the compounds of formula (III_a) or (III_b), when P' is a tertbutyldiphenylsilyl group can be carried out by the action of ammonium tetrabutyl fluoride in solution in tetrahydrofuran.

When P' is a tetrahydropyrannyl group, the deprotection is carried out in the presence of an aqueous acid in an alcoholic solvent and preferably by the action of chlorohydric acid in methanol.

The action of a compound of formula R_3-NH-R_4 on the compounds of formula (IV) is carried out in standard conditions of nucleophile substitutions, notably in the presence of an aprotic solvent such as tetrahydrofuran, OP" thus preferably represents an O-SO_2CH_3, OSO_2-PH-pMe, OSO_2CPh_3. OP can equally represent halogen (preferably bromine or iodine).

The alkylisation or acylsation reactions of the OH group in position 3 or 17 are carried out by standard methods known to the specialist.

The reduction of 17-ceto in a corresponding alcohol (R_5=OH and R_6=H) is carried out according to standard methods, notably by the action of an alkaline borohydrure such as sodium borohydrure in methanol or ethanol or by action of aluminium and lithium tetrahydrure.

The action of an organometallic on the 17-ceto makes it possible to have access to the products of formula (I) in which D represents the residue of a pentagonal ring as previously described, R_5 is hydroxyl and R_6 represents an alkyl, alkenyl, optionally substituted alkynyl radical.

The organometallic derived from an alkyl, alkenyl or alkynyl is chosen from amongst the magnesians of formula AlkMgHal and the lithiens of formula AlkLi in which Alk represents an alkyl, alkenyl or alkynyl group containing at the most 8 carbon atoms and Hal represents a halogen atom. In a preferred method of carrying out the process, Hal represents a chloride, bromine or iodine atom, preferably bromine.

The reaction preferably takes place in the presence of cerium chloride. In a preferred method of carrying out the process Hal represents a chloride, bromine or iodine atom, preferably bromine.

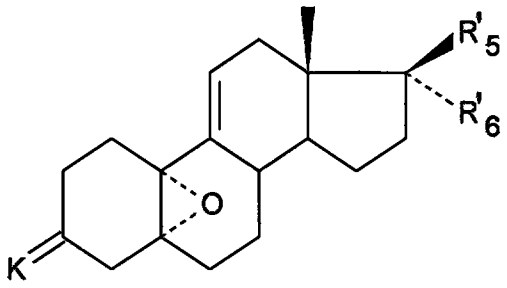
To obtain the compounds of formula (I) with R_5 is a hydroxyl and R_6 is a CF_3 group, the reaction is carried out by action of CF_3SiMe_3 on the 17-ceto, followed by the action of a deprotection reagent such as ammonium tetrabutyl fluoride.

The lactonisation reaction starting with 17 ceto is carried out according to the STURTZ method (ref: G STURTZ and J-J. YAOUANC, synthesis, (1980), 289) notably in the presence of allyl bisdimethylamidophosphate in the presence of an alkyllithien such as N-butyllithium in tetrahydrofuran.

The reaction of total or partial reduction when R_6 is an alkenyl or alkynyl radical or when R_5 and R_6 together with the carbon that carries them, form an O-$(CH_2)_{1'}$ –CH=CH- group, can be carried out either totally by the action of hydrogen in the presence of a catalyst such as palladium on carbon or a rhodium catalyst such as Wilkinson's reagent or partially (alkynyl becomes alkenyl) by the action of a poisoned catalyst such as palladium on barium sulphate poisoned by pyridine or triethylamine.

The reactions of esterification and salification are carried out by standard methods known to the specialist.

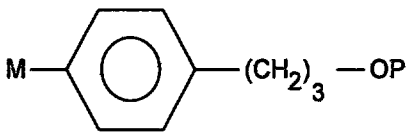
The invention has more particularly as its aim a process for preparing compounds of formula (I') as previously described, in which a compound of general formula (II') is submitted:



(II')

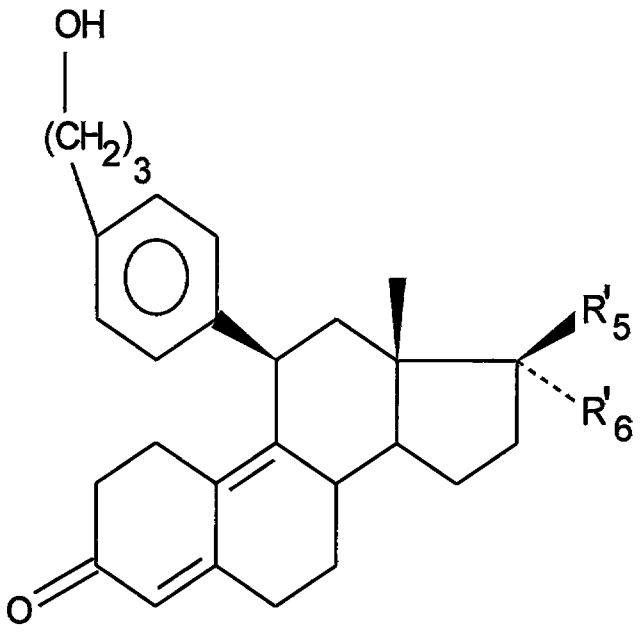
in which K, R'_5 and R'_6 are as previously described, or in which R'_5 is a CN radical and R'_6 is a protected hydroxyl, successive to the following reactions:

a) action of a compound of formula (III'):



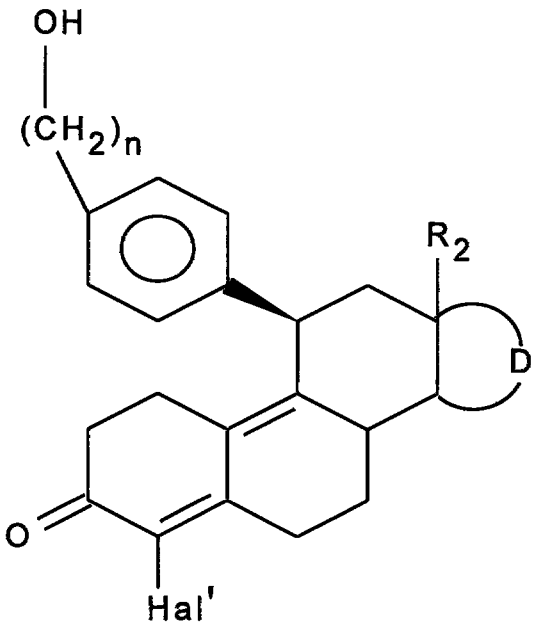
(III')

in which M and P are as previously described, then deprotection of one or several of the protected reactive functions, in order to obtain a compound of formula (III'$_a$):



(III'$_a$)

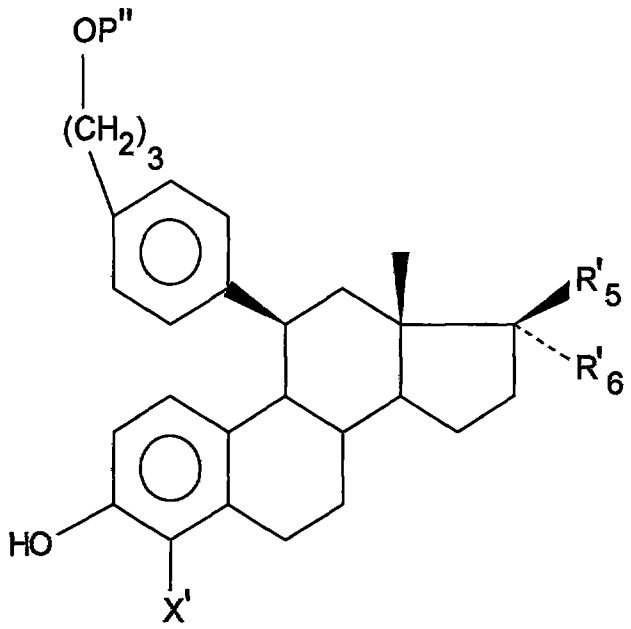
b) action, optionally, of a halogenation reagent in order to obtain a compound of formula (III'$_b$):



(III'$_b$)

Hal' representing a chlorine or bromine atom,

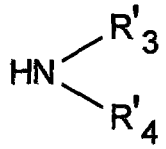
c) activation of the OH function then action of an aromatisation reagent of ring (A) on the compounds of formula (III_a) or (III_b), then the action of a base to obtain the compounds of formula (IV'):



(IV')

X' and P" are as previously described,

d) action of an amine of formula (V'):



(V')

R'_3 and R'_4 as previously described in order to obtain certain components of formula (I'), the compounds of formulas (III'_a), (III'_b), (IV') and (I') submitted, if desired or if necessary to one or several of the following reactions:

-protection/deprotection of the OH group(s),

-alkylation/acylation of the OH group(s),

-action of a reduction agent when R'_5 and R'_6 together form an oxo group,

-action of an organometallic or CF_3SiMe_3 on the compounds of formula (IV') or (I') with R'_5 and R'_6 together forming an oxo group,

-action of a lactonisation agent on the compounds of formula (IV') or (I') with R'_5 and R_6 together forming an oxo group,

-action of a reduction agent of the double bond, when R'_5 and R'_6 together with the carbon that carries them, form an $O-(CH_2)_{1'}-CH=CH-$ group,

action of a reduction agent, when R'_6 is an alkenyl or alkynyl radical containing from 2 to 6 carbon atoms,

-salification.

