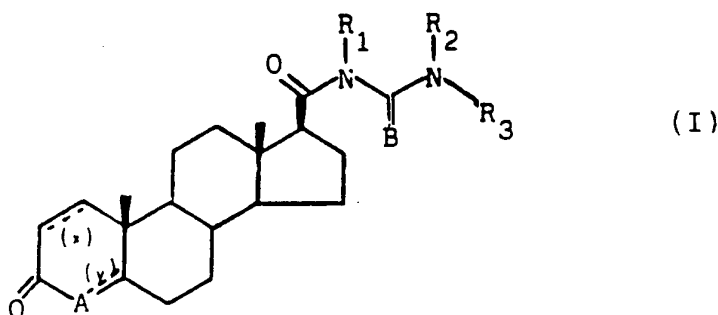




INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁵ : C07J 73/00, 41/00, A61K 31/56 A61K 31/58	A1	(11) International Publication Number: WO 94/03474 (43) International Publication Date: 17 February 1994 (17.02.94)
(21) International Application Number: PCT/EP93/02035 (22) International Filing Date: 29 July 1993 (29.07.93) (30) Priority data: 9216280.9 31 July 1992 (31.07.92) GB (71) Applicant: FARMITALIA CARLO ERBA S.R.L. [IT/IT]; Via Carlo Imbonati, 24, I-20159 Milan (IT). (72) Inventors: PANZERI, Achille ; Via San Francesco d'Assisi, 14, I-22055 Merate (IT). NESI, Marcella ; Via Donati, 12, I-20146 Milan (IT). DI SALLE, Enrico ; Via Andrea Doria, 5, I-20124 Milan (IT).		(74) Agent: FERRARIO, Vittorino; R.S./Documentation and Patent Department, Farmitalia Carlo Erba S.r.l., Via Carlo Imbonati, 24, I-20159 Milan (IT). (81) Designated States: JP, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>

(54) Title: STEROIDS WITH A FLUORINATED ACYLUREIDIC TYPE SIDE CHAIN



(57) Abstract

The present invention concerns steroidal 5 α -reductase inhibitors having formula (I), wherein the symbol ---- is a single or a double bond; A is a CH group or an N-R group wherein R is a hydrogen atom or a C₁-C₄ alkyl group provided that, when A is a CH group, (Y) is a double bond, and when A is an N-R group, (Y) is a single bond and in position 5 there is a hydrogen atom with α configuration; B is an oxygen atom or a sulphur atom; each of R₁, R₂, R₃ independently is a hydrogen atom or a C₁-C₆ alkyl group or an aryl group wherein, optionally, one or more hydrogen atoms are substituted by one or more fluorine atoms provided that at least one hydrogen atom in R₁, R₂, R₃ is substituted by a fluorine atom. The compounds of the invention are therapeutically useful in, e.g., benign prostatic hyperplasia, prostatic and breast cancers, seborrhoea, female hirsutism and male pattern baldness.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	FR	France	MR	Mauritania
AU	Australia	GA	Gabon	MW	Malawi
BB	Barbados	GB	United Kingdom	NE	Niger
BE	Belgium	GN	Guinea	NL	Netherlands
BF	Burkina Faso	GR	Greece	NO	Norway
BG	Bulgaria	HU	Hungary	NZ	New Zealand
BJ	Benin	IE	Ireland	PL	Poland
BR	Brazil	IT	Italy	PT	Portugal
BY	Belarus	JP	Japan	RO	Romania
CA	Canada	KP	Democratic People's Republic of Korea	RU	Russian Federation
CF	Central African Republic	KR	Republic of Korea	SD	Sudan
CG	Congo	KZ	Kazakhstan	SE	Sweden
CH	Switzerland	LI	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovak Republic
CM	Cameroon	LU	Luxembourg	SN	Senegal
CN	China	LV	Latvia	TD	Chad
CS	Czechoslovakia	MC	Monaco	TG	Togo
CZ	Czech Republic	MG	Madagascar	UA	Ukraine
DE	Germany	ML	Mali	US	United States of America
DK	Denmark	MN	Mongolia	UZ	Uzbekistan
ES	Spain			VN	Viet Nam
FI	Finland				

- 1 -

"STEROIDS WITH A FLUORINATED ACYLUREIDIC TYPE SIDE CHAIN"

The present invention relates to 4-aza-5 α -androstan-3-one and androst-1,4-dien-3-one derivatives with a fluorinated acylureidic type side chain, to a process for their
5 preparation, to pharmaceutical compositions containing them, and to the use of said compounds as inhibitors of androgen action, by means of testosterone 5 α -reductase inhibition.

In certain androgen responsive tissues the action of
10 testosterone is mediated primarily through its 5 α -reduced metabolite, dihydrotestosterone (DHT) (Bruchowsky N., - Wilson J.D.; J. Biol. Chem 243, 5953, 1968). The conversion of testosterone to dihydrotestosterone is catalyzed by the enzyme 5 α -reductase and if 5 α -reductase
15 is inhibited, the formation of dihydrotestosterone is reduced and its specific androgenic effect is attenuated or prevented.

The 5 α -reductase inhibitors may find medical application for the treatment of hyperandrogenic conditions, e.g.
20 certain prostatic diseases, such as benign prostatic hyperplasia and prostatic cancer, and certain skin-hair conditions, such as acne, seborrhoea, female hirsutism and male pattern baldness (Siiteri P.K., Wilson J.D., J.

- 2 -

Clin. Invest. 49, 1737, 1970; Price V.H., Arch. Dermatol. III, 1496, 1975; Sandberg A.A., Urology 17, 34, 1981).

Also breast cancer treatment can take advantage from use of 5 α -reductase inhibitors as the said tumor is known to
5 be aggravated by presence of androgens. Androst-4-en-3-one-17 β -carboxylic acid and its methyl ester (Voigt and Hsia, Endocrinology, 92, 1216 (1973); Canadian Patent No. 970,692) are among the first steroidal compounds described as 5 α -reductase inhibitors.

10 Two 5,10-secosteroids having a 3-keto-4,5-diene system in the expanded ring have been found to be selective inhibitors of rat epididymal 5 α -reductase (Robaire et al., J. Steroid Biochem, 8, 307-310 (1977)).

The (20R)-4-diazo-21-hydroxy-20-methyl-5 α -pregnan-3-one
15 and its analogs are reported to be enzyme activated inhibitors of testosterone 5 α -reductase (Blohm et al., Biochem. Biophys. Res. Comm 95, 273-80 (1980); United States, Patent 4, 317,817).

Another series of enzyme-directed irreversible inhibitors
20 of 5 α -reductase has been prepared by introducing a 6-methylene moiety into substrates type 3-keto- Δ^4 -progestins and androgens (Petrow et al., Steroids 38, 352-53 (1981); United States Patent 4,396,615).

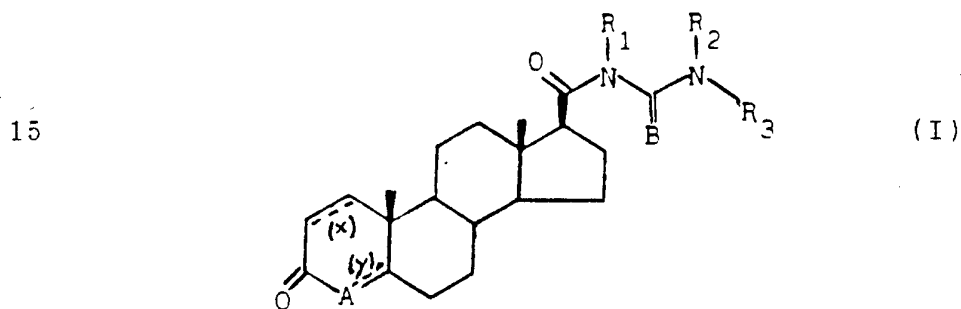
More recently unsaturated derivatives of 3-carboxy
25 steroids have been reported as uncompetitive 5 α -reductase inhibitors versus testosterone (Biorg. Chem. 17, 372-376

- 3 -

(1989); Eur. Pat. Appln. No. 0289327).

