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(54) Title: MEIOSIS REGULATING COMPOUNDS

(57) Abstract

Certain sterol derivatives, structurally related to natural compounds which can be extracted i.e. from bull testes and from human follicular fluid, can be used for regulating the meiosis in oocytes and in male germ cells.

MEIOSIS REGULATING COMPOUNDS

FIELD OF THE INVENTION

The present invention relates to pharmacologically active compounds and to their use as medicaments. More particularly it has been found that the sterol derivatives of the invention can be used for regulating the meiosis.

BACKGROUND OF THE INVENTION

Meiosis is the unique and ultimate event of germ cells on which sexual reproduction is based. Meiosis comprises two meiotic divisions. During the first division, exchange between maternal and paternal genes take place before the pairs of chromosomes are separated into the two daughter cells. These contain only half the number (1n) of chromosomes and 2c DNA. The second meiotic division proceeds without a DNA synthesis. This division therefore results in the formation of the haploid germ cells with only 1c DNA.

The meiotic events are similar in the male and female germ cells, but the time schedule and the differentiation processes which lead to ova and to spermatozoa differ profoundly. All female germ cells enter the prophase of the first meiotic division early in life, often before birth, but all are arrested as oocytes later in the prophase (dictyate state) until ovulation after puberty. Thus, from early life the female has a stock of oocytes which is drawn upon until the stock is exhausted. Meiosis in females is not completed until after fertilization, and results in only one ovum and two abortive polar bodies per germ cell. In contrast, only some of the male germ cells enter meiosis from puberty and leave a stem population of germ cells throughout life. Once initiated, meiosis in the male cell proceeds without significant delay and produces 4 spermatozoa.

Only little is known about the mechanisms which control the initiation of meiosis in the male and in the female. In the oocyte, new studies indicate that follicular purines, hypoxanthine or adenosine, could be responsible for meiotic arrest (Downs, SM *et al. Dev Biol* 82 (1985) 454-458; Eppig, JJ *et al. Dev Biol* 119 (1986) 313-321; and Downs, SM *Mol Reprod Dev* 35 (1993) 82-94). The presence of a diffusible meiosis regulating substance was first described by Byskov et al. in a culture system of fetal mouse gonads (Byskov, AG *et al. Dev Biol* 52 (1976) 193-200). A meiosis activating substance (MAS) was secreted by the fetal mouse ovary in which meiosis was ongoing, and a meiosis preventing substance (MPS) was released from the morphologically differentiated testis with resting, non-meiotic germ cells. It was suggested that the relative concentrations of MAS and MPS regulated the beginning, arrest and resumption of meiosis in the male and in the female germ cells (Byskov, AG *et al.* in *The Physiology of Reproduction* (eds. Knobil, E and Neill, JD, Raven Press, New York (1994)). Clearly, if meiosis can be regulated, reproduction can be controlled. A recent article (Byskov, AG *et al. Nature* 374 (1995) 559-562) describes the isolation from bull testes and from human follicular fluid of certain sterols that activate oocyte meiosis. Unfortunately, these sterols are rather labile and utilization of the interesting finding would thus be greatly facilitated if more stable meiosis activating compounds were available.

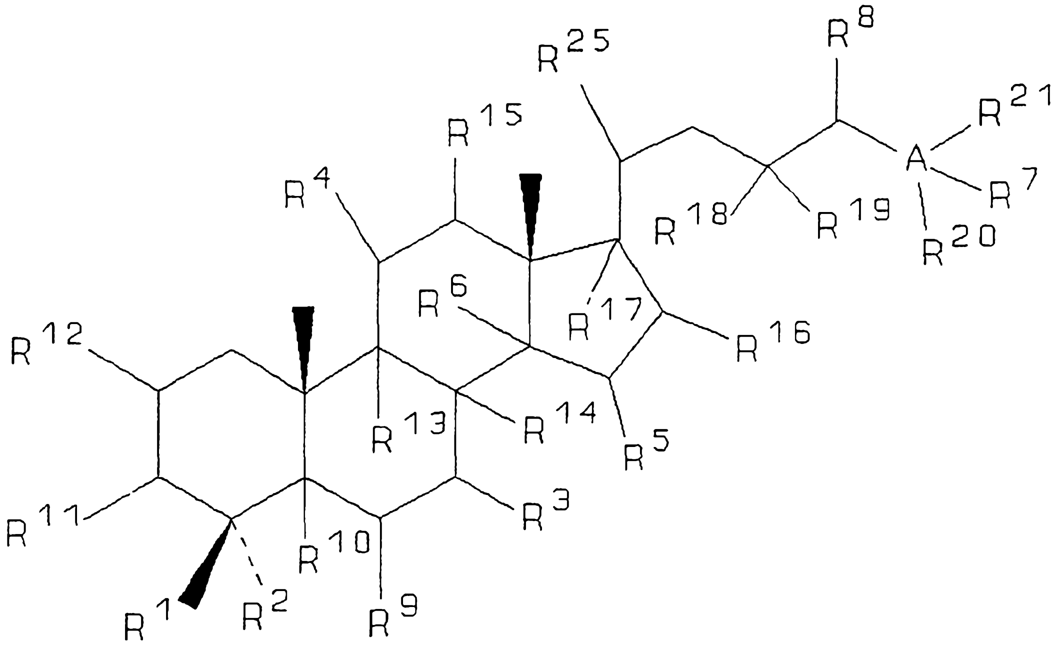
SUMMARY OF THE INVENTION

It is a purpose of the present invention to provide compounds and methods useful for relieving infertility in females and males, particularly in mammals, more particularly in humans.

It is a further purpose of the present invention to provide compounds and methods useful as contraceptives in females and males, particularly in mammals, more particularly in humans.

According to the present invention there are provided novel, stable compounds with interesting pharmacological properties. In particular, the compounds of the invention are useful for regulating the meiosis in oocytes and in male germ cells.

In its broadest aspect, the present invention relates to compounds of the general formula (I)



(I)

wherein R^1 and R^2, independently, are selected from the group comprising hydrogen and branched or unbranched C_1-C_6 alkyl which may be substituted by halogen, hydroxy or cyano, or wherein R^1 and R^2 together designate methylene or, together with the carbon atom to which they are bound, form a cyclopropane ring, a cyclopentane ring, or a cyclohexane ring; R^3 is selected from the group comprising hydrogen, methylene, hydroxy, methoxy, acetoxy, oxo, $=NOR^{26}$ wherein R^{26} is hydrogen or C_1-C_3 alkyl, halogen, and hydroxy and C_1-C_4 alkyl bound to the same carbon atom of the sterol skeleton, or R^3 designates, together with R^9 or R^{14}, an additional bond between the carbon atoms to which R^3 and R^9 or R^{14} are bound; R^4 is selected from the group comprising hydrogen, methylene, hydroxy, methoxy, acetoxy, oxo, $=NOR^{27}$ wherein R^{27} is hydrogen or C_1-C_3 alkyl, halogen, and hydroxy and C_1-C_4 alkyl bound to the same carbon atom of the sterol skeleton, or R^4 designates, together with R^{13} or R^{15}, an additional bond between the carbon atoms to which R^4 and R^{13} or R^{15} are bound; R^5 is selected from the group comprising hydrogen, C_1-C_4 alkyl, methylene, hydroxy, methoxy, oxo, and $=NOR^{22}$ wherein R^{22} is hydrogen or C_1-C_3 alkyl, or R^5 designates, together with R^6, an additional bond between the carbon atoms to which R^5 and R^6 are bound; R^6 is hydrogen or R^6 designates, together with R^5, an additional bond between the carbon atoms to which R^5 and R^6 are bound; R^9 is hydrogen or R^9 designates, together with R^3 or R^{10}, an additional bond between the carbon atoms to which R^9 and R^3 or R^{10} are bound; R^{10} is hydrogen or R^{10} designates, together with R^9, an additional bond between the carbon atoms to which R^{10} and R^9 are bound; R^{11} is selected from the group comprising hydroxy, alkoxy, substituted alkoxy, acyloxy, sulphonyloxy, phosphonyloxy, oxo, $=NOR^{28}$ wherein R^{28} is hydrogen or C_1-C_3 alkyl, halogen and hydroxy and C_1-C_4 alkyl bound to the same carbon atom of the sterol skeleton, or R^{11} designates, together with R^{12}, an additional bond between the carbon atoms to which R^{11} and R^{12} are bound; R^{12} is selected from the group comprising hydrogen, C_1-C_3 alkyl, vinyl, C_1-C_3 alkoxy and halogen, or R^{12} designates, together with R^{11}, an additional bond between the carbon atoms to which R^{12} and R^{11} are bound; R^{13} is hydrogen or R^{13} designates, together with R^4 or R^{14}, an additional bond between the carbon atoms to which R^{13} and R^4 or R^{14} are bound; R^{14} is hydrogen or R^{14} designates, together with R^3, R^6 or R^{13}, an additional bond between the carbon atoms to which R^{14} and R^3 or R^6 or R^{13} are bound; R^{15} is selected from the group comprising hydrogen, C_1-C_4 alkyl, methylene, hydroxy, methoxy, acetoxy, oxo, and $=NOR^{23}$ wherein R^{23} is hydrogen or C_1-C_3 alkyl, or R^{15} designates, together with R^4, an additional bond between the carbon atoms to which R^{15} and R^4 are bound; R^{16} is selected from the group comprising hydrogen, C_1-C_3 alkyl, methylene, hydroxy, methoxy, oxo and $=NOR^{24}$ wherein R^{24}