The compounds of general formula (I) as well as their addition salts with pharmaceutically acceptable acids notably having oestrogen, anti-oestrogen and antiproliferative activities.

As such, the compounds of formula (I) can be used in the treatment of disorders linked to hypofolliculitis, for example amenorrhea, dysmenorrhea, repeated abortions, premenstrual disorders, in the treatment of certain oestrogen dependent pathologies such as prostatic adenomas or carcinomas, mammary carcinomas and its metastases or the treatment of benign breast tumours, as anti-uterotrophic as well as in the hormone replacement treatment of the menopause or perimenopause.

Amongst the symptoms and the consequences linked to the menopause, are more precisely meant the hot flushes, sweats, vaginal atrophia and dryness, urinary indications and in the long term lessening of bone mass and the increase of the risk of fracture, as well as the loss of the cardio-vascular protection offered by oestrogens.

In particular, the compounds of formula (I) as well as their addition salts with pharmaceutically acceptable acids or the bases can thus be used in the prevention or the treatment of osteoporosis.

The compounds of formula (I) as well as their addition salts with pharmaceutically acceptable acids or bases, can equally be used in the prevention or treatment of osteoporosis in men.

They can equally be used in the prevention or the (for example cortisone or connected with immobilisation) treatment of secondary osteoporosis.

The compounds of formula (I) as well as their addition salts with pharmaceutically acceptable acids or bases notably have a dissociated oestrogenic activity.

By dissociated oestrogenic activity, is meant oestrogenic activity at bone level whilst only manifesting a minimal activity at uterine level thus leading to the absence of endometrial proliferation (activity well below that of oestradiol).

Furthermore, the compounds according to the invention present the following advantages:

-They show an anti-oestrogen and/or antiproliferative activity in the breast. Unlike oestradiol they do not stimulate the growth of human mammary tumour cells and can even inhibit their growth. The compounds according to the invention are thus particularly advantageous for the treatment of the menopause as far as women at risk from mammary cancer are concerned (prior family history) who are thus excluded from replacement oestradiol treatment.

They can equally be used in the treatment of mammary cancers.

-They lead to a lowering in the level of serum cholesterol to an at least equivalent level of that induced by oestradiol. They thus reinforce cardiovascular protection.

-Finally these compounds according to the invention do not show any oestrogen activity at uterine level, do not need to be administered in association with a progestomimetic compound.

The invention thus has as its object the compounds of formula (I) as well as their addition salts with pharmaceutically acceptable acids or bases, as medicines.

The invention has more particularly as its object the compounds of formula (I) as well as their addition salts with the pharmaceutically acceptable acids or bases, as medicines intended for the prevention or treatment of osteoporosis.

The invention extends to pharmaceutical compositions containing as active ingredient at least one of the medicines as described above.

The compounds of formula (I) are used by digestive, parenteral or local route, for example by percutaneous route. They can be prescribed in the form

of simple tablets or sugar coated pills, capsules, granules, suppositories, pessaries, injectable preparations, ointments, creams, gels, microspheres, implants, intravaginal rings, patches, which are prepared according to usual methods.

The active ingredient(s) can be incorporated into excipients usually used in these pharmaceutical compositions, such as talc, gum arabic, lactose, starch, magnesium stearate, cocoa butter, aqueous or non aqueous mediums, fatty bodies of animal or vegetable origin, paraffin derivatives, glycols, various dilution, dispersant or emulsifying agents, preservatives.

The useful dosage varies according to the condition to be treated and the administration route; it can vary for example from 1 to 1000mg per day in adults by oral route.

The compounds of general formula (II) or (II') are compounds known and described in the European Patent 0057115.

The compounds of formula (III) are known or are easily accessible to the specialist starting with the corresponding aromatic halides. The amines of formula (V) are equally known or easily accessible to a specialist.

The invention equally has as its aim, as intermediary products, the compounds of formula (III_a), (III_b), (III'_a), (III'_b), (IV) or (IV').

The examples below illustrate the invention without at the same time limiting it.

Solvents described in the examples: AcOEt (ethyl acetate), TEA (triethylamine), CH_2Cl_2 (dichloromethane), $CHCl_3$ (chloroform), MeOH (methanol), NH_4OH (ammonium hydroxide), iPrOH (isopropyl alcohol).

Preparation 1: 11β-[4(3-hydroxypropyl)phenyl]-estra-4,9-diene-3,17-dione.

Stage A: Alkylation

3-(4-bromophenyl)-2-propynol

To a solution under inert gas of 55.2g of 4-bromo iodo benzene at 97% in 230ml of DMF, 56ml of TEA is added, 12.2ml of propargylic alcohol, 1g of copper iodide and 1.1g of $PdCl_2(PPh_3)_2$ whilst maintaining the temperature at 47°C. After stirring for 3 hours 15 minutes at ambient temperature, it is poured into water, drawn off, washed dried and evaporated under reduced pressure until 48.3g of raw product is obtained that is purified by

chromatography on silica by eluting with the compound CH_2Cl_2/AcOEt 95/5. 36, 37g of expected pure product is obtained. (F=80°C)

Rf (CH_2Cl_2/AcOEt 95/5): 0.32

IR ($CHCl_3$)

OH 3609cm^{-1}

C=C 2240 cm^{-1}

Aromatic 1585 and 1486cm^{-1}

Stage B: Reduction

3-(4-bromophenyl)-propanol.

To a solution under inert gas of 36.4g of 3-(4-bromophenyl)-2-propynol (stage A) in 200ml of ethanol at 5% of toluene, is added 200ml of toluene, 7.9g of Wilkinson's reagent and hydrogen at 1900 mbar for 5 hours. It is evaporated at reduced pressure until the obtainment of 45.9g of raw product that is purified by chromatography on silica by eluting with the compound CH_2Cl_2/AcOEt 95/5. 30.1g of expected product is obtained.

Rf (CH_2Cl_2/AcOEt 95/5): 0.28

IR ($CHCl_3$)

OH 3626 cm^{-1}

Aromatic 1592 and 1489 cm^{-1}

Stage C: Protection of the alcohol

(1.1-dimethylethyl) dimethyl [[3-(4-bromophenyl) propyl] oxy] silane

To a solution under inert gas of 30.1g of 3-(4-bromophenyl)-propanol (stage B) in 300ml of CH_2Cl_2 is added 11.4g of imidazol and 23g of dimethylterbutylsilyl chloride. After stirring for 45 minutes at ambient temperature, it is washed in water, dried and evaporated under reduced pressure until 47.46g of raw product is obtained that is purified (after having added 1.5g of an identical trial) by redistillation. 44.8g of expected pure product is obtained.

Rf (CH_2Cl_2/AcOEt 95/5): 0.8

IR ($CHCl_3$)

OSi 1527 cm^{-1} and 836cm^{-1}

Aromatic 1590 cm^{-1}(f) and 1489 cm^{-1}

Stage D: Introduction of the aryl group in position 11 of the steroid

11β-[4-(3-hydroxypropyl)phenyl]-estra-4.9-diene-3.17dione

Preparation of the magnesian

To 2.67g of magnesium (shavings) in 5ml of THF under inert atmosphere and at ambient temperature, is added in 50 minutes at the reflux after priming to 1.2-dibromoethane, a solution of 32.9g of (1.1-dimethylethyl) dimethyl [[3-(4-bromophenyl) propyl] oxy] silane (stage C) in 100ml of THF and maintained 5 hours at reflux. (Heading by iodometry: 0.86M)

Epoxide opening

To the compound made up of 120ml of magnesian, obtained at the preceding stage and 600mg of copper chloride, under inert atmosphere at 0-5□Ca solution of 17.18g of 5α,10α-epoxy-3.3-[1.2-ethanediylbis(oxy)]-17α-[(trimethylsilyl)oxy]-estr-9(11)-ene-17α-carbonitrile is added (prepared according to the method described in J.C Gasc and L. Nedelec Tetrahedron Letters (1971), 2005) in 100ml of THF, stirred for 45 minutes at this temperature then poured into a solution of ammonium chloride, drawn off, washed and evaporated under reduced pressure until 43.5g of raw product is obtained.

Acid hydrolysis

To a solution of 43.5g of product obtained from the preceding stage in 300ml of methanol, under inert atmosphere and at ambient temperature, 60ml of chlorhydric acid 6m is added and stirred for 1 hour at ambient temperature. After distillation of the methanol, ethyl acetate is added, it is washed, dried and evaporated under reduced pressure until 30g of raw product is obtained (F=254°C).