4-Aza steroids are by far the most studied steroid 5 α -
 reductase inhibitors. The compounds known in the art are
 reported in a very large number of publications and
 5 patents. In particular the 17 β -acylamides and their
 metabolites are described in: J. Med. Chem. 27, 1690-1701
 (1984), J. Med. Chem. 29, 2298-2315 (1986), Eur. Pat.
 Appl. No. 0,004,949; U.S. Patent 4,377,584; Eur. Pat.
 Appl. 0,155,096; U.S. Patent 4,845,104; Eur. Pat. Appl.
 10 0,462,662; Eur. Pat. Appl. 0,484,094 A2; U.S. Patent
 4,859,681; WO 91/12261.

The present invention provides compounds of the following
 formula I:



wherein:

the symbol ---- is a single or a double bond;

A is a CH group or an N-R group wherein R is a hydrogen
 atom or a C₁-C₄ alkyl group provided that, when A is a CH
 20 group, (Y) is a double bond, and when A is an N-R group
 (Y) is a single bond and in position 5 there is a
 hydrogen atom with α -configuration;

- 4 -

B is an oxygen atom or a sulphur atom;

each of R_1 , R_2 , R_3 independently is a hydrogen atom or a C_1-C_6 alkyl group or an aryl group wherein, optionally, one or more hydrogen atoms are substituted by one or more
5 fluorine atoms provided that at least one hydrogen atom in R_1 , R_2 , R_3 is substituted by a fluorine atom.

In the formulae of this specification the dotted line ("...") indicates a substituent in the α configuration, i.e. below the plane of the ring, and the wedged line
10 () indicates a substituent in the β configuration, i.e. above the plane of the ring.

The invention includes also all the possible isomers of formula (I) and their mixtures.

Also the metabolites and the metabolic precursors of the
15 compounds of formula (I) are within the scope of the present invention.

In this specification the alkyl groups may be straight or branched chain.

A C_1-C_4 alkyl group may be, for example, methyl, ethyl,
20 n-propyl, isopropyl, tert-butyl;

A C_1-C_6 alkyl group may be, for example, a C_1-C_5 alkyl group or a C_1-C_4 alkyl group, such as e.g. $-CH_3$, $-C_2H_5$, $-CH(CH_3)CH_3$, $-CH_2CH(CH_3)CH_3$, $-C(CH_3)_3$, $-CH_2C(CH_3)_3$.

The C_1-C_6 alkyl group, may be unsubstituted or substituted
25 by one or more, preferably one to nine or one to three, fluorine atoms, for example:

- 5 -

$-\text{CH}_2\text{F}$, $-\text{CHF}_2$, CF_3 , CH_2CF_3 , $-\text{CH}(\text{CH}_3)\text{CF}_3$, $-\text{CH}(\text{CF}_3)_2$,
 $-\text{C}(\text{CH}_2\text{F})_3$, $-\text{C}(\text{CHF}_2)_3$, $-\text{C}(\text{CF}_3)_3$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CF}_3$,
 $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CF}_2\text{CF}_3$.

An aryl group may be, for example, phenyl or phenyl ($\text{C}_1\text{-C}_4$
 5 alkyl), in particular tolyl, preferably o-, m- or p-
 tolyl. The aryl group may be unsubstituted or substituted
 by one or more, preferably one, two or three, fluorine
 atoms, for example o-fluorophenyl, m-fluorophenyl, p-
 fluorophenyl, o-trifluoromethylphenyl, m-trifluoro-
 10 methylphenyl, p-trifluoromethylphenyl.

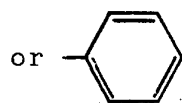
A preferred class of compounds according to the invention
 are the compounds of formula (I) wherein:

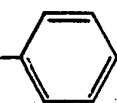
the symbol --- is a single or a double bond;

A is a CH group or an N-R group wherein R is a hydrogen
 15 atom or a methyl group provided that when A is a CH group
 (Y) is a double bond, and when A is an N-R group (Y) is
 a single bond and in position 5 there is a hydrogen atom
 with a configuration;

B is an oxygen atom or a sulphur atom;

20 each of R_1 , R_2 and R_3 independently is H, CH_3 , C_2H_5 ,
 $\text{CH}(\text{CH}_3)_2$, $\text{C}(\text{CH}_3)_3$, CH_2CF_3 , $\text{CH}(\text{CH}_3)\text{CF}_3$, $\text{CH}(\text{CF}_3)_2$, $\text{C}(\text{CF}_3)_3$,



or , provided that at least one hydrogen atom in
 R_1 , R_2 , R_3 is substituted by a fluorine atom.

Examples of specific compounds preferred under this

- 6 -

invention are:

- 1) 1-(3-oxo-4-aza-5 α -androst-1-ene-17 β -carbonyl)-1,3-di-(2,2,2-trifluoroethyl)urea;
- 2) 1-(3-oxo-4-aza-5 α -androstane-17 β -carbonyl)-1,3-di-
5 (2,2,2-trifluoroethyl)urea;
- 3) 1-(4-methyl-3-oxo-4-aza-5 α -androst-1-ene-17 β -carbonyl)-1,3-di-(2,2,2-trifluoroethyl)urea;
- 4) 1-(4-methyl-3-oxo-4-aza-5 α -androstane-17 β -carbonyl)-
-1,3-di-(2,2,2-trifluoroethyl)urea;
- 10 5) 1-(4-methyl-3-oxo-4-aza-5 α -androstane-17 β -carbonyl)-
-1,3-di-(2,2,2-trifluoroethyl)thiourea;
- 6) 1-(3-oxo-4-aza-5 α -androst-1-ene-17 β -carbonyl)-1,3-di-(3,3,3,1,1,1-hexafluoroprop-2-yl)urea;
- 7) 1-(4-methyl-3-oxo-4-aza-5 α -androstane-17 β -carbonyl)-
15 -1,3-di-(3,3,3,1,1,1-hexafluoroprop-2-yl)urea;
- 8) 1-(4-methyl-3-oxo-4-aza-5 α -androstane-17 β -carbonyl)-
-1-(2,2,2-trifluoroethyl)-3-ethylurea;
- 9) 1-(4-methyl-3-oxo-4-aza-5 α -androstane-17 β -carbonyl)-
-1-(2,2,2-trifluoroethyl)-3,3-diethylurea;
- 20 10) 1-(4-methyl-3-oxo-4-aza-5 α -androstane-17 β -carbonyl)-
-1-nonafluorotertbutyl-3-phenylurea;
- 11) 1-(4-methyl-3-oxo-4-aza-5 α -androstane-17 β -carbonyl)-
-1-(3,3,3,1,1,1-hexafluoroprop-2-yl)-3-phenylurea;
- 12) 1-(3-oxoandrost-4-ene-17 β -carbonyl)-1,3-di-
25 (3,3,3,1,1,1-hexafluoroprop-2-yl)urea;

- 7 -

- 13) 1-(3-oxoandrost-4-ene-17 β -carbonyl)-1,3-di-(2,2,2-trifluoroethyl)urea;
- 14) 1-(3-oxoandrost-4-ene-17 β -carbonyl)-1-(2,2,2-trifluoroethyl)-3-ethylurea;
- 5 15) 1-(3-oxoandrost-4-ene-17 β -carbonyl)-1-(2,2,2-trifluoroethyl)-3,3-diethylurea.