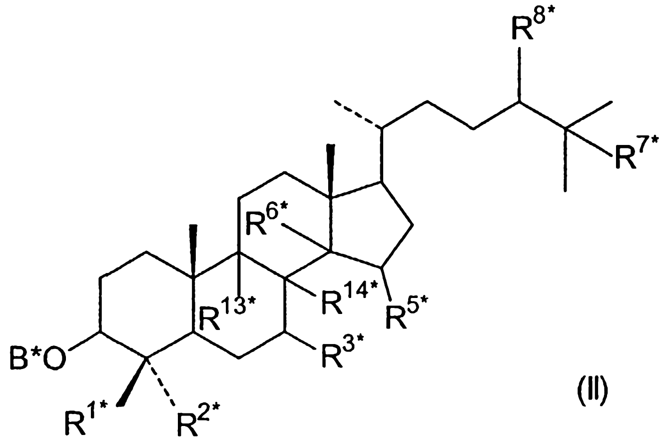
is hydrogen or C_1-C_3 alkyl, or R^{16} designates, together with R^{17}, an additional bond between the carbon atoms to which R^{16} and R^{17} are bound; R^{17} is hydrogen or R^{17} designates, together with R^{16}, an additional bond between the carbon atoms to which R^{17} and R^{16} are bound; R^{18} and R^{19} are independently hydrogen or fluoro; R^{25} is selected from the group comprising C_{1-4} alkyl, methylene, hydroxy and oxo; A is a carbon atom or a nitrogen atom; when A is a carbon atom, R^7 is selected from the group comprising hydrogen, hydroxy and fluoro, and R^8 is selected from the group comprising hydrogen, C_1-C_4 alkyl, methylene and halogen, or R^7 designates, together with R^8, an additional bond between the carbon atoms to which R^7 and R^8 are bound; R^{20} is selected from the group comprising C_1-C_4 alkyl, trifluoromethyl and C_3-C_6 cycloalkyl and R^{21} is selected from the group comprising C_1-C_4 alkyl, C_1-C_4 hydroxyalkyl, C_1-C_4 haloalkyl containing up to three halogen atoms, methoxymethyl, acetoxymethyl, and C_3-C_6 cycloalkyl, or R^{20} and R^{21}, together with the carbon atom to which they are bound, form a C_3-C_6 cycloalkyl ring; and when A is a nitrogen atom, R^7 designates a lone pair of electrons and R^8 is selected from the group comprising hydrogen, C_1-C_4 alkyl and oxo; R^{20} and R^{21} are, independently, C_1-C_4 alkyl or C_3-C_6 cycloalkyl; with the proviso that the compound of the general formula (I) does not have any cumulated double bonds and with the further proviso that the compound is not one of the following compounds:

Cholest-7-ene-3ß-ol;
4-Methylcholest-7-ene-3ß-ol;
4-Ethylcholest-7-ene-3ß-ol;
4,4-Dimethylcholest-7-ene-3ß-ol;
4α-Methyl-4ß-ethylcholest-7-ene-3ß-ol;
4α-Ethyl-4ß-methylcholest-7-ene-3ß-ol;
4,4-Diethylcholest-7-ene-3ß-ol;
4-Propylcholest-7-ene-3ß-ol;
4-Butylcholest-7-ene-3ß-ol;
4-Isobutylcholest-7-ene-3ß-ol;

4,4-Tetramethylenecholest-7-ene-3ß-ol;
4,4-Pentamethylenecholest-7-ene-3ß-ol;
Cholest-8-ene-3ß-ol;
4-Methylcholest-8-ene-3ß-ol;
4-Ethylcholest-8-ene-3ß-ol;
4,4-Dimethylcholest-8-ene-3ß-ol;
4α-Methyl-4ß-ethylcholest-8-ene-3ß-ol;
4α-Ethyl-4ß-methylcholest-8-ene-3ß-ol;
4,4-Diethylcholest-8-ene-3ß-ol;
4-Propylcholest-8-ene-3ß-ol;
4-Butylcholest-8-ene-3ß-ol;
4-Isobutylcholest-8-ene-3ß-ol;
4,4-Tetramethylenecholest-8-ene-3ß-ol;
4,4-Pentamethylenecholest-8-ene-3ß-ol;
Cholest-8(14)-ene-3ß-ol;
4-Methylcholest-8(14)-ene-3ß-ol;
4-Ethylcholest-8(14)-ene-3ß-ol;
4,4-Dimethylcholest-8(14)-ene-3-ol;
4α-Methyl-4ß-ethylcholest-8(14)-ene-3ß-ol;
4α-Ethyl-4ß-methylcholest-8(14)-ene-3ß-ol;
4,4-Diethylcholest-8(14)-ene-3ß-ol;
4-Propylcholest-8(14)-ene-3ß-ol;
4-Butylcholest-8(14)-ene-3ß-ol;
4-Isobutylcholest-8(14)-ene-3ß-ol;
4,4-Tetramethylenecholest-8(14)-ene-3ß-ol;
4,4-Pentamethylenecholest-8(14)-ene-3ß-ol;
Cholesta-8,14-diene-3ß-ol;
4-Methylcholesta-8,14-diene-3ß-ol;
4-Ethylcholesta-8,14-diene-3ß-ol;
4,4-Dimethylcholesta-8,14-diene-3ß-ol;
4α-Methyl-4ß-ethylcholesta-8,14-diene-3ß-ol;
4α-Ethyl-4ß-methylcholesta-8,14-diene-3ß-ol;
4,4-Diethylcholesta-8,14-diene-3ß-ol;
4-Propylcholesta-8,14-diene-3ß-ol;
4-Butylcholesta-8,14-diene-3ß-ol;
4-Isobutylcholesta-8,14-diene-3ß-ol;
4,4-Tetramethylenecholesta-8,14-diene-3ß-ol;

4,4-Pentamethylenecholesta-8,14-diene-3β-ol;
Cholesta-8,24-diene-3β-ol;
4-Methylcholesta-8,24-diene-3β-ol;
4-Ethylcholesta-8,24-diene-3β-ol;
4,4-Dimethylcholesta-8,24-diene-3β-ol;
4α-Methyl-4β-ethylcholesta-8,24-diene-3β-ol;
4α-Ethyl-4β-methylcholesta-8,24-diene-3β-ol;
4,4-Diethylcholesta-8,24-diene-3β-ol;
4-Propylcholesta-8,24-diene-3β-ol;
4-Butylcholesta-8,24-diene-3β-ol;
4-Isobutylcholesta-8,24-diene-3β-ol;
4,4-Tetramethylenecholesta-8,24-diene-3β-ol;
4,4-Pentamethylenecholesta-8,24-diene-3β-ol;
Cholesta-8,14,24-triene-3β-ol;
4-Methylcholesta-8,14,24-triene-3β-ol;
4-Ethylcholesta-8,14,24-triene-3β-ol;
4,4-Dimethylcholesta-8,14,24-triene-3β-ol;
4α-Methyl-4β-ethylcholesta-8,14,24-triene-3β-ol;
4α-Ethyl-4β-methylcholesta-8,14,24-triene-3β-ol;
4,4-Diethylcholesta-8,14,24-triene-3β-ol;
4-Propylcholesta-8,14,24-triene-3β-ol;
4-Butylcholesta-8,14,24-triene-3β-ol;
4-Isobutylcholesta-8,14,24-triene-3β-ol;
4,4-Tretramethylenecholesta-8,14,24-triene-3β-ol; and
4,4-Pentamethylenecholesta-8,14,24-triene-3β-ol;

and esters and ethers thereof. In a preferred embodiment, the present invention relates to compounds of the general formula (I) which are not compounds of the general formula (II).



(II)

wherein R^{1*} and R^{2*}, independently, are selected from the group comprising hydrogen, branched or unbranched C_1-C_6 alkyl which may be substituted by halogen or hydroxy or wherein R^{1*} and R^{2*}, together with the carbon atom to which they are bound, form a cyclopentane ring or a cyclohexane ring; R^{13*} and R^{14*} together designate an additional bond between the carbon atoms to which they are bound in which case R^{3*} is hydrogen and R^{6*} and R^{5*} are either hydrogen or together they designate an additional bond between the carbon atoms to which they are bound; or R^{3*} and R^{14*} together designate an additional bond between the carbon atoms to which they are bound in which case R^{13*} is hydrogen and R^{6*} and R^{5*} are either hydrogen or together they designate an additional bond between the carbon atoms to which they are bound; or R^{6*} and R^{14*} together designate an additional bond between the carbon atoms to which they are bound in which case R^{13*}, R^{3*} and R^{5*} are all hydrogen; R^{8*} and R^{7*} are hydrogen or together they designate an additional bond between the carbon atoms to which they are bound; and B^* is either hydrogen or an acyl group, including a sulphonyl group or a phosphonyl group, or a group which together with the remaining part of the molecule forms an ether.

In a preferred embodiment, the compound of formula (I) above is a compound wherein R^1 and R^2 are both hydrogen.