Cleaving of the cynhydrine

To a solution of 30g of product obtained at the preceding stage in 200ml of methanol, under inert atmosphere and at ambient temperature, 8ml of washing soda is added and stirred for 1 hour at ambient temperature. After distillation of the methanol, ethyl acetate is added, it is washed, dried and evaporated under reduced pressure until 27.9g of raw product is obtained that is firstly purified by chromatography by eluting with the compound

CH_2Cl_2/MeOH 95/5. 13g of expected product (F=192°C, Rf (CH_2Cl_2/MeOH 95/5): 0.28) is then obtained by dissolving in a compound of 70ml of CH_2Cl_2/ and 70ml of isopropylic ether that is concentrated to crystallisation.

11.92g of pure expected product is obtained. (Rf (CH_2Cl_2/AcOEt 95/5): 0.28)

F=192°C

RMN (CDCl3 300MHz)

0.55 (s)	CH_3 in 18
~1.33	OH
~3.66(m)	$C\underline{H_2}$-OH
4.41(d)	H11
5.80(s)	H4

EXAMPLE 1: 3-hydroxy-11β-[4-[3-(1-piperidinyl)propyl]phenyl]-estra-1.3.5(10)-trien-17-one

Stage A: formation of mesylate

11β-[4-[3-[(methylsulfonyl)oxy]propyl]phenyl]-estra-4.9-diene-3.17-dione

To a solution of 3.41g of 11β-[4-(3-hydroxypropyl)phenyl]estra-4.9-diene-3.17-dione prepared to preparation 1 in 30ml of CH_2Cl_2, under inert atmosphere and at ambient temperature, 1.53ml of TEA and 0.72ml of sulfonyl methane chloride in solution in 2ml of CH_2Cl_2 is added whilst maintaining the temperature at 0-5°C and stirring at this temperature. After washing and drying it is evaporated under reduced pressure until 4.15g of expected raw product is obtained.

F=196°C

Rf (CH_2Cl_2/Acetone 8/2): 0.51

RMN (CDCl3) 300MHz

0.54(s)		CH_3 in 18
3.00(s)		$OSO_2C\underline{H_3}$
4.21(t)	J=5.5	$C\underline{H_2}$-OSO_2 CH_3
4.41(dl)	J=7	H11
5.80(s)		H4
7.11		H aromatics

Stage B: Aromatisation of ring A

3-hydroxy-11β-[4-[3-[(methylsulfonyl)oxy]propyl]phenyl]estra-1.3.5(10)-trien-17-one

a) aromatisation

To a solution of 4.15g of dienone prepared in the preceding stage in 40ml of CH_2Cl_2, under inert atmosphere and at ambient temperature, whilst cooling in an ice bath, 4ml of acetic anhydride and 2 ml of acetyl bromide is added and stirred for 1 hour.

b) Saponification

It is evaporated under reduced pressure, 20ml of THF is added under inert atmosphere and 20ml of methanol then 28ml of soda 2N is added whilst cooling in an ice bath. It is stirred for 40mn, acidified with chlorhydric acid 2N, drawn off with ethyl acetate, washed in salt water then evaporated under reduced pressure until 4.54g of raw product is obtained that is purified by chromatography by eluting with the CH_2Cl_2/AcOEt 9/1 compound. 3.18g of expected product is obtained and 590mg of a second product (3-ceto-5(10),9(11)-diene).

Rf(CH_2Cl_2/AcOEt 9/1): 0.23

RMN($CDCl_3$) 300MHz

0.43(s)	CH_3 in 18
2.92(s)	$OSO_2C\underline{H}_3$
4.02(m)	H11
4.12(m)	$C\underline{H}_2$-OSO_2-
4.61(s)	OH in 3
6.41(dd)	H2
6.61	H4
6.81(d)	H1
6.89 and 7.01	H aromatics

Stage C: Introduction of the amine

3-hydroxy-11β-[4-[3-(1-piperidinyl)propyl]phenyl]-estra-1.3.5(10)-trien-17-one

To a solution of 1.45g of mesylate prepared in stage B in 15ml of THF, under inert atmosphere and at ambient temperature, 2.96ml of piperidine is added, brought to reflux for 3hrs, returned to ambient temperature, ethyl acetate is added, it is washed with sodium bicarbonate, with salt water then evaporated

under reduced pressure until 1.48g of raw product is obtained that is purified by chromatography by eluting with the compound CH_2Cl_2/AcOEt/NH_4OH 90/10/0.5. 1.2g of expected product is obtained.

Rf (CH_2Cl_2/AcOEt/NH_4OH 90/10/0.5) 0.35

RMN ($CDCl_3$) 300MHz

0.44(s)	CH_3 in 18
1.59	N-CH_2-$C\underline{H}_2$ of the ring
2.41	N-$C\underline{H}_2$-CH_2 of the ring
4.02(tl)	H11
6.31(dd)	H2
6.52(d)	H4
6.77(d)	H1
~6.81 and ~6.98	H aromatics

EXAMPLE 2: 3-hydroxy-11β-[4-[3-(1-pyrrolidinyl)propyl]phenyl]estra-1.3.5(10)-trien-17-one

It is carried out as in example 1 stage C from 456mg of the mesylate prepared in stage B of example 1 and 0.79ml of pyrrolidine. 441mg of raw product is obtained that is purified by chromatography by eluting with the AcOEt/TEA 7/3 compound then by crystallisation in isopropylic ether. 347mg of expected product is obtained.

F=180°C

Rf(CH_2Cl_2/AcOEt/NH_4OH 9/1/0.5):0.33

RMN($CDCl_3$) 300MHz

0.44(s)	CH_3 in 18
1.75	N-CH_2-$C\underline{H}_2$ of the ring
2.50	N-$C\underline{H}_2$-CH_2 of the ring
4.03(tl)	H11
6.25(dd)	H2
6.51(d)	H4
6.75(d)	H1
~6.84 and ~6.99	H aromatics

EXAMPLE 3: 3-hydroxy-11β-[4-[3-dimethylamino)propyl]phenyl]-estra-1.3.5(10)-trien-17-one

It is carried out as in example 1 but using dimethylamine as amine.

EXAMPLE 4: 4-chloro-3-hydroxy-11β-[4-[3-(piperidinyl)propyl]phenyl]-estra-1.3.5(10)-trien-17-one

Stage A: chlorination

4-chloro-11β-[4-(3-hydroxypropyl)phenyl]estra-4.9-diene-3-one.

To a solution of 11.9g of 11β-[4-(3-hydroxypropyl)phenyl]-estra-4.9-diene-3.17-dione prepared to preparation 1 in 100ml of DMF, under inert atmosphere and at 60°C, 4.93g of N-chloro succinimide is added and stirred for 10mn at this temperature. It is poured into water, drawn off, washed, dried, evaporated under reduced pressure until 16.2g of raw expected product is obtained that is purified by chromatography by eluting with the compound CH_2Cl_2/Acetone 85/15. 9.34g of pure expected product is obtained.

Rf (CH_2Cl_2/Acetone 85/15

RMN CDCl3) 300MHZ

0.56(s)	CH_3 in 18
3.24(dt)	H equatorial
3.65(t)	$C\underline{H_2}$-OH
4.42(d)	H11
~7.09	H aromatics

Stage B: formation of mesylate

4-chloro-11β-[4-[3-[(methylsulfonyl)oxy]propyl]phenyl]-estra-4.9-diene-3-one.

To a solution of 9.34g of alcohol prepared in stage A in 90ml of CH_2Cl_2, under inert atmosphere and at ambient temperature, 3.86ml of TEA and 1.82ml of sulfonyl methane chloride in solution in 5ml of CH_2Cl_2 is added whilst maintaining the temperature at 0-5°C and stirring for 30mn at this temperature. After washing and drying it is evaporated under reduced pressure until 11g of expected raw product is produced.

Rf (CH_2Cl_2/Acetone 85/15): 0.3

RMN (CDCl3) 250MHz

0.56(s)	CH_3 in 18

3.00(s)	$OSO_2C\underline{H}_3$
3.26(dt)	H equatorial
4.22(t)	$C\underline{H}_2$-OSO_2CH_3
4.42(dl)	H11
~7.10	H aromatics

Stage C: Aromatisation of ring A

4-chloro-3-hydroxy-11β-[4-[3-[(methanesulfonyl)oxy]propyl]-phenyl-estra-1.3.5(10)-trien-17-one

a) Aromatisation

To a solution of 10.37g of dienone prepared in the preceding stage in 100ml of CH_2Cl_2, under inert atmosphere and at ambient temperature, whilst cooling in an ice bath, 10ml of acetic anhydride and 2ml of acetyl bromide, is added and stirred for 6 hours at ambient temperature.

b) Saponification

It is evaporated under reduced pressure, 50ml of THF is added, 50ml of methanol then 70ml of Soda 2N is added whilst cooling in an ice bath. It is stirred for 45mn, acidified with 70ml of chlorohydric acid 2N, drawn off in ethyl acetate, washed in salt water then evaporated under reduced pressure until 11.5g of raw product is obtained that is purified by chromatography by eluting with the cyclohexane/AcOEt 9/1 compound. 6g of expected product is obtained (Rf=0.27) and 768mg of a second product (4-chloro-1.3.5(10), 9(11) tetraenone derivative not containing hydroxy in 3 (Rf=0.39)).