The structural formulae of the above listed compounds, according to their progressive number, are tabulated below, with reference to the formula (I) substituents:

- 8 -

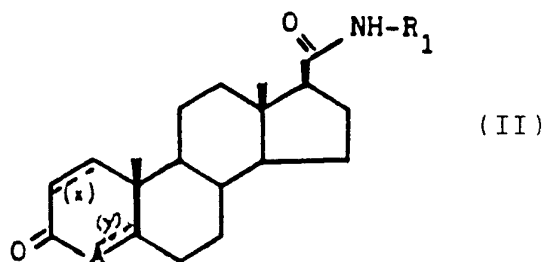
No.	B	A	R ₁	R ₂	R ₃	(x)	(y)
1	0	NH	CF ₃ -CH ₂ -	H	CF ₃ -CH ₂ -	double	single
2	0	NH	CF ₃ -CH ₂ -	H	CF ₃ -CH ₂ -	single	single
3	0	N CH ₃	CF ₃ -CH ₂ -	H	CF ₃ -CH ₂ -	double	single
4	0	N CH ₃	CF ₃ -CH ₂ -	H	CF ₃ -CH ₂ -	single	single
5	S	N CH ₃	CF ₃ -CH ₂ -	H	CF ₃ -CH ₂ -	single	single
6	0	N H	CF ₃ \ CH- / CF ₃	H	CF ₃ \ CH- / CF ₃	double	single
7	0	N CH ₃	CF ₃ \ CH- / CF ₃	H	CF ₃ \ CH- / CF ₃	single	single
8	0	N CH ₃	CF ₃ -CH ₂ -	H	CH ₃ CH ₂ -	single	single
9	0	N CH ₃	CF ₃ -CH ₂ -	CH ₃ CH ₂ -	CH ₃ CH ₂ -	single	single
10	0	N CH ₃	CF ₃ \ C- / CF ₃	H	Ph	single	single
11	0	N CH ₃	CF ₃ \ CH- / CF ₃	H	Ph	single	single
12	0	CH	CF ₃ \ CH- / CF ₃	H	CF ₃ \ CH- / CF ₃	single	double
13	0	CH	CF ₃ CH ₂ -	H	CF ₃ CH ₂ -	single	double
14	0	CH	CF ₃ CH ₂ -	H	CH ₃ CH ₂ -	single	double
15	0	CH	CF ₃ CH ₂ -	CH ₃ CH ₂ -	CH ₃ CH ₂ -	single	double

SUBSTITUTE SHEET

- 9 -

The compounds of formula (I) may be obtained by a process comprising:

a) reacting a compound of formula (II)

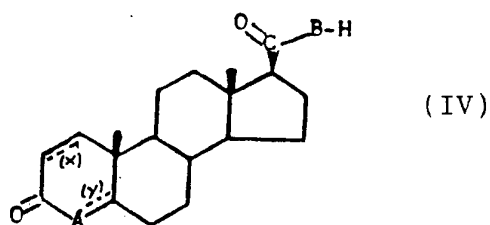


5 wherein the symbols ----, A and R₁ are as defined above with a compound of formula (III)



wherein R₂ and B are as defined above, so obtaining a compound of formula (I), wherein the symbol ----, A, B, R₁ and R₂ are as defined above and R₂ is hydrogen; or

10 b) reacting a compound of formula (IV)



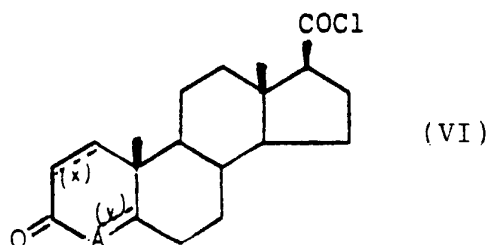
wherein the symbol ----, A and B are as defined above with a compound of formula (V)

- 10 -

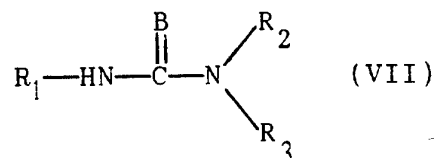


wherein each of R_1 and R_2 independently is a C_1-C_6 alkyl group or an aryl group wherein, optionally, one or more hydrogen atoms are substituted by one or more fluorine atoms, so obtaining a compound of formula (I) wherein the symbol ----, A and B are as defined above, each of R_1 and R_2 is independently a C_1-C_6 alkyl group or an aryl group wherein, optionally, one or more hydrogen atoms are substituted by one or more fluorine atoms and R_3 is hydrogen, provided that at least one hydrogen atom in R_1 or R_2 is substituted by a fluorine atom; or

c) reacting a compound of formula (VI)



wherein the symbol ---- and A are as defined above with a compound of formula (VII)



wherein R_1 , R_2 , R_3 and B are as defined above, so

- 11 -

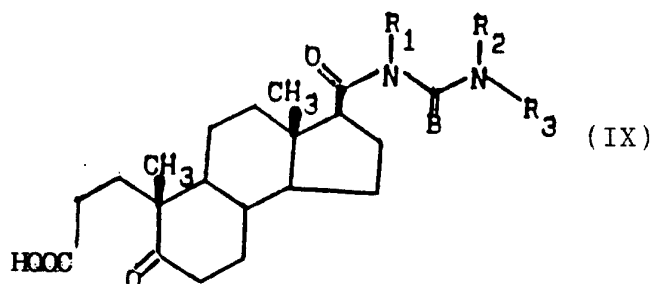
obtaining a compound of formula (I) wherein the symbol ---
 --- , A, B, R_1 , R_2 and R_3 are as defined above; or

d) reacting a compound of formula (VI), as defined above,
 with a compound of formula (VII), wherein R_1 is hydrogen
 5 and R_2 , R_3 , B are as defined above, and a compound of
 formula (VIII)



wherein R_1 is as defined above, but it isn't hydrogen,
 and W is a halogen atom, so obtaining a compound of
 10 formula (I) wherein the symbol --- , A, B, R_2 and R_3 are
 as defined above and R_1 is as defined above, but it isn't
 hydrogen; or

e) oxidative opening the A-ring of a compound of formula
 (I), wherein the (X) bond is a single bond, A is a CH
 15 group, (Y) is a double bond and R_1 , R_2 , R_3 and B are as
 defined above, so obtaining a compound of formula (IX)



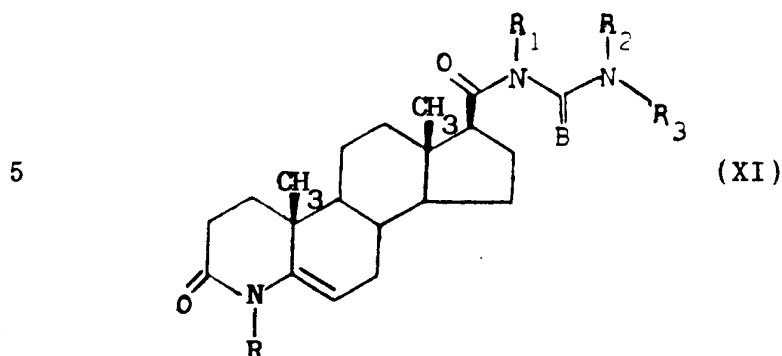
wherein R_1 , R_2 , R_3 and B are as defined above and
 cyclizing a compound of formula (IX) as defined above, in

- 12 -

the presence of a compound of formula (X)



wherein R is as defined above, so obtaining a compound of formula (XI)



wherein R, R₁, R₂, R₃ and B are as defined above and
 reducing a compound of formula (XI) as defined above, so
 obtaining a compound of formula (I) wherein the (X) bond
 and the (Y) bond are single bonds, A is an N-R group
 10 wherein R is as defined above and R₁, R₂, R₃ and B are as
 defined above and/or, if desired,
 f) dehydrogenating a compound of formula (I) wherein A,
 B, R₁, R₂, R₃ are as defined above, the (X) bond is a
 single bond and (Y) is a single or a double bond, so
 15 obtaining a compound of formula (I) wherein A, B, R₁, R₂,
 R₃ are as defined above and the (X) bond is a double bond
 and the (Y) bond is a single or double bond and, if
 desired, separating a mixture of isomers into the single

- 13 -

isomers.