In another preferred embodiment, the compound of formula (I) above is a compound wherein one of R^1 and R^2 is hydrogen while the other is methyl.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^1 and R^2 are both methyl.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^1 is branched or unbranched C_1-C_6 alkyl, optionally substituted by halogen, hydroxy or cyano.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^2 is branched or unbranched C_1-C_6 alkyl, optionally substituted by halogen, hydroxy or cyano.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^1 and R^2 together designate methylene.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^1 and R^2, together with the carbon atom to which they are bound, form a cyclopropane ring.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^1 and R^2, together with the carbon atom to which they are bound, form a cyclopentane ring.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^1 and R^2, together with the carbon atom to which they are bound, form a cyclohexane ring.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^3 is hydrogen.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^3 is methylene.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^3 is hydroxy.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^3 is methoxy or acetoxy.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^3 is halogen.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^3 is oxo.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^3 is =NOH.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^3 is $=NOR^{26}$, wherein R^{26} is C_1-C_3 alkyl.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^3 is hydroxy and C_1-C_4 alkyl bound to the same carbon atom of the sterol skeleton.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^3, together with R^9, designates an additional bond between the carbon atoms to which R^3 and R^9 are bound.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^3, together with R^{14}, designates an additional bond between the carbon atoms to which R^3 and R^{14}

are bound.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^4 is hydrogen.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^4 is methylene.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^4 is hydroxy.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^4 is methoxy or acetoxy.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^4 is oxo.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^4 is =NOH.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^4 is $=NOR^{27}$, wherein R^{27} is C_1-C_3 alkyl.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^4 is hydroxy and C_1-C_4 alkyl bound to the same carbon atom of the sterol skeleton.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^4, together with R^{13}, designates an additional bond between the carbon atoms to which R^4 and R^{13} are bound.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^4, together with R^{15}, designates an additional bond between the carbon atoms to which R^4 and R^{15} are bound.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^5 is hydrogen.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^5 is C_1-C_4 alkyl.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^5 is methylene.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^5 is hydroxy.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^5 is methoxy.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^5 is oxo.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^5 is =NOH.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^5 is $=NOR^{22}$, wherein R^{22} is C_1-C_3 alkyl.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^5, together with R^6, designates an additional bond between the carbon atoms to which R^5 and R^6 are bound.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^6 is hydrogen.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^6, together with R^{14}, designates an additional bond between the carbon atoms to which R^6 and R^{14}

are bound.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^9 is hydrogen.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^9, together with R^{10}, designates an additional bond between the carbon atoms to which R^9 and R^{10} are bound.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{10} is hydrogen.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{11} is hydroxy.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{11} is alkoxy, aralkyloxy, alkoxyalkoxy or alkanoyloxyalkyl, each group comprising a total of up to 10 carbon atoms, preferably up to 8 carbon atoms.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{11} is C_1-C_4 alkoxy.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{11} is methoxy.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{11} is ethoxy.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{11} is CH_3OCH_2O-.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{11} is pivaloyloxymethoxy.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R11 is an acyloxy group derived from an acid having from 1 to 20 carbon atoms.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{11} is an acyloxy group selected from the group comprising acetoxy, benzoyloxy, pivaloyloxy, butyryloxy, nicotinoyloxy, isonicotinoyloxy, hemi succinoyloxy, hemi glutaroyloxy, butylcarbamoyloxy, phenylcarbamoyloxy, butoxycarbonyloxy, _tert_-butoxycarbonyloxy and ethoxycarbonyloxy.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{11} is sulphonyloxy.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{11} is phosphonyloxy.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{11} is oxo.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{11} is =NOH.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{11} is $=NOR^{28}$, wherein R^{28} is C_1-C_3 alkyl.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{11} is halogen.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{11} is hydroxy and C_1-C_4 alkyl bound to the same carbon atom of the sterol skeleton.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{11}, together with R^{12}, designates an additional bond between the carbon atoms to which R^{11} and

R^{12} are bound.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{12} is hydrogen.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{12} is C_1-C_3 alkyl.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{12} is C_1-C_3 alkoxy.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{12} is halogen.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{13} is hydrogen.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{13}, together with R^{14}, designates an additional bond between the carbon atoms to which R^{13} and R^{14} are bound.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{14} is hydrogen.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{15} is hydrogen.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{15} is C_1-C_4 alkyl.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{15} is methylene.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{15} is hydroxy.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{15} is methoxy or acetoxy.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{15} is oxo.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{15} is =NOH.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{15} is $=NOR^{23}$, wherein R^{23} is C_1-C_3 alkyl.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{16} is hydrogen.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{16} is C_1-C_3 alkyl.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{16} is methylene.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{16} is hydroxy.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{16} is methoxy.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{16} is oxo.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{16} is =NOH.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{16} is $=NOR^{24}$, wherein R^{24} is C_1-C_3 alkyl.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{16}, together with R^{17}, designates an additional bond between the carbon atoms to which R^{16} and R^{17} are bound.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{17} is hydrogen.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{17} is hydroxy.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{18} and R^{19} are both hydrogen.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{18} and R^{19} are both fluoro.

In another preferred embodiment, the compound of formula (I) above is a compound wherein one of R^{18} and R^{19} is fluoro and the other is hydrogen.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{25} is hydrogen.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{25} is C_1-C_4 alkyl.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{25} is methylene.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{25} is hydroxy.

In another preferred embodiment, the compound of formula (I) above is a compound wherein R^{25} is oxo.

In another preferred embodiment, the compound of formula (I) above is a compound wherein A is a carbon atom.

In another preferred embodiment, the compound of formula (I) above is a compound wherein A is a carbon atom and R^7 is hydrogen.

In another preferred embodiment, the compound of formula (I) above is a compound wherein A is a carbon atom R^7 is hydroxy.

In another preferred embodiment, the compound of formula (I) above is a compound wherein A is a carbon atom R^7 is fluoro.

In another preferred embodiment, the compound of formula (I) above is a compound wherein A is a carbon atom R^7, together with R^8, designates an additional bond between the carbon atoms to which R^7 and R^8 are bound.

In another preferred embodiment, the compound of formula (I) above is a compound wherein A is a carbon atom R^8 is hydrogen.

In another preferred embodiment, the compound of formula (I) above is a compound wherein A is a carbon atom R^8 is C_1-C_4 alkyl.

In another preferred embodiment, the compound of formula (I) above is a compound wherein A is a carbon atom R^8 is methylene.

In another preferred embodiment, the compound of formula (I) above is a compound wherein A is a carbon atom R^8 is halogen.

In another preferred embodiment, the compound of formula (I) above is a compound wherein A is a carbon atom R^{20} is C_1-C_4 alkyl.

In another preferred embodiment, the compound of formula (I) above is a compound wherein A is a carbon atom R^{20} is trifluoromethyl.

In another preferred embodiment, the compound of formula (I) above is a compound wherein A is a carbon atom R^{20} is C_3-C_6 cycloalkyl.

In another preferred embodiment, the compound of formula (I) above is a compound wherein A is a carbon atom R^{21} is C_1-C_4 alkyl.

In another preferred embodiment, the compound of formula (I) above is a compound wherein A is a carbon atom R^{21} is C_1-C_4 hydroxyalkyl.

In another preferred embodiment, the compound of formula (I) above is a compound wherein A is a carbon atom R^{21} is C_1-C_4 haloalkyl containing up to three halogen atoms.

In another preferred embodiment, the compound of formula (I) above is a compound wherein A is a carbon atom R^{21} is acetoxymethyl.

In another preferred embodiment, the compound of formula (I) above is a compound wherein A is a carbon atom R^{21} is methoxymethyl.

In another preferred embodiment, the compound of formula (I) above is a compound wherein A is a carbon atom and R^{21} is C_3-C_6 cycloalkyl.

In another preferred embodiment, the compound of formula (I) above is a compound wherein A is a carbon atom and R^{20} and R^{21}, together with the carbon atom to which they are bound, form a C_3-C_6 cycloalkyl ring, preferably a cyclopropyl ring, a cyclopentyl ring or a cyclohexyl ring.

In another preferred embodiment, the compound of formula (I) above is a compound wherein A is a nitrogen and R^7 designates a lone pair of electrons.

In another preferred embodiment, the compound of formula (I) above is a compound wherein A is a nitrogen atom, R^7 designates a lone pair of electrons and R^8 is hydrogen.

In another preferred embodiment, the compound of formula (I) above is a compound wherein A is a nitrogen atom, R^7 designates a lone pair of electrons and R^8 is C_1-C_4 alkyl.

In another preferred embodiment, the compound of formula (I) above is a compound wherein A is a nitrogen atom, R^7 designates a lone pair of electrons and R^8 is oxo.

In another preferred embodiment, the compound of formula (I) above is a compound wherein A is a nitrogen atom, R^7 designates a lone pair of electrons and R^{20} and R^{21}, independently, are selected from the group comprising C_1-C_4 alkyl, cyclopropyl, cyclopentyl and cyclohexyl.

In a further preferred aspect, the present invention relates to the use of a compound of formula (I) above as a medicament, in particular as a medicament for use in the regulation of meiosis. The compound may be used neat or in the form of a liquid or solid composition containing auxiliary ingredients conventionally used in the art.

In the present context, the expression "regulating the meiosis" is used to indicate that certain of the compounds of the invention can be used for stimulating the meiosis *in vitro*, *in vivo*, or *ex vivo*. Thus, the compounds which may be agonists of a naturally occurring meiosis activating substance, can be used in the treatment of infertility which is due to insufficient stimulation of meiosis in females and in males. Other compounds of the invention, which may be antagonists of a naturally occurring meiosis activating substance, can be used for regulating the meiosis, preferably *in vivo*, in a way which makes them suited as contraceptives. In this case the "regulation" means partial or total inhibition.

In a still further preferred aspect, the present invention relates to the use of a compound of formula (I) above in the regulation of the meiosis of an oocyte, in particular a mammalian oocyte, more particularly a human oocyte.

In a still further preferred aspect, the present invention relates to the use of a compound of formula (I) above in the stimulation of the meiosis of an oocyte, in particular a mammalian oocyte, more particularly a human oocyte.

In a still further preferred aspect, the present invention relates to the use of a compound of formula (I) above in the inhibition of the meiosis of an oocyte, in particular a mammalian oocyte, more particularly a human oocyte.