Rf (CH_2Cl_2/AcOEt 9/1): 0.27

RMN ($CDCl_3$) 250MHz

0.43(s)	CH_3 in 18
2.93(s)	$OSO_2C\underline{H}_3$
4.02(m)	H11
4.14	$C\underline{H}_2$-OSO_2
5.46(s)	OH in 3
6.64	H2
6.81	H1
6.92	H aromatics

Stage D: Introduction of the amine
4-chloro-3-hydroxy-11β-[4-[3-(1-piperidinyl)propyl]phenyl]-estra-1.3.5(10)-trien-17-one

To a solution of 1.5g of mesylate prepared in the preceding stage in 15ml of THF, under inert atmosphere and at ambient temperature, 2.96ml of piperidine is added, brought to reflux for 3hrs, brought back to ambient temperature, ethyl acetate is added, it is washed with sodium bicarbonate, with salt water then evaporated under reduced pressure until 1.66g of raw product is obtained that is purified by chromatography by eluting with the compound CH_2Cl_2/MeOH/NH_4OH 90/10/0.5. 1.2g of expected product is obtained.

Rf (CH_2Cl_2/AcOEt/NH_4OH 90/10/0.5): 0.27

RMN ($CDCl_3$) 300MHz

0.43(s)	CH_3 in 18
1.62	N-CH_2-CH_2 of the ring
2.46	N-CH_2-CH_2 of the ring
4.01(tl)	H11
6.61(d)	H2
6.79(d)	H1
~6.89	H aromatics

EXAMPLE 5: 4-chloro-3-hydroxy-11β-[4-[3-(1-pyrrolidinyl)propyl]phenyl]-estra-1.3.5(10)-trien-17-one

It is carried out as in example 4 stage D but from 517mg of mesylate (example 4 stage C) and 0.84ml of pyrrolidine.

510mg of raw product is obtained that is purified by chromatography by eluting with the compound CH_2Cl_2/MeOH/NH_4OH 90/10/1. 380mg of expected product is obtained.

Rf (CH_2Cl_2/AcOEt/NH_4OH 90/10/1): 0.3

RMN ($CDCl_3$) 300MHz

0.42(s)	CH_3 in 18
1.75	N-CH_2-CH_2 of the ring
2.46	N-CH_2-CH_2 of the ring

4.02(sl)	H11
6.56(d)	H2
6.79(d)	H1
6.89(AA'BB')	H aromatic

EXAMPLE 6: 4-chloro-3-hydroxy-11β-[4-[3-(diethylamino)propyl]phenyl]-estra-1.3.5(10)-trien-17-one

It is carried out as in example 4 stage D but from 517mg of mesylate (example 4 stage C) and 1ml of diethylamine.

500mg of raw product is obtained that is purified by chromatography by eluting with the compound CH_2Cl_2/MeOH/NH_4OH 90/10/1. 385mg of expected product is obtained.

Rf (CH_2Cl_2/AcOEt/NH_4OH 90/10/1): 0.31

RMN ($CDCl_3$) 300MHz

0.42(s)	CH_3 in 18
0.95	N-CH_2-$\underline{C}H_3$
2.49	N-$\underline{C}H_2$-CH_3
4.02(t)	H11
6.59(d)	H2
6.80(d)	H1
6.90(AA' BB')	H aromatics

EXAMPLE 7: 11β-[4-[3-(1-pyrrolidinyl)propyl]phenyl]-estra-1.3.5(10)-trien-3.17β-diol

To a solution of 310mg of the product obtained in example 2 in 3ml of methanol, 54mg of sodium borohydrure at 97% is added at 0-5°C, stirred for 1 hour at this temperature, salt water is added, it is drawn off, washed, dried and evaporated under reduced pressure until 320mg of raw product is obtained that is purified by chromatography by eluting with the compound CH_2Cl_2/MeOH/NH_4OH 90/10/1. 217mg of pure expected product is obtained.

Rf (CH_2Cl_2/MeOH/NH_4OH): 0.23

RMN ($CDCl_3$) 300MHz

0.33(s)	CH_3 in 18
1.76	N-CH_2-$\underline{C}H_2$ of the ring

2.52	N-C$\underline{H_2}$-CH_2 of the ring
3.69(dd)	H17
3.96(tl)	H11
6.27(dd)	H2
6.47(d)	H4
6.76(d)	H1
~6.83 and ~6.98	H aromatics

EXAMPLE 8: 11β-[4-(3-diethylamino)propyl]phenyl]-estra-1.3.5(10)-trien-3.17β-diol

It is carried out as in example 7 (reduction with sodium borohydrure) but from the product obtained in example 3.

Rf AcOEt/iPrOH/ NH_4OH 70/30/1: 0.17

RMN ($CDCl_3$ + 1 drop of C_5D_5N) 300MHz

0.32(s)	CH_3 in 18
2.18(s)	N-C$\underline{H_3}$
3.67	H17
3.95	H11
6.46(dd)	H2
6.64(d)	H4
6.81(d)	H1
~6.88~7.00	H aromatics

EXAMPLE 9: 11β-[4-(1-piperidynyl)propyl]phenyl]-estra-1.3.5(10)-trien-3.17β-diol

It is carried out as in example 7 (reduction with sodium borohydrure) but from the product obtained in example 1.

Rf ethyl acetate/TEA 90/10: 0.30

RMN ($CDCl_3$) 300MHz

0.33(s)	CH_3 in 18
2.1 to 2.5	N-C$\underline{H_2}$, Ph-C$\underline{H_2}$
3.70(dd)	H17
3.96(tl)	H11
6.32(dd)	H2

6.47(d)	H4
6.78(d)	H1
~6.82~6.98	H aromatics

EXAMPLE 10: 4-chloro-11β-[4-[3-(1-pyrrolidinyl)propyl]phenyl]-estra-1.3.5(10)-trien-3.17β-diol

It is carried out as in example 7 but from 257mg of product obtained in example 5 and 42mg of sodium borohydrure at 97%. 221mg of raw product is obtained that is purified by cristallisation to obtain 154mg of pure expected product.

Rf (CH_2Cl_2/MeOH/NH_4OH 90/10/1): 0.15

RMN ($CDCl_3$) 300MHz

0.33(s)	CH_3 in 18
1.73(m)	N-CH_2-CH_2 of the ring
~2.37; ~2.50	N-CH_2 and PH-CH_2 of the chain
2.43(m)	N-CH_2-CH_2 of the ring
3.71 (dd)	H17
3.93 (tl)	H11
6.58(d)	H2
6.76(d)	H1
6.91	H aromatics

EXAMPLE 11: 4-chloro-11β-[4-[3-(1-piperidinyl)propyl]phenyl]-estra-1.3.5(10)-trien-3.17β-diol

It is carried out as in example 7 but from 305mg of product obtained in example 4 and 48mg of sodium borohydrure at 97%. 275mg of raw product is obtained that is purified by crystallisation in acetone to obtain 170mg of pure expected product.

F=128°C

Rf (CH_2Cl_2/MeOH/NH_4OH 90/10/1): 0.25

RMN ($CDCl_3$) 300MHz

0.30(s)	CH_3 in 18
1.55(m)	N-CH_2-CH_2 of the ring
2.23; 2.41	N-CH_2 and Ph-CH_2 of the chain

2.36(m)	N-C<u>H</u>$_2$-CH$_2$ of the ring
3.68 (dd)	H17
3.95 (t)	H11
6.58 (d)	H2
6.79 (d)	H1
6.88	H aromatics

<u>EXAMPLE 12</u>: 4-chloro-11β-[4-[3-(1-diethylamino)propyl]phenyl]-estra-1.3.5(10)-trien-3.17β-diol

It is carried out as in example 7 but from 262mg of product obtained in example 5 and 42mg of sodium borohydrure at 97%. 231mg of raw product is obtained that is purified by chromatography to obtain 223mg of pure expected product.

Rf (CH_2Cl_2/MeOH/NH_4OH 90/10/1): 0.18

RMN ($CDCl_3$) 300MHz

0.30 (S)	CH_3 in 18
0.95 (t)	N-CH_2-C<u>H</u>$_3$
2.49(q)	N-C<u>H</u>$_2$-CH_3
3.69 (t)	H17
3.95 (t)	H11
6.57 (d)	H2
6.78 (d)	H1
6.91	H aromatics

<u>EXAMPLE 13</u>: 17α-methyl-11β-[4-[3-(1-piperidininyl)propyl]phenyl]-estra-1.3.5(10)-trien-3.17β-diol

1.2g of finely ground cerium chloride heptahydrate (CeC13, 7H20), is heated for 2 hours under reduced pressure, brought to ambient temperature under inert gas, 12ml of THF is added, it is stirred for 2 hours at ambient temperature then 1.9ml of an etherised solution of methyllithium is added at -68°C. After having stirred for 30mn at -72°C 300mg of the product of example 1 in solution in 3 ml of THF is added. The temperature is left to rise to room temperature, then the solution is filtered, washed, dried and evaporated under reduced pressure to obtain 325mg of raw product that is purified by

chromatography by eluting with the compound CH_2Cl_2/MeOH/NH_4OH 90/10/0.5.