The reaction between a compound of formula (II) and a compound of formula (III), according to the process variant a), may be carried out, e.g., refluxing the compound of formula (II) with a large excess of the compound of formula (III) in an organic solvent such as, for example, dioxane, toluene or xylene, or in pyridine in the presence of sodium, for a time varying from about 1 hour to about 48 hours, under inert atmosphere, of, e.g., nitrogen at a temperature varying from room temperature to about the refluxing temperature of the reaction mixture.

In particular, for example, the reaction may be carried out by methods analogous to those described in Eur. J. Med. Chem. 24, 421-26 (1989).

The reaction between a compound of formula (IV) and a compound of formula (V), according to the process variant b), may be carried out, e.g., stirring the mixture of the two compounds in a suitable anhydrous solvent such as, for example, diethyl ether, benzene, dioxane, methylene chloride, dimethylformamide, tetrahydrofuran, ethyl acetate or a mixture of them, optionally in the presence of an organic base such as, for example, pyridine or triethylamine at a temperature ranging from about 0°C to the reflux temperature of the reaction mixture, for a time ranging from about 2 hours to about 48 hours.

- 14 -

Alternatively, the reaction may be carried out by gradual addition of a compound of formula (IV) to a compound of formula (V) in hot pyridine.

The reaction between a compound of formula (VI) and a
5 compound of formula (VII) according to the process
variant c), may be carried out, e.g., by adding a
solution of freshly prepared acyl chloride of formula
(VI) dissolved in a solvent such as, for example,
tetrahydrofuran, dimethylformamide, dimethoxyethane,
10 preferably tetrahydrofuran, into a solution of the
compound (VII) or its potassium salt [obtained treating
the compound (VII) in a solvent such as, for example,
tetrahydrofuran, with excess of an alkaline metal
hydride, for instance, sodium or potassium hydride, and
15 then refluxing the mixture for, e.g., about 2 hours] in
a solvent such as, for example, tetrahydrofuran or
dimethylformamide, optionally in the presence of an
organic base such as pyridine or triethylamine, stirring
the mixture so obtained at room temperature for some
20 hours, and then quenching the reaction with diluted acid
such as, for example, hydrochloric acid, or with water.
The reaction between a compound of formula (VI) and a
compound of formula (VII) in the presence of a compound
of formula (VIII), according to the reaction variant d),
25 may be carried out following the procedure hereabove
described and quenching the reaction with a compound of

- 15 -

formula (VIII).

The oxidation of a compound of formula (I) according to the process variant e) may be carried out, for example, in the presence of an oxidizing agent such as sodium
5 metaperiodate and potassium permanganate and a base such as aqueous potassium carbonate in an organic solvent.

It is suitably performed at a temperature of from room temperature to about 60°C, typically for a period of from about one hour to about five hours.

10 Preferably the organic solvent is methanol, ethanol, acetone, tetrahydrofuran, dioxane, isopropanol, tert-butanol or a mixture of any of these.

The reaction is suitably performed by adding a solution of the oxidizing agent, for example sodium metaperiodate
15 and potassium permanganate, and the base such as potassium carbonate, in water to a solution of a compound of formula (I) in an organic solvent, or by adding simultaneously an aqueous solution of sodium metaperiodate and an aqueous solution of potassium
20 permanganate to a solution of a compound of formula (I) in an organic solvent and aqueous potassium carbonate. Alternatively, the oxidation of a compound of formula (I) may be carried out with ozone in an organic solvent.

The reaction is typically continued until all the
25 starting material is consumed. The temperature of the reaction is suitably from about -78°C to room

- 16 -

temperature. An oxidizing agent is then added to the reaction mixture to destroy the resulting ozonide. Preferably, the solvent is methylene chloride, ethylacetate, methanol or a mixture of any of these. The
5 oxidizing agent is preferably hydrogen peroxide.

The reaction between a compound of formula (IX) and a compound of formula (X) is preferably carried out in an anhydrous organic solvent at a temperature from about 60°C to the reflux temperature of the solvent. It is
10 suitably continued for a period of from about 30 minutes to about four hours.

Preferably the solvent is ethylene glycol, dimethylformamide, dimethylsulphoxide, ethanol, methanol, dioxane, ethylacetate or a mixture of any of these. When
15 the oxidation of a compound of formula (I) is carried out with ozone, it is possible to perform the cyclization reaction by treating directly the ozonide containing reaction mixture with the amine of formula (X), typically in excess, thereby directly obtaining a compound of
20 formula (XI).

The reduction of a compound of formula (XI) is preferably carried out in an organic solvent under hydrogen pressure varying from about 1 atm to about 10 atm, in the presence of hydrogenation catalyst. The temperature is typically
25 from room temperature to about 60°C. The reduction time typically varies from about 30 minutes to about five

- 17 -

hours.

Preferably the solvent is ethanol, acetic acid or a mixture of any of these and the hydrogenation catalyst is platinum oxide (Adam's Catalyst), 5 % or 10 % palladium
5 on charcoal or palladium hydroxide.

The dehydrogenation of a compound of formula (I) according to the above process variant f), which is preferably performed on a compound of formula (I) wherein R_1 is hydrogen, may be carried out by treatment with a
10 suitable dehydrogenating agent such as, e.g., chloranil, benzeneseleninic anhydride or dichlorodicyanobenzoquinone (DDQ), operating in an anhydrous solvent, such as, for example, chlorobenzene, dioxane, xylene, toluene or benzene, and, optionally, in the presence of BSTFA [bis-
15 (trimethylsilyl)trifluoroacetamide]. The reaction temperature may range from the room temperature to the reflux temperature of the solvent and the reaction time may vary approximately from about 2 hours to about 24 hours. Preferably the reaction is carried out under inert
20 atmosphere, e.g., nitrogen atmosphere.

The compounds of formula (II) wherein (X), (Y), A and R_1 are as defined above, are known compounds or they can be prepared by the methods usually used in the synthesis of amides (J.M.C. 29, 2298-2315, 1986) excluding the
25 compounds of formula (II) wherein A is an N-R group wherein R is as defined above, (Y) is a single bond, (X)

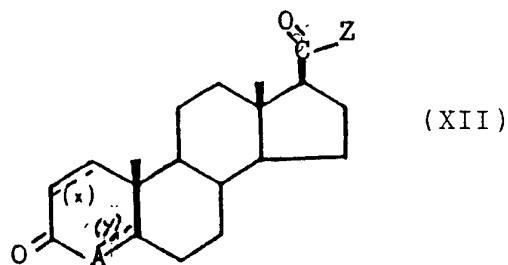
- 18 -

is a single or double bond and R_1 is a C_1-C_6 alkyl group wherein one or more hydrogen atoms are substituted by one or more fluorine atoms.