In a still further preferred aspect, the present invention relates to the use of a compound of formula (I) above in the regulation of the meiosis of a male germ cell, in particular a mammalian male germ cell, more particularly a human male germ cell.

In a still further preferred aspect, the present invention relates to the use of a compound of formula (I) above in the stimulation of the meiosis of a male germ cell, in particular a mammalian male germ cell, more particularly a human male germ cell.

In a still further preferred aspect, the present invention relates to the use of a compound of formula (I) above in the inhibition of the meiosis of a male germ cell, in particular a mammalian male germ cell, more particularly a human male germ cell.

In a yet still further preferred aspect, the present invention relates to a method of regulating the meiosis in a mammalian germ cell which method comprises administering an effective amount of a compound of formula (I) above to a germ cell in need of such a treatment.

In a still further aspect, the present invention relates to a method of regulating the meiosis in a mammalian germ cell wherein a compound of formula (I) above is administered to the germ cell by administering the compound to a mammal hosting said cell.

In a still further aspect, the present invention relates to a method wherein the germ cell the meiosis of which is to be regulated by means of a compound of formula (I) above is an oocyte.

In a still further aspect, the present invention relates to a method of regulating the meiosis in an oocyte wherein a compound of formula (I) above is administered to the oocyte *ex vivo*.

In a still further aspect, the present invention relates to a method of regulating the meiosis of a male germ cell by administering a compound of formula (I) above to the cell.

In a still further aspect, the present invention relates to a method whereby mature male germ cells are produced by administering *in vitro* a compound of formula (I) above to testicular tissue containing immature cells.

DETAILED DESCRIPTION OF THE INVENTION

As used in the present description and claims, the expression C_1-C_3 alkyl designates an alkyl group having from one to three carbon atoms; preferred examples are methyl, ethyl and propyl, more preferred methyl and ethyl. Similarly, the expression C_1-C_4 alkyl designates an alkyl group having from one to four carbon atoms; preferred examples are methyl, ethyl, propyl, isopropyl and butyl, more preferred methyl and ethyl. The expression C_1-C_6 alkyl designates an alkyl group having from one to six carbon atoms; preferred examples are methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, pentryl and hexyl, more preferred methyl, ethyl, propyl, isopropyl, butyl and tert-butyl, still more preferred methyl and ethyl.

As used in the present description and claims, the expression C_1-C_3 alkoxy designates an alkoxy group having from one to three carbon atoms; preferred examples are methoxy, ethoxy and propoxy, more preferred methoxy and ethoxy.

As used in the present description and claims, the expression halogen preferably designates fluoro and chloro, more preferred fluoro.

The compounds of the invention have a number of chiral centres in the molecule and thus exists in several isomeric forms. All these isomeric forms and mixtures thereof are within the scope of the invention.

The compounds of the present invention will influence the meiosis in oocytes as well as in male germ cells.

The existence of a meiosis inducing substance in nature has been known for some time. However, until recently the identity of the meiosis inducing substance or substances was unknown.

The prospects of being able to influence the meiosis are several. According to a preferred embodiment of the present invention, the compounds of the invention are used to stimulate the meiosis. According to another preferred embodiment of the present invention, the compounds of the invention are used to stimulate the meiosis in humans. Thus, the compounds of the invention are promising as new fertility regulating agents without the usual side effect on the somatic cells which are known from the hitherto used hormonal contraceptives which are based on estrogens and/or gestagens.

For use as a contraceptive agent in females, a meiosis inducing substance can be administered so as to prematurely induce resumption of meiosis in oocytes while they are still in the growing follicle, before the ovulatory peak of gonadotropins occurs. In women, the resumption of the meiosis can, for example, be induced a week after the preceding menstruation has ceased. When ovulated, the resulting overmature oocytes are then most likely not to be fertilised. The normal menstrual cycle is not likely to be affected. In this connection it is important to notice, that the biosynthesis of progesterone in cultured human granulose cells (somatic cells of the follicle) is not affected by the presence of a meiosis inducing substance whereas the estrogens and gestagens used in the hitherto used hormonal contraceptives do have an adverse effect on the biosynthesis of progesterone.

According to another aspect of this invention, a meiosis inducing substance of the invention can be used in the treatment of certain cases of infertility in females, including women, by administration thereof to females who, due to an insufficient own production of meiosis activating substance, are unable to produce mature oocytes. Also, when *in vitro* fertilisation is performed, better results are achieved, when a compound of the invention is added to the medium in which the oocytes are kept.

When infertility in males, including men, is caused by an insufficient own production of the meiosis activating substance and thus a lack of mature sperm cells, administration of a compound of the invention may relieve the problem.

As an alternative to the method described above, contraception in females can also be achieved by administration of a compound of the invention which inhibits the meiosis, so that no mature oocytes are produced. Similarly, contraception in males can be achieved by administration of a compound of the invention which inhibits the meiosis, so that no mature sperm cells are produced.

The route of administration of compositions containing a compound of the invention may be any route which effectively transports the active compound to its site of action.

Thus, when the compounds of this invention are to be administered to a mammal, they are conveniently provided in the form of a pharmaceutical composition which comprises at least one compound of the invention in connection with a pharmaceutically acceptable carrier. For oral use, such compositions are preferably in the form of capsules or tablets.

From the above it will be understood that administrative regimen called for will depend on the condition to be treated. Thus, when used in the treatment of infertility the administration may have to take place once only, or for a limited period, e.g. until pregnancy is achieved. When used as a contraceptive, the compound of the invention will either have to be administered continuously or cyclically. When used as a contraceptive by females and not taken continuously, the timing of the administration relative to the ovulation will be important.

Pharmaceutical compositions comprising a compound of the invention may further comprise carriers, diluents, absorption enhancers, preservatives, buffers, agents for adjusting the osmotic pressure, tablet disintegrating agents and other ingredients which are conventionally used in the art. Examples of solid carriers are magnesium carbonate, magnesium stearate, dextrin, lactose, sugar, talc, gelatin, pectin, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, low melting waxes and cocoa butter.

Liquid compositions include sterile solutions, suspensions and emulsions. Such liquid compositions may be suitable for injection or for use in connection with *ex vivo* and *in vitro* fertilisation. The liquid compositions may contain other ingredients which are conventionally used in the art, some of which are mentioned in the list above.

Further, a composition for transdermal administration of a compound of this invention may be provided in the form of a patch and a composition for nasal administration may be provided in the form of a nasal spray in liquid or powder form.

The dose of a compound of the invention to be used will be determined by a physician and will depend, *inter alia*, on the particular compound employed, on the route of administration and on the purpose of the use.

The compounds of the invention can be synthesised by methods known per se.

The present invention is further illustrated by the following examples which, however, are not to be construed as limiting the scope of protection. The features disclosed in the foregoing description and in the following examples may, in any combination thereof, be material for realising the invention in diverse forms thereof.

Examples

Example 1

Preparation of 7-oxo-5α-cholest-8-ene-3β-ol

0.50g of 3β-acetoxy-7-oxo-5α-cholest-8-ene (Fieser, LF J *Am Chem Soc* (1953) 4395) was refluxed in a mixture of 30ml of ethanol and 20ml of 1M aqueous sodium hydroxide for 1 hour. After cooling to room temperature, 23ml of 1M hydrochloric acid and 100ml of water were added. After cooling on an ice

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bath, the precipitate was filtered off, washed with water and dried to give 0.435 g of the crude compound which was purified by chromatography on silica gel (methylene chloride/methanol, 40:1 (w/w)) and crystallized from methanol/water to give 0.198 g of the title compound.

Melting point: 115-117° C.
The ^{1}H-NMR spectrum ($CDCl_3$,δ) showed characteristic signals at: 0.59 (s,3H); 1.18 (s,3H); 3.64 (m,1H).
The ^{13}C-NMR spectrum ($CDCl_3$, 100.6 MHz) showed characteristic signals at: 69.5; 132.8; 164.8; 198.6.

EXAMPLE 2

Preparation of 7-oxo-5α-cholesta-8.14-diene-3ß-ol.

The compound was prepared as described by Fieser, LF *et al. J Am Chem Soc* (1953) 4719) and showed the following characteristic physical constants:

Melting point: 140-142° C.
^{1}H-NMR spectrum ($CDCl_3$,δ): 0.79 (s,3H), 1.14 (s,3H), 3.66 (m,1H), 6.45 (s,1H).
^{13}C-NMR spectrum ($CDCl_3$, 100.6 MHz): 69.4; 126.1; 126.6; 140.8; 164.9; 197.2.

EXAMPLE 3

Preparation of 7α-methyl-5α-cholest-8-ene-3ß,7ß-diol.

0.50 g of 3ß-acetoxy-7-oxo-5α-cholest-8-ene (Fieser, LF *J Am Chem Soc* (1953) 4395) was dissolved in 10 ml of tetrahydrofuran and 3 ml of 3M methylmagnesium chloride in tetrahydrofuran was added dropwise at 0° C over 15 minutes. The mixture was stirred at room temperature for 1 hour, cooled to 0° C, and 50 ml of a

1M solution of ammonium chloride was added dropwise over 5 minutes. The mixture was extracted twice with 50 ml of ethylacetate. The combined organic phases were washed with water and brine and evaporated to yield 474 mg of the crude product which was crystallized from ethylacetate/heptane to yield 168 mg of the title compound.