Rf (CH_2Cl_2/MeOH/NH_4OH 90/10/0.5): 0.25

RMN ($CDCl_3$) 300MHz

0.45 (s)	CH_3 in 18
1.29	CH_3 in 17
4.00 (tl)	H11
6.35 (dd)	H2
6.49 (d)	H4
6.79 (d)	H1
~6.81 and ~6.98	H aromatics

EXAMPLE 14: 4-chloro-17α-methyl-11β-[4-[3-(1-piperidininyl)propyl]phenyl]-estra-1.3.5(10)-trien-3.17β-diol

It is carried out as in example 13 but from 300mg of the product prepared in example 4 and 12ml of an etherised solution of methyllithium. 312mg of raw product is obtained that is purified by chromatography by eluting with the compound CH_2Cl_2/MeOH/NH_4OH 90/10/1 to obtain 275mg of pure expected product

Rf (CH_2Cl_2/MeOH/NH_4OH 90/10/1): 0.25

RMN ($CDCl_3$) 300MHz

0.45 (s)	CH_3 in 18
1.29 (s)	CH_3 in 17
1.56 (m)	N-CH_2-CH_2 (ring)
2.34 (m)	N-CH_2-CH_2 (ring)
2.26 (m) and 2.46 (t)	CH_2-N and CH_2-Ph (chain)
3.99 (tl)	H11
6.59 (d, J=8, 5Hz)	H2
6.8 (d)	H1
~6.87	H aromatics

EXAMPLE 15: 11β-[4-[3-(1-piperidininyl)propyl]phenyl]-17α-(trifluoromethyl)-estra-1.3.5(10)-trien-3.17β-diol

1) Preparation of the 17β-trimethylsilyloxy, 17α-trifluormethyl.

83mg of tetrahydrated tetramethylammonium fluoride is dried for 2 hours at 120°C, brought to ambient temperature under inert gas and 236mg of the product of example 1, 3ml of THF, and 0.3ml of trimethyl (trifluoromethyl) silane (CF_3SiMe_3) is added whilst maintaining the temperature at 0-5°C. The temperature is left to rise to 10°C and it is stirred for 2 hours 30 at 0-5°C, then it is poured into salt water, drawn off, washed, dried and evaporated under reduced pressure to obtain 340mg of raw product.

2) Deprotection of the alcohol.

To a solution of 340mg of previously obtained raw product in 4ml of THF, under inert atmosphere and at room temperature, 2ml of terabutylammonium fluoride in solution 1M in the THF is added, stirred for 2 hours at room temperature, poured into water, drawn off, washed, dried and evaporated under reduced pressure until 530mg of raw product is obtained that is purified by chromatography by eluting with the compound CH_2Cl_2/MeOH/NH_4OH 90/10/1 then with the compound AcOEt/TEA 95/5. 96mg of pure expected product is obtained.

Rf (AcOEt/TEA 95/5): 0.25

RMN ($CDCl_3$) 300MHz

0.50(s)	CH_3 in 18
4.03 (tl)	H11
6.36 (dd)	H2
6.52 (dd)	H4
6.78 (d)	H1
~6.85 and ~6.96	H aromatics

EXAMPLE 16: (17R) 11β-[4-[3-(dimethylamino)propyl) phenyl]-spiro-(estra-1.3,5(10)-trien-17.2'(5'H)-furan)-3-ol

It is carried out as in example 1 but from dimethylamine and 11β-[4-[3-hydroxypropyl)phenyl]-spiro-estra-4.9-diene-17,2'(5'H)-furan)-3-one.

EXAMPLE 17: (17R) 4', 5' dihydro-11β-[4-[3-(dimethylamino)propyl) phenyl]-spiro-(estra-1.3,5(10)-trien-17.2'(3'H)-furan)-3-ol

The reduction is carried out by hydrogenation of the product of example 16 with palladium at 10% on carbon.

Rf (AcOEt/TEA 8/2): 0.25

RMN ($CDCl_3$) 300MHz

0.46 (s)	CH_3 in 18
2.20 (s)	N-$C\underline{H_3}$
3.76 (m)	H'3
3.98 (m)	H11
6.32 (dd)	H2
6.47 (d)	H4
6.78 (d)	H1
~6.83~6.97	H aromatics

Pharmacological tests

1– Effect on the proliferation of mammary cells

The proliferative activity of the molecules is studied comparatively with that of oestradiol on the human mammary cells MCF-7 in culture.

To highlight the agonist effect of oestradiol and/or the molecules tested, the culture medium for the maintenance of the cells (rich in growth factors and in steroids) is replaced by a more impoverished medium, amongst others lacking in steroids (DMEM supplemented by 5% of serum with steroid removed and without phenol red). The cells undergo this deprivation two days before the start of the trial.

After 7 days of culture in the presence of the products to be studied, the cellular proliferation is evaluated by quantitive analysis of the DNA. In each trial, the effect of the oestradiol at 10^{-10}M (cellular growth in the presence of oestradiol less cellular growth in the presence of solvent) determines the agonist activity at 100%. The activity of the molecules is evaluated in comparison to this internal control. The molecules inducing a cellular growth identical to that observed with the solvent alone are classed "inactivated", those inducing cellular growth lower than that observed with the solvent are classed "inhibitor".

	ACTIVITY
Oestradiol	Agonist
Example 12	Inhibitor
Example 7	Inhibitor
Example 9	Inhibitor
Example 13	Inhibitor
Example 11	Mixed

*Mixed: slight agonist activity in very weak concentrations and inhibitory activity in stronger concentrations.

Conclusion:

The products tested are not agonist of the growth of MCF-7 cells, certain ones are even inhibitors of these.

2- Affinity of the human oestrogen receptor (REH)

A cytosolic extract of SF9 cells containing the recombinant human oestrogen receptor is obtained by over-expression in an insect-Baculo-viros system of cells, according to the general methodology described by N.R. WEBB et al. (Journal of Methods in cell and Molecular Biology, (1990) vol 2 n°4, 173-188) and whose application is described for the expression of human hormonal receptors, for example the human glucocorticoid receptor (G.SRINIVASAN et al. Molecular Endocrinology (1990) vol 4 n°2 209-216).

The BaculoGold Transfection Kit (PharMingen, reference 21000K) is used to generate the recombinant baculovirus containing the fragment of DNAc described in the expression vector HEGO by L. TORA et al. (The EMBO Journal (1989) vol 8 n°7 1981-1986) comprising the coding region for the human oestrogen receptor of wild type with glycine in position 400.

The recombinant virus obtained in this way is used to express the progestogen receptor in the cells of insects SF9 (ATCC CRL1711), according to the known methodology previously cited.

2×10^7 SF9 cells are cultivated in a 175 cm^2 "Falcon" flask in TNM-FH "SIGMA" medium supplemented with 10% of foetal calf serum (FCS) and 50 micrograms/ml of gentamycine. After infection then incubation at 27°C for 40

to 42 hours, the cells are lysed in 1ml of lyse buffer (Tris 20 mM-HCl pH8, EDTA 0.5 mM, DTT 2mM, Glycerol 20%, KCl 400mM) by a freezing-defrosting cycle that is repeated twice more. The supernatant, containing the recombinant human oestrogen receptor is preserved in liquid nitrogen in 0.5ml amounts.

The supernatant is incubated at 0°C for 24 hours with a consistent concentration (T) of oestradiol tritiated in the presence of growing concentrations either of cold oestradiol (0-1000 x 10^{-9}M), or of cold product to be tested (0 – 25000 x 10^{-9}M). The concentration of linked triated oestradiol (B) is then measured in each incubation by the dextran carbon adsorption technique.

3- Calculation of the affinity relative to linking (ARL)

The 2 following curves are plotted: the percentage of 100xB/BO linked tritiated hormone in comparison to the logarithm of the concentration of cold reference hormone or in comparison to the logarithm of the concentration of cold product tested.

The soundness of the following equation is determined:

$I_{50} = 100\ (B_0/B_0+Bmin/B_0)/2 = 100\ (1+Bmin/B_0) = 50\ (1+Bmin/B_0)$

B_0 = Concentration of the linked tritiated hormone in the absence of any cold product,

B = Concentration of the linked tritiated hormone in the presence of an X concentration of cold product,

Bmin = Concentration of linked tritiated hormone for an incubation of this tritiated hormone in concentration (T) in the presence of a large excess of cold reference hormone ($1000x10^{-9}$) for human receptor.

The intersections of the right angle I_{50} and the curves, make it possible to evaluate the concentration of cold reference hormone (CH) and the tested cold product (CX) which inhibit 50% of the bond of the tritiated hormone on the receptor.