These latter compounds of formula (II) may be prepared,

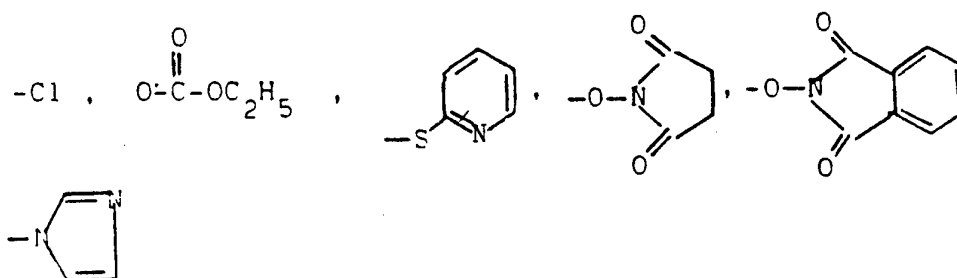
5 e.g.,

A) reacting a compound of formula (XII)



wherein the symbol ---- and R are as defined above and Z is an activating group of the carboxy function useful, in particular, in the formation of amidic and peptidic linkages; for instance one of the following groups:

10



with a compound of formula (XIII) or a salt thereof



- 19 -

wherein R_1 is as defined above, or

B) dehydrogenating a compound of formula (II) wherein A is a -N-R group wherein R, R_1 and the symbol ---- are as defined above and (X) and (Y) are single bonds so

5 obtaining a compound of formula (II) wherein (Y) is a single bond, A and R_1 , are as defined immediately hereabove and (X) is a double bond.

The reaction of a compound of formula (XII) with a compound of formula (XIII), according to the process
10 variant A), may be carried out in a solvent such as, for example, methylene chloride, ethyl acetate, tetrahydrofuran, dimethylformamide, benzene or toluene at a temperature ranging from about 0°C to about 100°C, for a time varying from about 1 hour to about 48 hours. If the
15 compound of formula (XIII) is in the salt-form a stoichiometric amount of an organic base, such as, for example, pyridine, or a tri- C_1 - C_6 -alkylamine, preferably triethylamine has to be added to the reaction mixture.

The dehydrogenation of a compound of formula (II) wherein
20 A is an -N-R group wherein R is as defined above according to the process variant B), which is preferably performed on a compound of formula (II) wherein R is hydrogen, may be carried out by treatment with a suitable dehydrogenating agent such as, e.g., chloranil, benzene-
25 seleninic anhydride or dichlorodicyanobenzoquinone (DDQ), operating in an anhydrous solvent, such as, for example,

- 20 -

chlorobenzene, dioxane, xylene, toluene or benzene, and, optionally, in the presence of BSTFA [bis-(trimethylsilyl)trifluoro acetamide]. The reaction temperature may range from the room temperature to the reflux temperature
5 of the solvent and the reaction time may vary approximately from about 2 hours to about 24 hours. Preferably the reaction is carried out under inert atmosphere, e.g., nitrogen atmosphere.

The compounds of formula (IV), are known compounds or can
10 be prepared by known procedures (e.g. according to PCT/WO 91/12261).

The compounds of formula (V) wherein each of R_1 and R_2 independently is a hydrogen atom a C_1-C_6 alkyl group or an aryl group are known compounds.

15 The compounds of formula (V), wherein each of R_1 and R_2 is independently a C_1-C_6 alkyl group or an aryl group, wherein one or more hydrogen atoms are substituted by one or more fluorine atoms, are known compounds (see, for example: Izv. Akad. Nauk. SSSR, Ser. Khim. 1967 (9),
20 2086-8, C.A. 68: 39719v; Izv. Akad. Nauk. SSSR, Ser. Khim. 1971 (7), 1481-6, C.A. 75: 140773c) or can be obtained according to the methods known for the synthesis of carbodiimides (see, for example Chem. Ber. 104, 1335-1336 (1971)).

25 The fluorinated ureas of formula (VII) are known compounds (see, for example, J. Med. Chem. 9, 892-911

- 21 -

(1966)) or they can be prepared by known methods for the synthesis of ureas (see, for example, J.O.C. 45, 886 (1980) or J. Chem. Soc. 1936, 1273).

The compounds of formulae (III), (VI), (VII), (VIII),
5 (X), (XII) and (XIII) are known compounds or they can be prepared by known procedures.

The compounds of the present invention inhibit specifically the testosterone 5 α -reductase enzyme and, therefore, are potent antiandrogens.

10 For example, the inhibitory effect of the compounds of the invention on 5 α -reductase was determined in vitro, according to the procedure reported herebelow.

Assay of 5 α -reductase inhibition:

Inhibition of 5 α -reductase was evaluated using the
15 particulate fraction from homogenates of hyperplastic human prostates as the enzyme source. The particulate fraction was prepared centrifuging prostate homogenate at 140,000 x g. The resulting pellet, washed several times, was resuspended in buffer and stored at -80°C in aliquots
20 containing a 10 mg protein/ml.

The assay for 5 α -reductase was done in a final volume of 0.5 ml, in 40 mM TRIS-HCl buffer pH 5.5, containing 1 mM dithiothreitol, 5 mM NADPH, 1 μ M [¹⁴C] testosterone, an aliquot of the enzyme preparation and various
25 concentrations of the inhibitors. After 30 min incubation

- 22 -

at 37°C the reaction was terminated by addition of 2 ml cold diethyl ether and the organic phase was separated, evaporated under N₂ and resuspended in ethyl acetate. Testosterone metabolites in this extract were separated
5 in TLC on silica gel F 254 plates (Merck) using chloroform, acetone and n-hexane (2:1:2) as developing solvent system.

Radioactivity on the plate was scanned and analyzed from quantitative plots printed by a TLC-analyzer (Berthold).
10 The fractional 5α-reduction of testosterone was calculated by relating the ¹⁴C-radioactivity in the 5α-reduced metabolites (5α-dihydrotestosterone, 3α- and 3β-androstanediols) regions to the total radioactivity in the testosterone and 5α-reduced metabolites regions.
15 The concentration of each compound required to reduce control 5α-reductase activity by 50% (IC₅₀) was determined.

In view of the above indicated activity the compounds of the invention are therapeutically useful in the
20 situations in which a decrease in androgen action, by means of 5α-reductase inhibition, is desirable such as, for example, benign prostatic hyperplasia, prostatic and breast cancers and certain skin-hair conditions such as, e.g. acne, seborrhoea, female hirsutism and male pattern
25 baldness. A mammal, e.g. a human or animal, may thus be treated by a method which comprises administering thereto

- 23 -

a pharmaceutically effective amount of a compound of formula (I) as defined above.

The toxicity of the compounds of the invention is quite negligible so that they can be safely used in therapy.

5 The compounds of the invention can be administered in a variety of dosage forms, e.g. orally, in the form of tablets, capsules, sugar- or film-coated tablets, liquid solutions or suspensions; rectally, in the form of suppositories; parenterally, e.g. intramuscularly, or by
10 intravenous injection or infusion; topically, e.g. in the form of creams.

The dosage depends on the age, weight, conditions of the patient and administration route; for example, the dosage adopted for oral administration to adult humans may range
15 from about 1 to 200 mg pro dose, from 1 to 3 times daily. As already said the invention includes pharmaceutical compositions comprising a compound of the invention in association with a pharmaceutically acceptable excipient (which can be carrier or diluent).

20 The pharmaceutical compositions containing the compounds of the invention are usually prepared following conventional methods and are administered in a pharmaceutically suitable form.

For example, the solid oral forms may contain, together
25 with the active compound, diluents, e.g., lactose, dextrose, saccharose, cellulose, corn starch or potato

- 24 -

starch; lubricants, e.g. silica, talc, stearic acid, magnesium or calcium stearate, and/or polyethylene glycols; binding agents, e.g. starches, arabic gums, gelatin, methylcellulose, carboxymethylcellulose or
5 polyvinyl pyrrolidone; dis-aggregating agents, e.g. a starch, alginic acid, alginates or sodium starch glycolate; effervescing mixtures; dyestuffs; sweeteners; wetting agents such as lecithin, polysorbates, lauryl-sulphates; and, in general, non-toxic and pharma-
10 cologically inactive substances used in pharmaceutical formulations. Said pharmaceutical preparations may be manufactured in known manner, for example, by means of mixing, granulating, tableting, sugar-coating, or film-coating processes.