Melting point: 92-94° C.
The ^{1}H-NMR spectrum ($CDCl_3$, δ) showed characteristic signals at: 0.69 (s,3H), 1.03 (s,3H), 1.37 (s,3H), 3.62 (m,1H).
The ^{13}C-NMR spectrum ($CDCl_3$, 50.3 MHz) showed characteristic signals at: 70.7; 73.8; 132.9; 139.2.

From the mother liquor another crop (107 mg) of the title compound was isolated.

EXAMPLE 4
Preparation of 11-oxo-5α-cholest-8-ene-3ß-ol.

This compound was prepared as described by Parish, ES *et al.* *Steroids* 48 (1986) 407) and showed physical constants as described in the literature.

EXAMPLE 5
Preparation of 3ß-Hydroxy-5α-cholest-8-ene-7-oxime.

0.25 g of 7-oxo-5α-cholest-8-ene-3ß-ol (cf. Example 1) was dissolved in 10 ml of dry pyridine. 0.43 g of hydroxylamine hydrochloride was added, and the mixture was stirred at 70° C for 3 hours. After evaporation to dryness, the residue was triturated with water to give 238 mg of the crude product. Recrystallisation from methanol yielded 164 mg of the title compound.

Melting point: 218-223° C.

The ^{1}H-NMR spectrum ($CDCl_3$,δ) showed characteristic signals at: 0.62 (s,3H), 1.03 (s,3H), 3.0 (dd,1H), 3.62 (m,1H), 7.52 (broad s,1H).

The ^{13}C-NMR spectrum ($CDCl_3$, 100.6 MHz) showed characteristic signals at: 69.9, 126.7, 149.8, 157.7.

EXAMPLE 6

Preparation of 3β-acetoxy-7-oxo-5α-cholest-8-ene.

This compound was prepared as described by Fieser, LF *J Am Chem Soc* (1953) 4395 and showed physical constants as described in the literature.

EXAMPLE 7

Preparation of 3β-acetoxy-7-oxo-5α-cholesta-8,14-diene.

This compound was prepared as described by Fieser, LF *et al. J Am Chem Soc* (1953) 4719 and showed physical constants as described in the literature.

EXAMPLE 8

Preparation of 7-oxo-5α-cholest-8-ene-3β-yl benzoate.

This compound was prepared as described by Parish EJ *et al. Steroids* 48 (1986) 407 and showed physical constants as described in the literature.

EXAMPLE 9

Preparation of 7-methylene-5α-cholest-9-ene-3ß-ol.

0.54 g of sodium hydride (60%) was dissolved in 10 ml of dimethyl sulfoxide at 70° C. After 15 minutes a solution of 5.24 g of methyltriphenylphosphonium bromide in 33 ml of dimethyl sulfoxide and then a solution of 3ß-acetoxy-7-oxo-5α-cholest-8-ene (cf. Example 6) in 28 ml benzene was added. The mixture was stirred at 60° C for 22 hours, cooled to room temperature, poured on 1M hydrochloride acid/ice, and extracted several times with benzene. The combined organic phases were evaporated to dryness and the residue was dissolved in a mixture of methanol/water/cyclohexane, 13:7:20 (w/w). The methanol/water phase was extracted several times with cyclohexane and the combined cyclohexane phases were evaporated to dryness to give 1.32 g of an oil which was dissolved in 15 ml of heptane, filtered and evaporated to dryness. The residue (0.80 g) was chromatographed on 40 g silica gel (toluene/ethylacetate, 9:1 (w/w)) to give 247 mg of an almost pure product, which was crystallized from methanol to yield 110 mg of the title compound.

Melting point: 44-50° C.
The ^{1}H-NMR spectrum ($CDCl_3$, δ) showed characteristic signals at: 0.65 (s,3H); 1.06 (s,3H); 2.62 (d,1H); 3.58 (m,1H); 4.68 (d,2H); 5.27 (d,1H).
The ^{13}C-NMR spectrum ($CDCl_3$, 100.6 MHz) showed characteristic signals at: 70.5; 105.2; 115.7; 146.1; 150.5.

EXAMPLE 10

Preparation of 7-methyl-5α-cholesta-6,8-diene-3ß-ol.

0.90 g of 7α-methyl-5α-cholest-8-ene-3ß,7ß-diol (cf. Example 3) was suspended in 55 ml of formic acid and stirred overnight at room temperature. The mixture was poured on ice water and the precipitated compound was filtered off, washed with water, and dried. The residue (0.84 g) was refluxed in a mixture of 50 ml ethanol and 25 ml 1M aqueous sodium carbonate for 15 minutes. The solvent was evaporated and the residue was redissolved in methylene chloride and water. The organic phase was evaporated to dryness and crystallized from ethanol/water to yield 395 mg of the title compound.

Melting point: 112-113° C.
The ^{1}H-NMR spectrum ($CDCl_3$, δ) of the product showed characteristic signals at: 0.58 (s,3H), 0.88 (s,3H), 1.83 (s.3H), 3.58 (m,1H), 5.37 (d,1H).
The ^{13}C-NMR spectrum ($CDCl_3$, 100.6 MHz) showed characteristic signals at: 70.9, 116.6, 129.0, 129.6, 145.3.

EXAMPLE 11
Preparation of 11-oxo-5α-cholest-8-ene-3ß-yl benzoate.

This compound was prepared as described by Parish, EJ *et al. Steroids* **48** (1986) 407) and showed physical constants as described in literature.

EXAMPLE 12
Preparation of cholesta-8,14-diene-5α-H-3-one.

Cholesta-8,14-diene-5α-3-one was prepared according to Dolle *J Org Chem* **51** (1986) 4047-4053. The product showed the following physical characteristics:
^{1}H-NMR: Hδ: 5.78 (d 1H, C4H), 5.16 (1H, m, C7H)
Elementary analysis:

Cal: C: 84.7; H: 11.1; O: 4.18
Found: C: 84.7; H: 11.4.

EXAMPLE 13

Preparation of 3α-flourocholesta-8,14-diene.

Cholesta-8,14-diene-3ß-ol (1.17 g, 3 mmol) was dissolved in 10 ml of methylenechloride and cooled to -78° C. Over 10 min a solution of diethylaminosulfur trifluoride (1.4 g, 8.7 mmol) in 10 ml of methylenechloride was added at -78° C. The mixture was stirred for 1 1/2 hour at -78° C and was then slowly heated to room temperature. To the reaction mixture was added 15 ml of water while stirring was continued. The organic phase was separated and washed with 30 ml of 5% $NaHCO_3$ and then with water. The organic phase was dried with $MgSO_4$ and evaporated to dryness. The residue was purified by column chromatography using heptane for a first fraction and heptane/acetone, 95:5 (w/w) for a second fraction containing 3α-fluorocholesta-8,14 diene, 0.14 g (12%).

Melting point: 98.6° C

Elementary analysis:

Cal C: 83.88; H: 11.21; F: 4.91.

Found C: 83.92; H: 11.75.

^{19}F-NMR: δ 181.0 and 181.2 (J_{HCF} 45.2 Hz, C_3-αF).

EXAMPLE 14

Preparation of cholesta-2,8,14-triene.

The title compound was prepared by using a method analogous to a method described in *J Chemical Research* (miniprint) (1979) 4714-4755.

Cholesta-8,14-diene-3ß-ol (1.17 g, 3 mmol) was dissolved in 10 ml of methylenechloride and cooled to -78° C. Over 10 min a solution of diethylaminosulfur trifluoride (1.4 g, 8,7 mmol) in 10 ml of methylenechloride was added at -78° C. The mixture was stirred and was then slowly heated to the room temperature. The reaction mixture was added 15 ml water while stirring was continued. The organic phase was separated and washed with 30 ml of 5% $NaHCO_3$ and then with water. The organic phase was dried with $MgSO_4$ and evaporated to dryness. The residue was purified by column chromatography using heptane for a first fraction A giving cholesta-2,8,14-triene, 0.23 g.

Melting point: 104.7° C.

Elementary analysis:

Cal C: 88.45; H: 11.55.

Found C: 88.58; H: 11.89.

NMR: Hδ: 5.64 (m 2H; C_2-H; C_3-H)δ 5.35 (s,1H C 15H).

Cδ: 125.95 (C_3), 125.67 (C_2).

EXAMPLE 15

Preparation of cholesta-8,14-diene-5α(H)-3-(E),(Z)-oxime.

Cholesta-8,14-diene-3-one (1.0 g, 2.61 mmol) was dissolved in 15 ml of pyridine and hydroxylamine, HCl (0.29 g, 4.23 mmol) was added. The reaction mixture was heated at 70-72° C for 1 1/2 hour while stirred. The reaction mixture was cooled and evaporated to dryness. 30 ml of 50% acetic acid/water was added and the crystals formed were separated by filtration. The crystals were dissolved in heptane and washed with water. The organic phase was separated and evaporated to dryness. The crystals were recrystallized from ethanol to give 0.91 g of 5α-cholesta-8,14-diene-3-(E) and (Z)-oxime.

Elementary analysis:

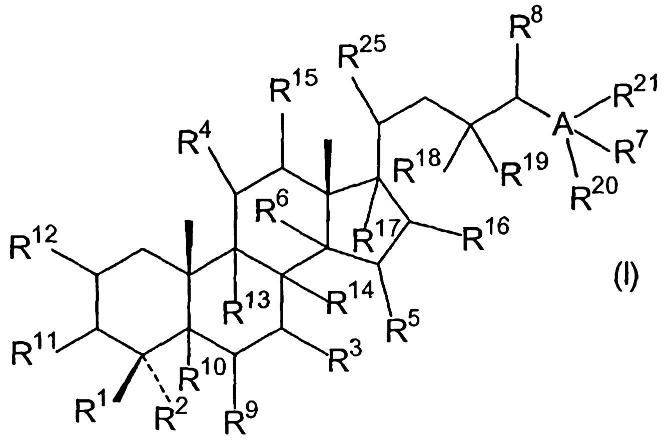
Cal C: 81.55; H: 10.90; N: 3.52; O: 4.02.