The relative affinity of the link (ARL) of the tested product is determined by the equation:

ARL = 100 (CH)/(CX)

The obtained results are the following:

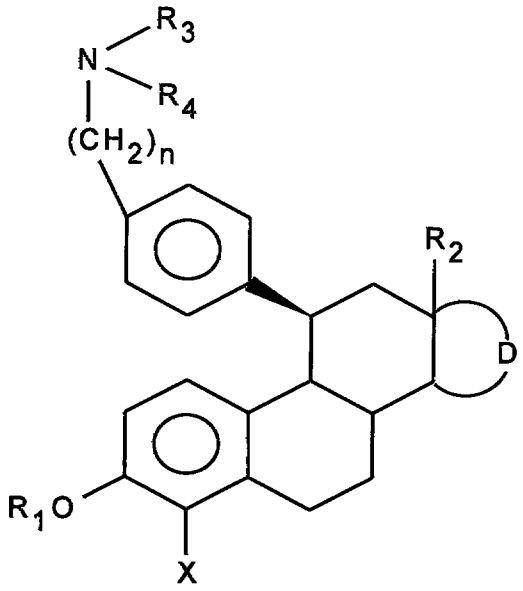
EXAMPLES	EH oestradiol =100 24H
12	28
7	59
9	28
13	42
11	14

Conclusion:

The tested products present good affinities for the human oestrogen receptor.

CLAIMS

1) Compounds of general formula (I):



(I)

in which:

R_1 represents a hydrogen atom, a $(CH_2)_m$-Ar, (CO)-Ar, $(CH_2)_m$-Alk or (CO)-Alk radical,

R_2 represents a radical derived from a, linear or branched, saturated or unsaturated hydrocarbure containing from 1 to 6 carbon atoms

D represents the residue of a pentagonal or hexagonal ring optionally substituted and optionally unsaturated,

X represents a halogen atom or a hydrogen atom, n is equal to 3, 4 or 5,

either identical or different R_3 and R_4 represent a hydrogen atom, a $(CH_2)_m$-Ar, $(CH_2)_m$-Het or $(CH_2)_m$-Alk group,

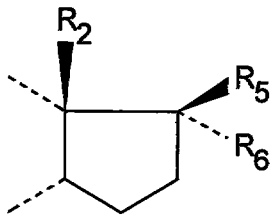
or R_3 and R_4 together with the nitrogen atom to which they are linked form a mono or polyclic, saturated or unsaturated, aromatic or non aromatic heterocycle, with 3 to 15 bonds optionally containing from 1 to 3 additional heteroatoms chosen from amongst non substituted or substituted oxygen, sulphur and nitrogen,

Ar represents a carbocyclic aryl group containing from 6 to 18 carbon atoms,

Het represents an aromatic or non aromatic, saturated or unsaturated

heterocycle comprising from 1 to 9 carbon atoms and from 1 to 5 heteroatoms chosen from amongst the atoms of oxygen, nitrogen or sulphur, Alk represents a radical derived from a non aromatic, linear, branched or cyclic, saturated or unsaturated hydrocarbure and comprising from 1 to 12 carbon atoms, the Ar radicals, Het or Alk able to be substituted or non substituted, m represents 0, 1, 2 or 3, as well as their addition salts with the bases or the acids.

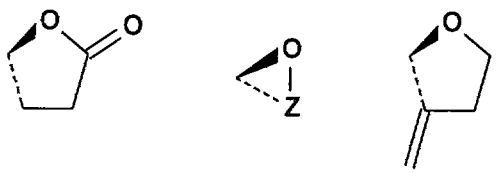
2) Compounds of general formula (I) as is described in claim 1, in which D represents the residue of a pentagonal ring of formula:



in which, R_2 retains the same signification as in claim 1,

either R_5 represents an OH, O-$(CH_2)_m$-Alk, O-(CO)-Alk, O-$(CH_2)_m$-Ar or O-(CO)-Ar, O-$(CH_2)_m$-Het, O-(CO)-Het, O-(CO)-Het and R_6 represent a hydrogen atom, an alkyl, alkenyl or alkynyl radical containing from 1 to 6 substituted or non substituted carbon atoms, m, Alk, Ar and Het being as they are described in claim 1,

or R_5 and R_6 together with the carbon atom that carries them form one of the following rings:

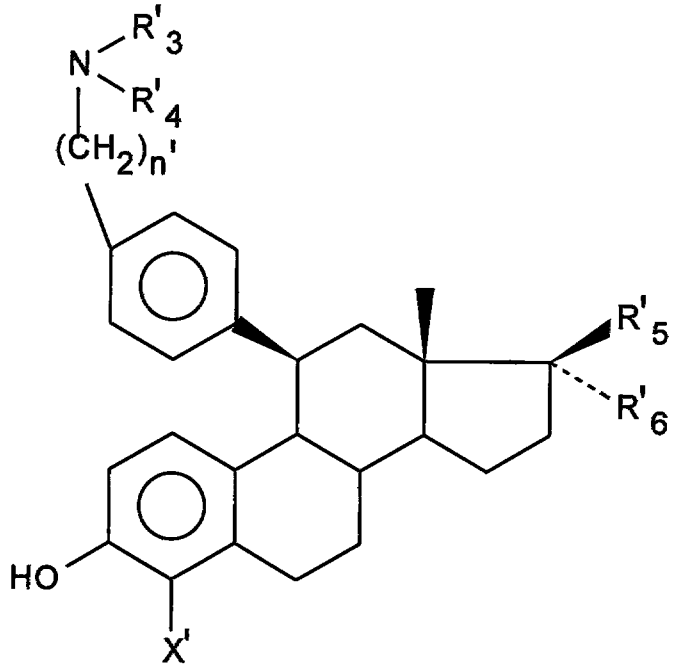


in which Z represents a -$(CH_2)_1$- or -CH=CH-$(CH_2)_{1'}$ group, 1 being an integer between 1 and 4 and 1' being an integer equal to 1 or 2,

* C L M S *

or R_5 and R_6 together form an oxo group, as well as their addition salts with the acids or the bases.

3) Compounds of general formula (I) as described in claim 1 or 2, corresponding to the general formula (I'):



(I')

in which:

X represents a chlorine, bromine or hydrogen atom, n' is equal to 3,

either identical or different R'_3 and R'_4 represent an alkyl radical containing from 1 to 6 carbon atoms

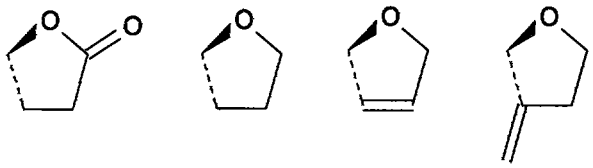
or R'_3 and R'_4 together form, with the nitrogen atom to which they are linked, a saturated mono or polyclic residue with 3 to 15 bonds optionally containing an additional heteroatom chosen from amongst oxygen, sulphur and nitrogen,

R'_5 and R'_6 have the same meaning as R_5 and R_6, according to claim 2 as well as their addition salts with the acids and the bases.

4) Compounds of general formula (I') as described in claim 3, in which:

either R'_5 represents an OH radical and R'_6 represents a hydrogen atom, an alkyl, alkenyl or alkynyl radical containing from 1 to 6 carbon atoms, substituted or non substituted,

* C L M S *



or R'_5 and R'_6 together form an oxo group, as well as their addition salts with the acids or the bases.

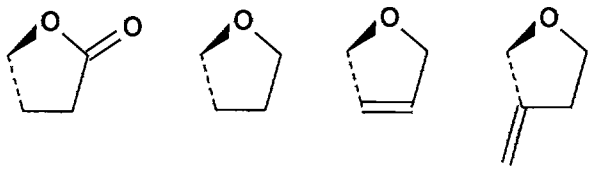
6) Compounds of general formula (I) as they are described in any of the claims 1 to 5, in which X is a hydrogen atom.

7) Compounds of general formula (I) as they are described in any of the claims 1 to 5, in which X is a chlorine atom.

8) Compounds of formula (I) or (I') as they are described in any of the claims 1 to 7, the names of which follow:

3-hydroxy-11β-[4-[3-(1-piperidinyl)propyl]phenyl]-estra-1.3.5(10)-trien-17-one,
3-hydroxy-11β-[4-[3-(1-pyrrolidinyl)propyl]phenyl]-estra-1.3.5(10)-trien-17-one,
3-hydroxy-11β-[4-[3-dimethylamino)propyl]phenyl]-estra-1.3.5(10)-trien-17-one,
4-chloro-3-hydroxy-11β-[4-[3-(1-piperidinyl)propyl]phenyl]-estra-1.3.5(10)-trien-17-one
4-chloro-3-hydroxy-11β-[4-[3-(1-pyrrolidinyl)propyl]phenyl]-estra-1.3.5(10)-trien-17-one
4-chloro-3-hydroxy-11β-[4-[3-(diethylamino)propyl]phenyl]-estra-1.3.5(10)-trien-17-one
11β-[4-[3-(1-pyrrolidinyl)propyl]phenyl]-estra-1.3.5(10)-trien-3.17β-diol,
11β-[4-(3-dimethylamino)propyl)phenyl]-estra-1.3.5(10)-trien-3.17β-diol
11β-[4-(1-piperidinyl)propyl)phenyl]-estra-1.3.5(10)-trien-3.17β-diol
4-chloro-11β-[4-[3-(1-pyrrolidinyl)propyl]phenyl]-estra-1.3.5(10)-trien-3.17β-diol
4-chloro-11β-[4-[3-(1-piperidinyl)propyl]phenyl]-estra-1.3.5(10)-trien-3.17β-diol
4-chloro-11β-[4-[3-(diethylamino)propyl]phenyl]-estra-1.3.5(10)-trien-3.17β-diol
17α-methyl-11β-[4-[3-(1-piperidinyl)propyl]phenyl]-estra-1.3.5(10)-trien-3.17β-diol,

or R'_5 and R'_6 together with the carbon atom that carries them form one of the following rings:



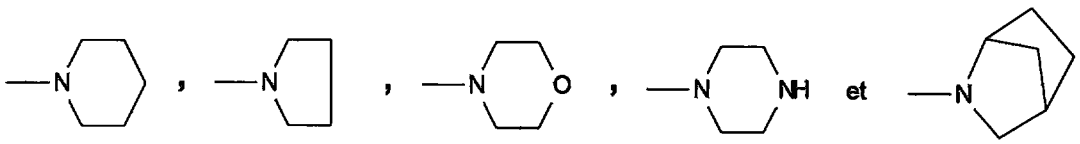
or R'_5 and R'_6 together form an oxo group, as well as their addition salts with the acids or the bases.