15 The liquid dispersions for oral administration may be, e.g. syrups, emulsions and suspensions.

The syrups may contain as carrier, for example, saccharose or saccharose with glycerine and/or mannitol and/or sorbitol; in particular a syrup to be administered
20 to diabetic patients can contain as carriers only products not metabolizable to glucose, or metabolizable in very small amount to glucose, for example sorbitol.

The suspensions and the emulsions may contain as carrier, for example, a natural gum, agar, sodium alginate,
25 pectin, methylcellulose, carboxymethylcellulose, or polyvinyl alcohol.

- 25 -

The suspensions or solutions for intramuscular injections may contain, together with the active compound, a pharmaceutically acceptable carrier, e.g. sterile water, olive oil, ethyl oleate, glycol, e.g. propylene glycol and if
5 desired, a suitable amount of lidocaine hydrochloride.

The solutions for intravenous injections or infusions may contain as carrier, for example, sterile water or preferably they may be in the form of sterile, aqueous, isotonic saline solutions.

10 The suppositories may contain together with the active compound a pharmaceutically acceptable carrier, e.g. cocoa-butter, polyethylene glycol, a polyoxyethylene sorbitan fatty acid ester surfactant or lecithin.

Conventional carriers may be used for topical
15 formulations.

The following examples illustrate but do not limit the invention.

The reported NMR data are determined in deuteriochloroform (CDCl_3), unless otherwise specified, and are reported as
20 parts per million (δ) downfield from tetramethylsilane.

- 26 -

Example 1

1-(3-oxo-4-aza-5 α -androst-1-ene-17 β -carbonyl)-1,3-di-(2,2,2-trifluoroethyl)urea.

[(I):(X)=double, (Y)=single, A=NH, B=O, R₁=CH₂-CF₃, R₂=H,
5 R₃=CH₂-CF₃].

A mixture of 1-(3-oxo-4-aza-5 α -androstane-17 β -carbonyl)-1,3-di-(2,2,2-trifluoroethyl)urea (36.1 mg) and benzene-seleninic anhydride (36.0 mg) in chlorobenzene (5.0 ml) are heated at 120°C for 14 hours.

10 The solvent is removed in vacuo and the residue is chromatographed on silica gel (eluant methylene chloride/acetone 9:1), so obtaining 11.2 mg of the title compound.

Following an analogous procedure 1-(3-oxo-4-aza-5 α -
15 androst-1-ene-17 β -carbonyl)-1,3-di-(3,3,3,1,1,1-hexafluoroprop-2-yl)urea can be prepared.

Example 2

1-(4-methyl-3-oxo-4-aza-5 α -androstane-17 β -carbonyl)-1-(2,2,2-trifluoroethyl)-3-ethylurea.

20 [(I):(X)=single; (Y)=single, A=N-CH₃, B=O, R₁=CH₂CF₃, R₂=H, R₃=CH₂-CH₃].

- 27 -

A mixture of N-(2,2,2-trifluoroethyl)-4-methyl-3-oxo-4-aza-5 α -androstane-17 β -carboxamide (104 mg) in toluene (3 ml) and ethyl isocyanate (0.2 ml) were refluxed overnight.

- 5 The solvents were removed under vacuum and the residue dissolved in methylene chloride, washed with water and anhydriified over sodium sulphate.

The solvent was evaporated under vacuum and the crude product was purified by flash chromatography on silica
10 gel (eluant methylene chloride/acetone 9:1), so obtaining 37 mg of the title compound.

Using the appropriate starting material and following an analogous procedure 1-(3-oxoandrost-4-ene-17 β -carbonyl)-1-(2,2,2-trifluoroethyl)-3-ethylurea can be prepared.

15 Example 3

1-(4-methyl-3-oxo-4-aza-5 α -androstane-17 β -carbonyl)-1,3-di-(2,2,2-trifluoroethyl)urea.

[(I):(X)=single, (Y)=single, A=N-CH₃, B=O, R₁=CH₂-CF₃, R₂=H, R₃=CH₂-CF₃].

- 20 1,3-di-(2,2,2-trifluoroethyl)urea (obtained treating 2,2,2-trifluoroethylamine hydrochloride with triethylamine and trifosgene) (500 mg) in methylene chloride (20 ml) was treated with carbon tetrachloride

- 28 -

(0.215 ml), triethylamine (0.310 ml) and triphenylphosphine (702 mg) and the mixture was refluxed for 2 hours.

The yellow solution was cooled at room temperature, solid
 5 4-methyl-3-oxo-4-aza-5 α -androstande-17 β -carboxylic acid (595 mg) was added and the mixture was stirred overnight at room temperature.

The solvent was evaporated under vacuum and the crude was purified by flash chromatography on silica gel (eluant:
 10 benzene/methanol 98:2) to afford 127 mg of the title compound as a white solid (m.p. 90-95°C)

MS (m/z): 513 M⁺

414 M - O=C=N-CH₂CF₃⁺

399 M - O=C=N-CH₂CF₃ - CH₃⁺

15 NMR (CDCl₃) δ : 9.60 (bs, 1H, CONH), 5.10 and 4.25 (2m, 2H, CON(CH₂CF₃)CO), 3.98 (m, 2H, CONHCH₂CF₃), 3.03 (dd, 1H, H(5 α)), 2.97 (t, 1H, H(17 α)), 2.92 (s, 3H, N-CH₃), 0.88 (s, 3H, CH₃(19)), 0.72 (s, 3H, CH₃(18)).

Using the appropriate starting material and following an
 20 analogous procedure the compounds listed below can be prepared:

1-(3-oxo-4-aza-5 α -androstand-1-ene-17 β -carbonyl)-1,3-di-(2,2,2-trifluoroethyl)urea;

1-(3-oxo-4-aza-5 α -androstande-17 β -carbonyl)-1,3-di-(2,2,2-trifluoroethyl)urea;

25 1-(4-methyl-3-oxo-4-aza-5 α -androstand-1-ene-17 β -carbonyl-

- 29 -

- 1,3-di-(2,2,2-trifluoroethyl)urea;
 1-(4-methyl-3-oxo-4-aza-5 α -androstane-17 β -carbonyl)-1,3-
 di-(2,2,2-trifluoroethyl)thiourea;
 1-(3-oxo-4-aza-5 α -androst-1-ene-17 β -carbonyl)-1,3-di-
 5 (3,3,3,1,1,1-hexafluoroprop-2-yl)urea;
 1-(4-methyl-3-oxo-4-aza-5 α -androstane-17 β -carbonyl)-1,3-
 di-(3,3,3,1,1,1-hexafluoroprop-2-yl)urea;
 1-(4-methyl-3-oxo-4-aza-5 α -androstane-17 β -carbonyl)-1-
 nonafluorotertbutyl-3-phenylurea;
 10 1-(4-methyl-3-oxo-4-aza-5 α -androstane-17 β -carbonyl)-1-
 (3,3,3,1,1,1-hexafluoroprop-2-yl)-3-phenylurea;
 1-(3-oxoandrost-4-ene-17 β -carbonyl)-1,3-di-(2,2,2-
 trifluoroethyl)urea;
 1-(3-oxoandrost-4-ene-17 β -carbonyl)-1-(2,2,2-trifluoro-
 15 ethyl)-3-ethylurea;
 1-(3-oxoandrost-4-ene-17 β -carbonyl)-1,3-di-(3,3,3,1,1,1-
 hexafluoroprop-2-yl)urea.

Example 4

- 1-(4-methyl-3-oxo-4-aza-5 α -androstane-17 β -carbonyl)-1-
 20 (2,2,2-trifluoroethyl)-3,3-diethylurea.

[(I):(X)=single, (Y)=single, A=N-CH₃, B=O, R₁=CH₂-CF₃,
 R₂=CH₂-CH₃, R₃=CH₂-CH₃].