Found: 81.65; H: 11.30; N: 3.43.

^{13}C-NMR: δ 159,66 and 159.51 (3-C).

The claims defining the invention are as follows:

1. A compound of the general formula (I)



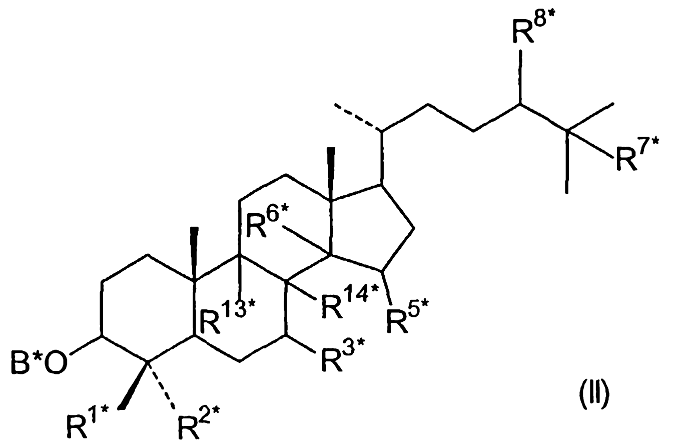
(I)

wherein R^1 and R^2, independently, are selected from the group comprising hydrogen and branched or unbranched C_1-C_6 alkyl which may be substituted by halogen, hydroxy or cyano, or wherein R^1 and R^2 together designate methylene or, together with the carbon atom to which they are bound, form a cyclopropane ring, a cyclopentane ring, or a cyclohexane ring; R^3 is selected from the group comprising hydrogen, methylene, hydroxy, methoxy, acetoxy, oxo, $=NOR^{26}$ wherein R^{26} is hydrogen or C_1-C_3 alkyl, halogen, and hydroxy and C_1-C_4 alkyl bound to the same carbon atom of the sterol skeleton, or R^3 designates, together with R^9 or R^{14}, an additional bond between the carbon atoms to which R^3 and R^9 or R^{14} are bound; R^4 is selected from the group comprising hydrogen, methylene, hydroxy, methoxy, acetoxy, oxo, $=NOR^{27}$ wherein R^{27} is hydrogen or C_1-C_3 alkyl, halogen, and hydroxy and C_1-C_4 alkyl bound to the same carbon atom of the sterol skeleton, or R^4 designates, together with R^{13} or R^{15}, an additional bond between the carbon atoms to which R^4 and R^{13} or R^{15} are bound; R^5 is selected from the group comprising hydrogen, C_1-C_4 alkyl, methylene, hydroxy, methoxy, oxo, and $=NOR^{22}$ wherein R^{22} is hydrogen or C_1-C_3 alkyl, or R^5 designates, together with R^6, an additional bond between the carbon atoms to which R^5 and R^6 are bound; R^6 is hydrogen or R^6 designates, together with R^5, an additional bond between the carbon atoms to which R^5 and R^6 are bound; R^9 is hydrogen or R^9 designates, together with R^3 or R^{10}, an additional bond between the carbon atoms to which R^9 and R^3 or R^{10} are bound; R^{10} is hydrogen or R^{10} designates, together with R^9, an additional bond between the carbon atoms to which R^{10} and R^9 are bound; R^{11} is selected from the group comprising hydroxy, alkoxy, substituted alkoxy, acyloxy, sulphonyloxy, phosphonyloxy, oxo, $=NOR^{28}$ wherein R^{28} is hydrogen or C_1-C_3 alkyl, halogen and hydroxy and C_1-C_4 alkyl bound to the same carbon atom of the sterol skeleton, or R^{11} designates, together with R^{12}, an additional bond between the carbon atoms to which R^{11} and R^{12} are bound; R^{12} is selected from the group comprising hydrogen, C_1-C_3 alkyl, vinyl, C_1-C_3 alkoxy and halogen, or R^{12}

designates, together with R^{11}, an additional bond between the carbon atoms to which R^{12} and R^{11} are bound; R^{13} is hydrogen or R^{13} designates, together with R^4 or R^{14}, an additional bond between the carbon atoms to which R^{13} and R^4 or R^{14} are bound; R^{14} is hydrogen or R^{14} designates, together with R^3, R^6 or R^{13}, an additional bond between the carbon atoms to which R^{14} and R^3 or R^6 or R^{13} are bound; R^{15} is selected from the group comprising hydrogen, C_1-C_4 alkyl, methylene, hydroxy, methoxy, acetoxy, oxo, and $=NOR^{23}$ wherein R^{23} is hydrogen or C_1-C_3 alkyl, or R^{15} designates, together with R^4, an additional bond between the carbon atoms to which R^{15} and R^4 are bound; R^{16} is selected from the group comprising hydrogen, C_1-C_3 alkyl, methylene, hydroxy, methoxy, oxo and $=NOR^{24}$ where R^{24} is hydrogen or C_1-C_3 alkyl, or R^{16} designates, together with R^{17}, an additional bond between the carbon atoms to which R^{16} and R^{17} are bound; R^{17} is hydrogen or hydroxy or R^{17} designates, together with R^{16}, an additional bond between the carbon atoms to which R^{17} and R^{16} are bound; R^{18} and R^{19} are, independently, hydrogen or fluoro; R^{25} is selected from the group comprising hydrogen, C_1-C_4 alkyl, methylene, hydroxy and oxo; A is a carbon atom or a nitrogen atom; when A is a carbon atom, R^7 is selected from the group comprising hydrogen, hydroxy and fluoro, and R^8 is selected from the group comprising hydrogen, C_1-C_4 alkyl, methylene and halogen, or R^7 designates, together with R^8, an additional bond between the carbon atoms to which R^7 and R^8 are bound; R^{20} is selected from the group comprising C_1-C_4 alkyl, trifluoromethyl and C_3-C_6 cycloalkyl and R^{21} is selected from the group comprising C_1-C_4 alkyl, C_1-C_4 hydroxyalkyl, C_1-C_4 haloalkyl containing up to three halogen atoms, methoxymethyl, acetoxymethyl, and C_3-C_6 cycloalkyl, or R^{20} and R^{21}, together with the carbon atom to which they are bound, from a C_3-C_6 cycloalkyl ring; and when A is a nitrogen atom, R^7 designates a lone par of electrons and R^8 is selected from the group comprising hydrogen, C_1-C_4 alkyl and oxo; R^{20} and R^{21} are, independently, C_1-C_4 alkyl or C_3-C_6 cycloalkyl; with the proviso that the compound of the general formula (I) does not have any cumulated double bonds and with the further proviso that the compound is not one of the following compounds: Cholest-7-ene-3β-ol; 4-Methylcholest-7-ene-3β-ol; 4-Ethylcholest-7-ene-3β-ol; 4,4-Dimethylcholest-7-ene-3β-ol; 4α-Methyl-4β-ethylcholest-7-ene-3β-ol; 4α-Ethyl-4β-methylcholest-7-ene-3β-ol; 4,4-Diethylcholest-7-ene-3β-ol; 4-Propylcholest-7-ene-3β-ol; 4-Butylcholest-7-ene-3β-ol; 4-Isobutylcholest-7-ene-3β-ol; 4,4-Tetramethylenecholest-7-ene-3β-ol; 4,4-Pentamethylenecholest-7-ene-3β-ol; Cholest-8-ene-3β-ol; 4-Methylcholest-8-ene-3β-ol; 4-Ethylcholest-8-ene-3β-ol; 4,4-Dimethylcholest-8-ene-3β-ol; 4α-Methyl-4β-ethylcholest-8-ene-3β-ol; 4α-Ethyl-4β-methylcholest-8-ene-3β-ol; 4,4-Diethylcholest-8-ene-3β-ol; 4-Propylcholest-8-ene-3β-ol; 4-Butylcholest-8-ene-3β-ol; 4-Isobutylcholest-8-ene-3β-ol; 4,4-Tetramethylenecholest-8-ene-3β-ol; 4,4-Pentamethylenecholest-8-ene-3β-ol; Cholest-8(14)-ene-3β-ol; 4-Methylcholest-8(14)-ene-