5) Compounds of general formula (I') as they are described in claim 3 or 4, in which:

X' represents a chlorine or hydrogen atom,

either identical or different R'_3 and R'_4 represent an alkyl radical containing from 1 to 6 carbon atoms,

or R'_3 and R'_4 together with the nitrogen atom form the following saturated heterocycles:



and either R'_5 represents an OH radical and R'_6 represents a hydrogen atom, an alkyl, alkenyl or alkynyl radical containing from 1 to 6 carbon atoms, substituted or non substituted,

or R'_5 and R'_6 together with the carbon atom that carries them form one of the following rings:

* C L M S *

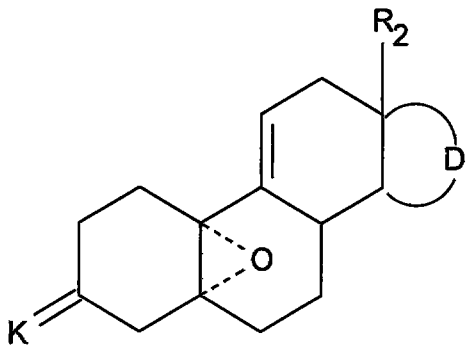
4-chloro-17α-methyl-11β-[4-[3-(1-piperidinyl)propyl]phenyl]-estra-1.3.5(10)-trien-3.17β-diol,

11β-[4-[3-(1-piperidinyl)propyl]phenyl]-17α-(trifluoromethyl)-estra-1.3.5(10)-trien-3.17β-diol

(17R) 11β-[4-[3-(dimethylamino)propyl]phenyl]-spiro-(estra-1.3.5(10)-trien-17.2'(5'H)-furan)-3-ol

(17R) 4',5'-dihydro-11β-[4-[3-(dimethylamino)propyl] phenyl]-spiro-(estra-1.3.5(10)-trien-17.2'(3'H)-furan)-3-ol.

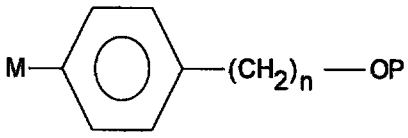
9) Preparation process of the compounds of formula (I) as described in claim 1, in which a compound of formula (II) is submitted:



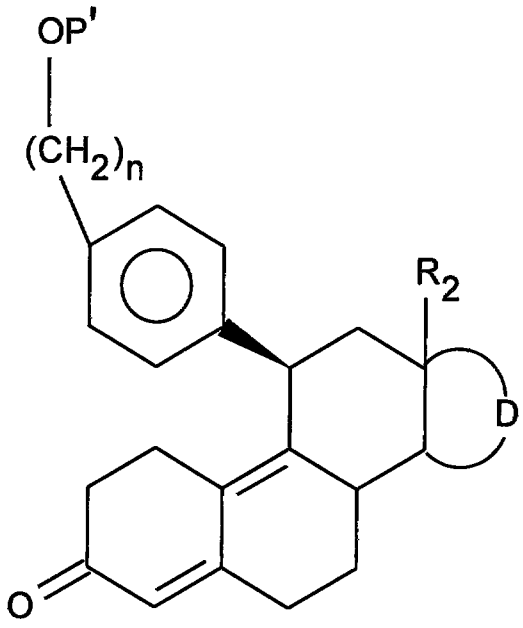
(II)

in which D and R_2 are as described in claim 1 and K represents a protector group of the 3-ceto function, successive to the following reactions:

a) action of a compound of formula (III):



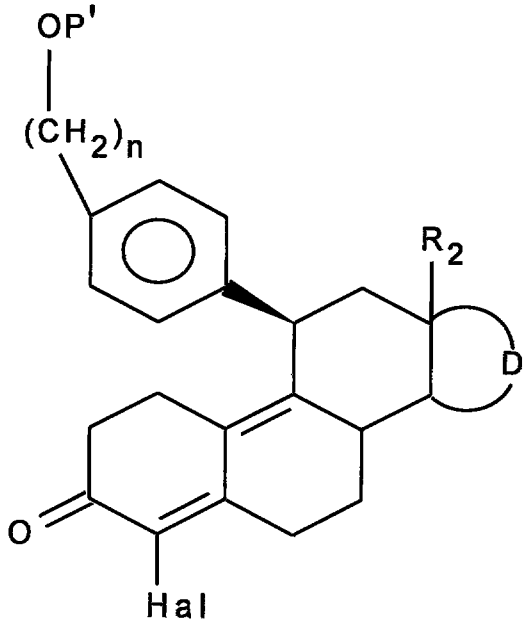
in which, M represents a metallic derivative, P represents a protector group, alcohol and n is an integer equal to 3, 4, or 5, then if need be deprotection of one or several protected reactive functions, in order to obtain a compound of formula (III_a):



(III_a)

P' having the same values as P as well as hydrogen,

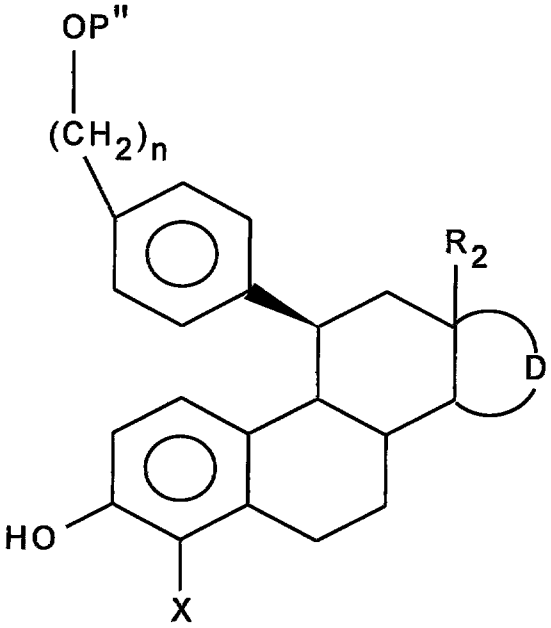
b) action if need be, of a halogenation reagent, in order to obtain a formula (III_b) compound:



(III_b)

Hal represents a halogen atom,

c) action of an aromatisation reagent of ring (A) on the compounds of formulas (III_a) and (III_b), after having, if need be, protected and/or activated the OH function, then action of a base to obtain the compound of formula (IV):

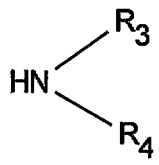


(IV)

P" having the same values as P' and able to represent moreover an activating group,

X as described in claim 1,

d) action of an amine of formula (V):



(V)

R_3 and R_4 are as described in claim 1, this compound optionally being in the form of a salt, in order to obtain certain compounds of formula (I), the compounds of formulas (III_a), (III_b), (IV) and (I) being submitted if desired or

* C L M S *

necessary, in an appropriate order, to one or several of the following reactions:

-protection/deprotection of the OH group(s),

-alkylation/acylation of the OH group(s),

-action of a reduction agent when D represents the residue of a pentagonal ring as described in claim 2 and R_5 and R_6 together form an oxo group,

-action of an organometallic or CF_3SiMe_3 on the compounds of formula (IV) or (I) with D representing the residue of a pentagonal ring as described in claim 2 and R_5 and R_6 together form an oxo group,

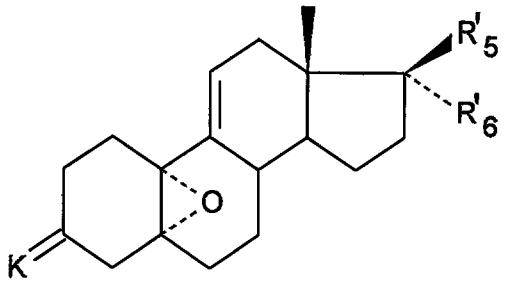
-action of a lactonisation agent on the compounds of formula (IV) or (I) with D representing the residue of a pentagonal ring as described in claim 2 and R_5 and R_6 together forming an oxo group,

-action of a reduction agent of the double bond, when D represents the residue of a pentagonal ring as described in claim 2 and R_5 and R_6 together with the carbon that carries them, form a O-$(CH_2)_1$'-CH=CH- group,

-action of a reduction agent of the double bond, when D represents the residue of a pentagonal ring as described in claim 2, and R_6 is an alkenyl or alkynyl radical containing from 2 to 6 carbon atoms,

-salification.