- 30 -

1,1-diethyl-3-(2,2,2-trifluoroethyl)urea [obtained
acylating the 2,2,2-trifluoroethylamine with N,N-
diethylcarbamoyl chloride] (119 mg) in tetrahydrofuran
(2.0 ml) was added dropwise to a mixture of pentane
5 washed potassium hydride (20%; excess) in tetrahydrofuran
(2.0 ml) at room temperature under inert atmosphere of
nitrogen.

The reaction mixture was then heated to reflux for 80
minutes, cooled to room temperature and treated dropwise
10 with a solution of 4-methyl-3-oxo-4-aza-5 α -androstane-
17 β -carbonyl chloride (150 mg) in tetrahydrofuran (3 ml).
After stirring at room temperature for 36 hours the
mixture was cooled with an ice-bath, acidified with 1N
hydrochloric acid and extracted thoroughly with ethyl
15 acetate.

The organic layers were combined, washed with water,
dried over sodium sulphate to give, after removal of the
solvents, 277 mg of a yellow oil that was purified by
flash chromatography (eluant methylene chloride/acetone
20 8:2) to yield 80 mg of the title compound.

MS (m/z): 513 M⁺

NMR (CDCl₃) δ : 4.45 and 4.13 (2m, 2H, 2CH₂CF₃), 3.42 (m,
4H, N(CH₂CH₃)₂), 3.03 (dd, 1H, H(5 α)), 2.93 (s, 3H, N-
CH₃), 1.20 (t, 6H, N(CH₂CH₃)₂), 0.88 (s, 3H, CH₃(19)), 0.76
25 (s, 3H, CH₃(18)).

- 31 -

Following the same procedure 1-(3-oxoandrost-4-ene-17 β -carbonyl)-1-(2,2,2-trifluoroethyl)-3,3-diethylurea was obtained.

Example 5

5 1-(4-methyl-3-oxo-4-aza-5 α -androstane-17 β -carbonyl)-1,3-di-(2,2,2-trifluoroethyl)urea.

[(I):(X)=single, (Y)=single, A=N-CH₃, B=O, R₁=CH₂-CF₃, R₂=H, R₃=CH₂-CF₃].

To a solution of 1-(3-oxoandrost-4-ene-17 β -carbonyl)-1,3-
10 di-(2,2,2-trifluoroethyl)urea (353 mg) in tert-butanol (4 ml) and methylene chloride (4 ml) maintained at 35-40°C, 2M sodium carbonate (0.518 ml) is added.

Aqueous 2% potassium permanganate solution (0.441 ml) and sodium metaperiodate (1.05 g in 6.53 ml of water) are
15 added dropwise simultaneously to the mixture over a period of 30 minutes.

The resulting suspension is stirred for 3 hours and then the tert-butanol is removed under vacuum.

After acidification with 1N hydrochloric acid and
20 dilution with water the reaction mixture is extracted with methylene chloride.

The combined extracts are washed several times with water, anhydried over sodium sulphate and the solvent

- 32 -

is removed under vacuum, so obtaining 300 mg of solid seco-ketoacid.

[(IX): B=O, $R_1=CH_2-CF_3$, $R_2=H$, $R_3=CH_2CF_3$].

A suspension of seco-ketoacid (300 mg) in dioxane (10 ml)
5 is treated with an excess of liquid methylamine and heated to about 80°C for 1 hour into an autoclave.

After removing the excess of methylamine by a nitrogen flow, the solution is concentrated, poured into water and extracted with ethyl acetate; the organic extracts are
10 washed with 1N hydrochloric acid, with brine, anhydriified over sodium-sulphate and the solvent is removed under vacuum.

The brown crude oil is purified by flash chromatography (eluant: methylene chloride/acetone 9:1), so obtaining
15 130 mg of 1-(4-methyl-3-oxo-4-aza-5 α -androst-5-ene-17 β -carbonyl)-1,3-di-(2,2,2-trifluoroethyl)urea.

The $\Delta^{5,6}$ -unsaturated-4-aza-steroid (130 mg) is dissolved in absolute ethanol and hydrogenated over platinum oxide (Adams' Catalyst) under about 50 psi of hydrogen at about
20 45-50°C.

The catalyst is filtered off and the solvent is evaporated under vacuum, so affording 125 mg of the title compound as a whitish solid (m.p. 88-93°C).

The final mixture was encapsulated in the conventional
25 manner.

- 33 -

Example 6

Scored tablets for oral use, each containing 250 mg of the active substance, were manufactured as follows.

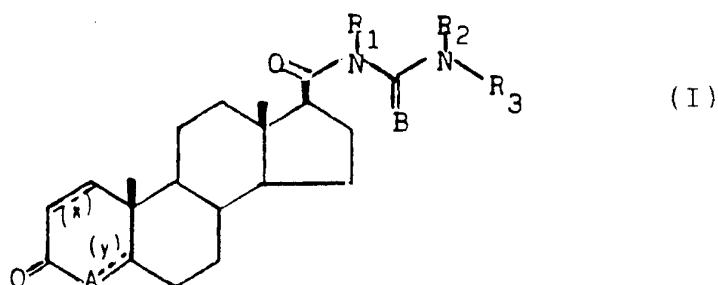
Composition (for 10,000 tablets)

5	1-(4-methyl-3-oxo-4-aza-5 α -androstane-17 β -carbonyl)-1,3-di-(2,2,2-trifluoroethyl)urea	2500 g
	Corn starch	280 g
	Talc powder	180 g
	Calcium stearate	40 g

- 10 The active substance was granulated with a 4% w/v aqueous solution of methyl cellulose. To the dried granules a mixture of the remainder of the ingredients is added and the final mixture compressed into tablets of proper weight.

CLAIMS

1. A compound of formula (I)



wherein:

- 5 The symbol ---- is a single or a double bond;
- A is a CH group or an N-R group wherein R is hydrogen or a C₁-C₄ alkyl group provided that, when A is a CH group, (Y) is a double bond and when A is an N-R group (Y) is a single bond, and in position 5
- 10 there is a hydrogen atom with α-configuration;
- B is an oxygen atom or a sulphur atom;
- each of R₁, R₂, R₃ independently is a hydrogen atom or a C₁-C₆ alkyl or aryl group wherein, optionally, one or more hydrogen atoms are substituted by one or more
- 15 fluorine atoms provided that at least one hydrogen atom in R₁, R₂, R₃ is substituted by a fluorine atom.

2. A compound of formula (I) wherein:

The symbol ---- is a single or a double bond;

- 35 -

A is a CH group or an N-R group wherein R is a hydrogen atom or a methyl group provided that when A is a CH group (Y) is a double bond, and when A is an N-R group (Y) is a single bond and in position 5 there is a hydrogen atom with α -configuration;

B is an oxygen atom or a sulphur atom;

each of R_1 , R_2 and R_3 independently is H, CH_3 , C_2H_5 , $CH(CH_3)_2$, $C(CH_3)_3$, CH_2CF_3 , $CH(CH_3)CF_3$, $CH(CF_3)_2$, $C(CF_3)_3$ or phenyl, provided that at least one hydrogen atom in R_1 , R_2 , R_3 is substituted by a fluorine atom.