3β-ol; 4-Ethylcholest-8(14)-ene-3β-ol; 4,4-Dimethylcholest-8(14)-ene-3-ol; 4α-Methyl-4β-ethylcholest-8(14)-ene-3β-ol; 4α-Ethyl-4β-methylcholest-8(14)-ene-3β-ol; 4,4-Diethylcholest-8(14)-ene-3β-ol; 4-Propylcholest-8(14)-ene-3β-ol; 4-Butylcholest-8(14)-ene-3β-ol; 4-Isobutylcholest-8(14)-ene-3β-ol; 4,4-Tetramethylenecholest-8(14)-ene-3β-ol; 4,4-Pentamethylenecholest-8(14)-ene-3β-ol; Cholesta-8,14-diene-3β-ol; 4-Methylcholesta-8,14-diene-3β-ol; 4-Ethylcholesta-8,14-diene-3β-ol; 4,4-Dimethylcholesta-8,14-diene-3β-ol; 4α-Methyl-4β-ethylcholesta-8,14-diene-3β-ol; 4α-Ethyl-4β-methylcholesta-8,14-diene-3β-ol; 4,4-Diethylcholesta-8,14-diene-3β-ol; 4-Propylcholesta-8,14-diene-3β-ol; 4-Butylcholesta-8,14-diene-3β-ol; 4-Isobutyl-cholesta-8,14-diene-3β-ol; 4,4-Tetramethylenecholesta-8,14-diene-3β-ol; 4,4-Pentamethylenecholesta-8,14-diene-3β-ol; Cholesta-8,24-diene-3β-ol; 4-Methylcholesta-8,24-diene-3β-ol; 4-Ethylcholesta-8,24-diene-3β-ol; 4,4-Dimethylcholesta-8,24-diene-3β-ol; 4α-Methyl-4β-ethylcholest-8,24-diene-3β-ol; 4α-Ethyl-4β-methylcholesta-8,24-diene-3β-ol; 4,4-Diethylcholesta-8,24-diene-3β-ol; 4-Propylcholesta-8,24-diene-3β-ol; 4-Butylcholesta-8,24-diene-3β-ol; 4-Isobutylcholesta-8,24-diene-3β-ol; 4,4-Tetramethylenecholesta-8,24-diene-3β-ol; 4,4-Pentamethylenecholesta-8,24-diene-3β-ol; Cholesta-8,14,24-triene-3β-ol; 4-Methylcholesta-8,14,24-triene-3β-ol; 4-Ethylcholesta-8,14,24-triene-3β-ol; 4,4-Dimethylcholesta-8,14,24-triene-3β-ol; 4α-Methyl-4β-ethylcholesta-8,14,24-triene-3β-ol;4α-Ethyl-4β-methylcholesta-8,14,24-triene-3β-ol; 4,4-Diethylcholesta-8,14,24-triene-3β-ol; 4-Propylcholesta-8,14,24-triene-3β-ol; 4-Butylcholesta-8,14,24-triene-3β-ol; 4-Isobutylcholesta-8,14,24-triene-3β-ol; 4,4-Tetramethylenecholesta-8,14,24-triene-3β-ol; 4,4-Pentamethylenecholesta-8,14,24-triene-3β-ol; 3β-acetoxy-5α-cholesta-8,14,24-triene-7β-ol; 7-oxo-5α-cholest-8-enyl benzoate; 11-oxo-5α-cholest-8-enyl benzoate; 3β-hydroxy-5α-cholest-8-en-11-one; and 4,4-dimethylcholest-5-ene-3β,7α-diol and esters and ethers thereof.

2. A compound according to claim 1 with the proviso that it is not a compound of the general formula (II)



(II)

wherein R^{1*} and R^{2*}, independently, are selected from the group comprising hydrogen, branched or unbranched C_1-C_6 alkyl which may be substituted by halogen or hydroxy or wherein R^{1*} and R^{2*}, together with the carbon atom to which they are bound, form a cyclopentane ring or a cyclohexane ring; R^{13*} and R^{14*} together designate an additional bond between the carbon atoms to which they are bound in which case R^{3*} is hydrogen and R^{6*} and R^{5*} are either hydrogen or together they designate an additional bond between the carbon atoms to which they are bound; or R^{3*} and R^{14*} together designate an additional bond between the carbon atoms to which they are bound in which case R^{13*} is hydrogen and R^{6*} and R^{5*} are either hydrogen or together they designate an additional bond between the carbon atoms to which they are bound; or R^{6*} and R^{14*} together designate an additional bond between the carbon atoms to which they are bound in which case R^{13*}, R^{3*} and R^{5*} are all hydrogen; R^{8*} and R^{7*} are hydrogen or together they designate an additional bond between the carbon atoms to which they are bound; and B^* is either hydrogen or an acyl group, including a sulphonyl group or a phosphonyl group, or a group which together with the remaining part of the molecule forms an ether.

3. A compound according to claim 1 or claim 2 wherein R^1 and R^2 are both hydrogen.

4. A compound according to claim 1 or 2 wherein one of R^1 and R^2 is hydrogen while the other is methyl.

5. A compound according to claim 1 or 2 wherein R^1 and R^2 are both methyl.

6. A compound according to claim 1 or 2 wherein R^1 is branched or unbranched C_1-C_6 alkyl, optionally substituted by halogen, hydroxy or cyano.

7. A compound according to claim 1 or 2 wherein R^2 is branched or unbranched C_1-C_6 alkyl, optionally substituted by halogen, hydroxy or cyano.

8. A compound according to claim 1 or 2 wherein R^1 and R^2 together designate methylene.

9. A compound according to claim 1 or 2 wherein R^1 and R^2, together with the carbon atom to which they are bound, form a cyclopropane ring.

10. A compound according to claim 1 or 2 wherein R^1 and R^2, together with the carbon atom to which they are bound, form a cyclopentane ring.

11. A compound according to claim 1 or 2 wherein R^1 and R^2, together with the carbon atom to which they are bound, form a cyclohexane ring.

12. A compound according to any one of the preceding claims wherein R^3 is hydrogen.

13. A compound according to any one of the claims 1 to 11 wherein R^3 is methylene.

14. A compound according to any one of the claims 1 to 11 wherein R^3 is hydroxy.

15. A compound according to any one of the claims 1 to 11 wherein R^3 is methoxy or acetoxy.

16. A compound according to any one of the claims 1 to 11 wherein R^3 is halogen.

17. A compound according to any one of the claims 1 to 11 wherein R^3 is oxo.

18. A compound according to any one of the claims 1 to 11 wherein R^3 is =NOH.

19. A compound according to any one of the claims 1 to 11 wherein R^3 is $=NOR^{26}$, wherein R^{26} is C_1-C_3 alkyl.

20. A compound according to any one of the claims 1 to 11 wherein R^3 is hydroxy and C_1-C_4 alkyl bound to the same carbon atom of the sterol skeleton.

21. A compound according to any one of the claims 1 to 11 wherein R^3, together with R^9, designates an additional bond between the carbon atoms to which R^3 and R^9 are bound.

22. A compound according to any one of the claims 1 to 11 wherein R^3, together with R^{14}, designates an additional bond between the carbon atoms to which R^3 and R^{14} are bound.

23. A compound according to any one of the claims 1 to 22 wherein R^4 is hydrogen.

24. A compound according to any one of the claims 1 to 22 wherein R^4 is methylene.

25. A compound according to any one of the claims 1 to 22 wherein R^4 is hydroxy.

26. A compound according to any one of the claims 1 to 22 wherein R^4 is methoxy or acetoxy.

27. A compound according to any one of the claims 1 to 22 wherein R^4 is oxo.

28. A compound according to any one of the claims 1 to 22 wherein R^4 is =NOH.

29. A compound according to any one of the claims 1 to 22 wherein R^4 is $=NOR^{27}$, wherein R^{27} is C_1-C_3 alkyl.

30. A compound according to any one of the claims 1 to 22 wherein R^4 is hydroxy and C_1-C_4 alkyl bound to the same carbon atom of the sterol skeleton.

31. A compound according to any one of the claims 1 to 22 wherein R^4, together with R^{13}, designates an additional bond between the carbon atoms to which R^4 and R^{13} are bound.

32. A compound according to any one of the claims 1 to 22 wherein R^4, together with R^{15}, designates an additional bond between the carbon atoms to which R^4 and R^{15} are bound.

33. A compound according to any one of the claims 1 to 32 wherein R^5 is hydrogen.

34. A compound according to any one of the claims 1 to 32 wherein R^5 is C_1-C_4 alkyl.

35. A compound according to any one of the claims 1 to 32 wherein R^5 is methylene.

36. A compound according to any one of the claims 1 to 32 wherein R^5 is hydroxy.

37. A compound according to any one of the claims 1 to 32 wherein R^5 is methoxy.

38. A compound according to any one of the claims 1 to 32 wherein R^5 is oxo.

39. A compound according to any one of the claims 1 to 32 wherein R^5 is =NOH.

40. A compound according to any one of the claims 1 to 32 wherein R^5 is =NOR^{22}, wherein R^{22} is C_1-C_3 alkyl.

41. A compound according to any one of the claims 1 to 32 wherein R^5, together with R^6, designates an additional bond between the carbon atoms to which R^5 and R^6 are bound.

42. A compound according to any one of the claims 1 to 41 wherein R^6 is hydrogen.

43. A compound according to any one of the claims 1 to 42 wherein R^6, together with R^{14}, designates an additional bond between the carbon atoms to which R^6 and R^{14} are bound.

44. A compound according to any one of the claims 1 to 43 wherein R^9 is hydrogen.

45. A compound according to any one of the claims 1 to 37 wherein R^9, together with R^{10}, designates an additional bond between the carbon atoms to which R^9 and R^{10} are bound.

46. A compound according to any one of the claims 1 to 40 wherein R^{10} is hydrogen.

47. A compound according to any one of the claims 1 to 41 wherein R^{11} is hydroxy.

48. A compound according to any one of the claims 1 to 41 wherein R^{11} is alkoxy, aralkyloxy, alkoxyalkoxy or alkanoyloxyalkyl, each group comprising a total of up to 10 carbon atoms, preferably up to 8 carbon atoms.

49. A compound according to any one of the claims 1 to 41 wherein R^{11} is C_1-C_4 alkoxy.

50. A compound according to any one of the claims 1 to 41 wherein R^{11} is methoxy.

51. A compound according to any one of the claims 1 to 41 wherein R^{11} is ethoxy.

52. A compound according to any one of the claims 1 to 41 wherein R^{11} is CH_3OCH_2O-.

53. A compound according to any one of the claims 1 to 41 wherein R^{11} is pivaloyloxymethoxy.

54. A compound according to any one of the claims 1 to 41 wherein R^{11} is an acyloxy group derived from an acid having from 1 to 20 carbon atoms.