10) Preparation process according to claim 9, compounds of general formula (I') as described in claim 3, in which a compound of formula (II') is submitted:

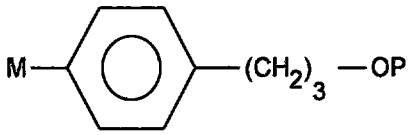


(II')

* C L M S *

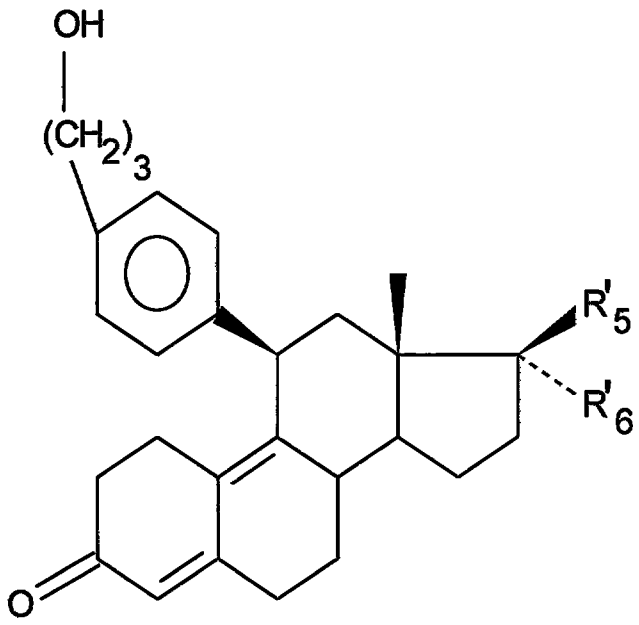
in which K, R'_5 and R'_6 are as described in claim 3, or in which R'_5 is a CN radical and R'_6 is a protected hydroxyl, successive to the following reactions:

a) action of a formula (III') compound:



(III')

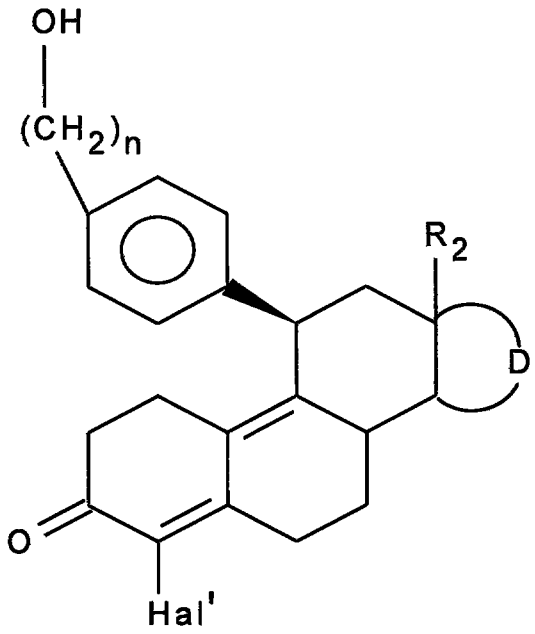
in which M and P are as previously described, then deprotection of one or several protected reactive functions, in order to obtain a compound of formula (III'_a):



(III'_a)

b) action, if need be, of a halogenation reagent in order to obtain a formula (III'_b) compound:

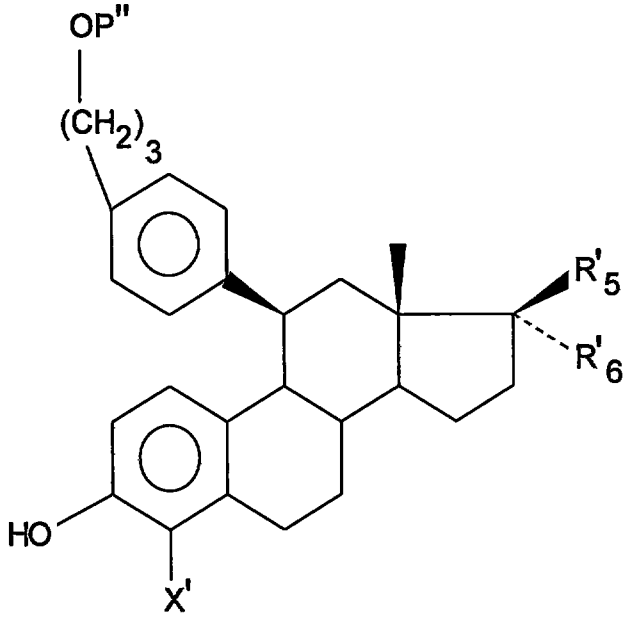
* C L M S *



(III'b)

Hal' representing a chlorine or bromine atom,

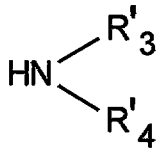
c) activation of the OH function then action of an aromatisation reagent of ring (A) on the compounds of formula (III_a) or (III_b), then action of a base to obtain the compounds of formula (IV'):



(IV')

X' and P" are as described in claim 9,

d) action of a formula (V') amine:



(V')

R'_3 and R'_4 are as previously described in order to obtain certain of the compounds of formula (I'), the compounds of formulas (III'_a), (III_b), (IV) (I) and (I') being submitted, if desired or if necessary to one or several of the following reactions:

-protection/deprotection of the OH group(s),

-alkylation/acylation of the OH group(s),

-action of a reduction agent when R'_5 and R'_6 together form an oxo group,

-action of an organometallic or CF_3SiMe_3 on the compounds of formula (IV') or (I') with R'_5 and R'_6 together forming an oxo group,

-action of a lactonisation agent on the compounds of formula (IV') or (I') with R'_5 and R'_6 together forming an oxo group,

-action of a reduction agent of the double bond, when R'_5 and R'_6 together with the carbon that carries them, form an $O-(CH_2)_{1'}-CH=CH-$ group,

-action of a reduction agent of the double bond, when R'_6 is an alkenyl or alkynyl radical containing from 2 to 6 carbon atoms,

-salification.

11)As medicines the compounds of formula (I) as described in claim 1, as well as their addition salts with pharmaceutically acceptable acids or the bases.

12) As medicines the compounds of formula (I) or (I') as it is described in any of the claims 2 to 7, as well as their addition salts with pharmaceutically acceptable acids or bases.

13) As medicines the compounds as they are described in claim 8 as well as their addition salts with pharmaceutically acceptable acids.

* C L M S *

14) Pharmaceutical compositions containing one or several of the medicines as described in any of the claims 11, 12 or 13.

15) As novel intermediate products, the compounds of general formulas (III_a), (III_b), (III'_a), (III'_b),(IV) or (IV') as they are described in claims 9 or 10.

* C L M S *

WORLD ORGANISATION OF INTELLECTUAL PROPERTY
International office

PCT

INTERNATIONAL APPLICATION PUBLISHED PURSUANT TO THE PATENTS COOPERATION TREATY

(51) International patent classification[6]: **C07J 41/00, A61K 31/565, C07J 43/00, A61K 31/58, C07J 31/00**	**A1**	(11) International publication number: **WO 99/25725** (43) International publication date: 27 May 1999 (27.05.99)

(21) International application number: PCT/FR98/02437

(22) Date of international filing: 16 November 1998 (16.11.98)

(30) Priority data:
97/14357 17 November 1997 (17.11.97) FR

(71) Applicant (*for all designated States except US*): HOECHST MARION ROUSSEL [FR/FR]; 1, terrasse Bellini, F-92800 Puteaux (FR)

(72) Inventors, and
(75) Inventors/Applicants (*US only*): NIQUE, François {FR/FR]; 1 bis, rue du Bac, F-94170 Le Perreux sur Marne (FR)

(74) Agent: VIEILLEFOSSE, Jean Claude; Hoechst Marion Roussel, 102, route de Noisy, F-93235 Romainville Cedex (FR)

(81) Designated States: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GD, GE, HR, HU, ID, IL, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, Patent ARIPO (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian Patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM,) European Patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), Patent OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: NOVEL 19-NOR STERIODS SUBSTITUTED IN POSITION 11β, PREPARATION METHOD AND INTERMEDIATES, APPLICATION AS MEDICINES AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

(57) Abstract:
The invention concerns compounds of formula (I) in which: X is a halogen atom; D represents the radical of a pentagonal or hexagonal cycle optionally substituted and optionally unsaturated; R1, R2, R3, R4, X and n are as defined in the description. The invention also concerns the preparation method and intermediate, their application as medicine and the pharmaceutical compositions containing them.