55. A compound according to any one of the claims 1 to 41 wherein R^{11} is an acyloxy group selected from the group comprising acetoxy, benzoyloxy, pivaloyloxy, butyryloxy, nicotinoyloxy, isonicotinoyloxy, hemi succinoyloxy, hemi glutaroyloxy, butylcarbamoyloxy, phenylcarbamoyloxy, butoxycarbonyloxy, **tert**-butoxycarbonyloxy and ethoxycarbonyloxy.

56. A compound according to any one of the claims 1 to 41 wherein R^{11} is sulphonyloxy.

57. A compound according to any one of the claims 1 to 41 wherein R^{11} is phosphonyloxy.

58. A compound according to any one of the claims 1 to 41 wherein R^{11} is oxo.

59. A compound according to any one of the claims 1 to 41 wherein R^{11} is =NOH.

60. A compound according to any one of the claims 1 to 41 wherein R^{11} is $=NOR^{28}$, wherein R^{28} is C_1-C_3 alkyl.

61. A compound according to any one of the claims 1 to 41 wherein R^{11} is halogen.

62. A compound according to any one of the claims 1 to 41 wherein R^{11} is hydroxy and C_1-C_4 alkyl bound to the same carbon atom of the sterol skeleton.

63. A compound according to any one of the claims 1 to 41 wherein R^{11}, together with R^{12}, designates an additional bond between the carbon atoms to which R^{11} and $R^{12}$are bound.

64. A compound according to any one of the claims 1 to 63 wherein R^{12} is hydrogen.

65. A compound according to any one of the claims 1 to 63 wherein R^{12} is C_1-C_3 alkyl.

66. A compound according to any one of the claims 1 to 63 wherein R^{12} is C_1-C_3 alkoxy.

67. A compound according to any one of the claims 1 to 63 wherein R^{12} is halogen.

68. A compound according to any one of the claims 1 to 67 wherein R^{13} is hydrogen.

69. A compound according to any one of the claims 1 to 67 wherein R^{13}, together with R^{14}, designates an additional bond between the carbon atoms to which R^{13} and R^{14} are bound.

70. A compound according to any one of the claims 1 to 68 wherein R^{14} is hydrogen.

71. A compound according to any one of the claims 1 to 70 wherein R^{15} is hydrogen.

72. A compound according to any one of the claims 1 to 70 wherein R^{15} is C_1-C_4 alkyl.

73. A compound according to any one of the claims 1 to 70 wherein R^{15} is methylene.

74. A compound according to any one of the claims 1 to 70 wherein R^{15} is hydroxy.

75. A compound according to any one of the claims 1 to 70 wherein R^{15} is methoxy or acetoxy.

76. A compound according to any one of the claims 1 to 70 wherein R^{15} is oxo.

77. A compound according to any one of the claims 1 to 70 wherein R^{15} is =NOH.

78. A compound according to any one of the claims 1 to 70 wherein R^{15} is $=NOR^{23}$, wherein R^{23} is C_1-C_3 alkyl.

79. A compound according to any one of the claims 1 to 78 wherein R^{16} is hydrogen.

80. A compound according to any one of the claims 1 to 78 wherein R^{16} is C_1-C_3 alkyl.

81. A compound according to any one of the claims 1 to 78 wherein R^{16} is methylene.

82. A compound according to any one of the claims 1 to 78 wherein R^{16} is hydroxy.

83. A compound according to any one of the claims 1 to 78 wherein R^{16} is methoxy.

84. A compound according to any one of the claims 1 to 78 wherein R^{16} is oxo.

85. A compound according to any one of the claims 1 to 78 wherein R^{16} is =NOH.

86. A compound according to any one of the claims 1 to 78 wherein R^{16} is $=NOR^{24}$, wherein R^{24} is C_1-C_3 alkyl.

87. A compound according to any one of the claims 1 to 78 wherein R^{16}, together with R^{17}, designates an additional bond between the carbon atoms to which R^{16} and R^{17} are bound.

88. A compound according to any one of the claims 1 to 87 wherein R^{17} is hydrogen or hydroxy.

89. A compound according to any one of the claims 1 to 88 wherein R^{18} and R^{19} are both hydrogen.

90. A compound according to any one of the claims 1 to 88 wherein R^{18} and R^{19} are both fluoro.

91. A compound according to any one of the claims 1 to 88 wherein one of R^{18} and R^{19} is fluoro and the other is hydrogen.

92. A compound according to any one of the preceding claims wherein R^{25} is hydrogen.

93. A compound according to any one of the preceding claims wherein R^{25} is C_1-C_4 alkyl.

94. A compound according to any one of the claims 1 to 91 wherein R^{25} is methylene.

95. A compound according to any one of the claims 1 to 91 wherein R^{25} is hydroxy.

96. A compound according to any one of the claims 1 to 91 wherein R^{25} is oxo.

97. A compound according to any one of the claims 1 to 96 wherein A is a carbon atom.

98. A compound according to claim 97 wherein R^7 is hydrogen.

99. A compound according to claim 97 wherein R^7 is hydroxy.

100. A compound according to claim 97 wherein R^7 is fluoro.

101. A compound according to claim 97 wherein R^7, together with R^8, designates an additional bond between the carbon atoms to which R^7 and R^8 are bound.

102. A compound according to claim 97 wherein R^8 is hydrogen.

103. A compound according to claim 97 wherein R^8 is C_1-C_4 alkyl.

104. A compound according to claim 97 wherein R^8 is methylene.

105. A compound according to claim 97 wherein R^8 is halogen.

106. A compound according to any one of the claims 1 to 105 wherein R^{20} is C_1-C_4 alkyl.

107. A compound according to any one of the claims 1 to 105 wherein R^{20} is trifluoromethyl.

108. A compound according to any one of the claims 1 to 105 wherein R^{20} is C_3-C_6 cycloalkyl.

109. A compound according to any one of the claims 1 to 108 wherein R^{21} is C_1-C_4 alkyl.

110. A compound according to any one of the claims 1 to 108 wherein R^{21} is C_1-C_4 hydroxyalkyl.

111. A compound according to any one of the claims 1 to 108 wherein R^{21} is C_1-C_4 haloalkyl containing up to three halogen atoms.

112. A compound according to any one of the claims 1 to 108 wherein R^{21} is methoxymethyl or acetoxymethyl.

113. A compound according to any one of the claims 1 to 108 wherein R^{21} is C_3-C_6 cycloalkyl.

114. A compound according to any one of the claims 1 to 105 wherein R^{20} and R^{21}, together with the carbon atom to which they are bound, form a C_3-C_6 cycloalkyl ring.

115. A compound according to claim 114 wherein the cycloalkyl ring is cyclopropyl ring, a cyclopentyl ring or a cyclohexyl ring.

116. A compound according to any one of the claims 1 to 96 wherein A is a nitrogen atom.

117. A compound according to claim 116 wherein R^8 is hydrogen.

118. A compound according to claim 116 wherein R^8 is C_1-C_4 alkyl.

119. A compound according to claim 116 wherein R^8 is oxo.

120. A compound according to any one of claims 116 or 47 to 93 wherein R^{20} and R^{21}, independently, are selected from the group comprising C_1-C_4 alkyl, cyclopropyl, cyclopentyl and cyclohexyl.

121. A meiosis regulating sterol derivative, substantially as hereinbefore described with reference to any one of the Examples.

122. A pharmaceutical composition comprising a compound according to any one of claims 1 to 121 together with a pharmaceutically acceptable carrier, diluent or adjuvant therefore.

123. A method of regulating meiosis in a mammalian germ cell which method comprises administering to the germ cell an effective amount of a compound of formula (I) according to any one of claims 1 to 121 or a pharmaceutical composition according to claim 122.

124. A method according to claim 123 wherein a compound according to any one of claims 2 to 121 is administered.

125. A method according to claim 123 or claim 24 wherein the compound or pharmaceutical composition is administered to the germ cell by administering it to a mammal hosting said cell.

126. A method according to any one of claims 123 to 125 wherein the germ cell, the meiosis of which is to be regulated, is an oocyte.

127. A method according to any one of claims 123 to 125 wherein the compound is administered to an oocyte *ex vivo*.

128. A method according to any one of claims 123 to 127 wherein the germ cell, the meiosis of which is to be regulated, is a male germ cell.

129. A method according to claim 123 whereby mature male germ cells are produced by administering the compound to testicular tissue *in vitro*.

130. A compound according to any one of claims 1 to 121 when used to regulate meiosis in a mammalian germ cell.

131. A compound according to claim 130 wherein the compound or pharmaceutical composition is administered to the germ cell by administering it to a mammal hosting said cell.

132. A compound according to claim 130 or claim 131 wherein the germ cell, the meiosis of which is to be regulated, is an oocyte.

133. A compound according to claim 130 wherein the compound is administered to an oocyte *ex vivo*.

134. A compound according to any one of claims 130 to 133 wherein the germ cell, the meiosis of which is to be regulated, is a male germ cell.

135. A compound according to claim 130 whereby mature male germ cells are produced by administering the compound to testicular tissue *in vitro*.

136. The use of a compound of any one of claims 1 to 121 for the manufacture of a medicament.

137. The use of a compound of any one of claims 1 to 121 for the manufacture of a medicament for regulating meiosis of a germ cell in a mammal.

138. A compound according to any one of claims 1 to 121 for use in the regulation of meiosis.

139. A compound according to any one of claims 2 to 121 for use in the regulation of meiosis.

Dated 4 February, 2000
Novo Nordisk A/S

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