3. A compound selected from the group consisting of:

1-(3-oxo-4-aza-5 α -androst-1-ene-17 β -carbonyl)-1,3-di-(2,2,2-trifluoroethyl)urea;

1-(3-oxo-4-aza-5 α -androstane-17 β -carbonyl)-1,3-di-(2,2,2-trifluoroethyl)urea;

1-(4-methyl-3-oxo-4-aza-5 α -androst-1-ene-17 β -carbonyl)-1,3-di-(2,2,2-trifluoroethyl)urea;

1-(4-methyl-3-oxo-4-aza-5 α -androstane-17 β -carbonyl)-1,3-di-(2,2,2-trifluoroethyl)urea;

1-(4-methyl-3-oxo-4-aza-5 α -androstane-17 β -carbonyl)-1,3-di-(2,2,2-trifluoroethyl)thiourea;

1-(3-oxo-4-aza-5 α -androst-1-ene-17 β -carbonyl)-1,3-di-(3,3,3,1,1,1-hexafluoroprop-2-yl)urea;

1-(4-methyl-3-oxo-4-aza-5 α -androstane-17 β -carbonyl)-1,3-di-(3,3,3,1,1,1-hexafluoroprop-2-yl)urea;

- 36 -

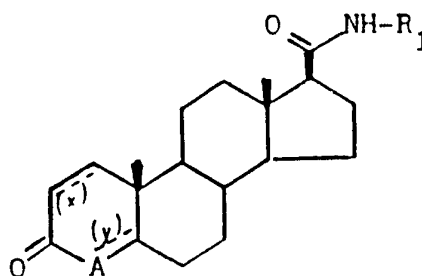
- 1-(4-methyl-3-oxo-4-aza-5 α -androstande-17 β -carbonyl)-1-(2,2,2-trifluoroethyl)-3-ethylurea;
 1-(4-methyl-3-oxo-4-aza-5 α -androstande-17 β -carbonyl)-1-(2,2,2-trifluoroethyl)-3,3-diethylurea;
 5 1-(4-methyl-3-oxo-4-aza-5 α -androstande-17 β -carbonyl)-1-nonafluorotertbutyl-3-phenylurea;
 1-(4-methyl-3-oxo-4-aza-5 α -androstande-17 β -carbonyl)-1-(3,3,3,1,1,1-hexafluoroprop-2-yl)-3-phenylurea;
 1-(3-oxoandrostande-4-ene-17 β -carbonyl)-1,3-di-(3,3,3,1,1,1-hexafluoroprop-2-yl)urea;
 10 1-(3-oxoandrostande-4-ene-17 β -carbonyl)-1,3-di-(2,2,2-trifluoroethyl)urea;
 1-(3-oxoandrostande-4-ene-17 β -carbonyl)-1-(2,2,2-trifluoroethyl)-3-ethylurea; and
 15 1-(3-oxoandrostande-4-ene-17 β -carbonyl)-1-(2,2,2-trifluoroethyl)-3,3-diethylurea.

4. A process for the preparation of a compound of formula

(I) according to claim 1 comprising:

a) reacting a compound of formula (II)

20



(II)

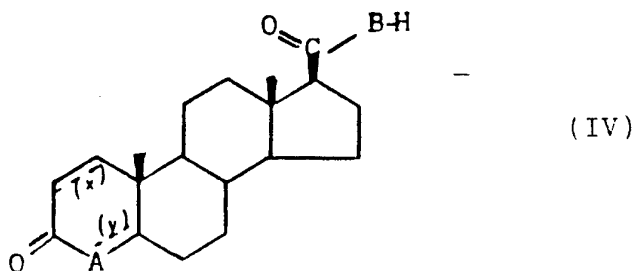
- 37 -

wherein the symbol ----, A and R_1 are as defined in claim 1 with a compound of formula (III)



wherein R_2 and B are as defined in claim 1, so obtaining a compound of formula (I) wherein the symbol ----, A, B, R_1 and R_2 are as defined in claim 1 and R_3 is hydrogen; or

b) reacting a compound of formula (IV)



wherein the symbol ----, A and B are as defined in claim 1 with a compound of formula (V)

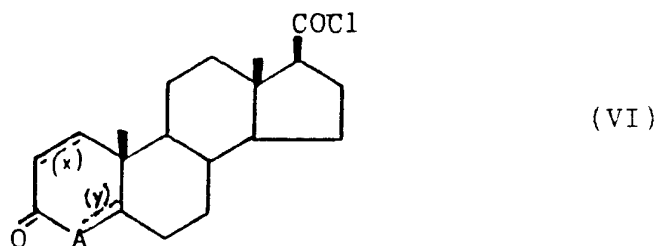


wherein each of R_1 and R_2 independently is a C_1-C_8 alkyl group or an aryl group wherein optionally one or more hydrogen atoms are substituted by one or more fluorine atoms, so obtaining a compound of formula (I) wherein the symbol ----, A and B, are

- 38 -

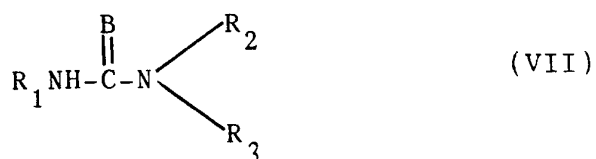
as defined in claim 1, each of R_1 and R_2 is independently a C_1-C_6 alkyl group or an aryl group, wherein optionally one or more hydrogen atoms are substituted by one or more fluorine atoms and R_3 is hydrogen, provided that at least one hydrogen atom in R_1 or R_2 is substituted by a fluorine atom; or

5 c) reacting a compound of formula (VI)



wherein the symbol ---- and A are as defined in claim 1 with a compound of formula (VII)

10



wherein R_1 , R_2 , R_3 and B are as defined in claim 1 so obtaining a compound of formula (I) wherein the symbol ----, A, B, R_1 , R_2 and R_3 are as defined in claim 1; or

15

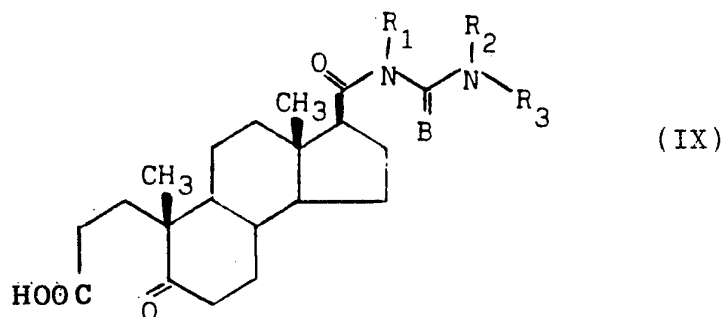
d) reacting a compound of formula (VI), as defined above with a compound of formula (VII), wherein R_1

- 39 -

is hydrogen and R_2 , R_3 and B are as defined above,
and a compound of formula (VIII)



wherein R_1 is as defined in claim 1 but it isn't
hydrogen and W is a halogen atom, so obtaining a
compound of formula (I) wherein the symbol ----,
A, B, R_2 and R_3 are as defined in claim 1, and R_1 is
as defined in claim 1, but it isn't hydrogen; or
e) oxidative opening of the A-ring of compound of
formula (I), wherein the (X) bond is a single
bond, A is a CH group, (Y) is a double bond and R_1 ,
 R_2 , R_3 and B are as defined in claim 1, so
obtaining a compound of formula (IX)

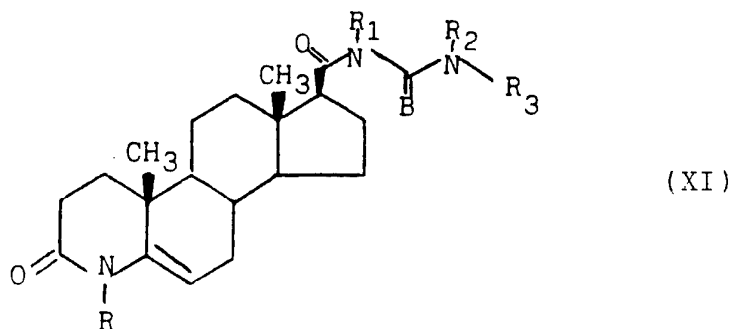


wherein R_1 , R_2 , R_3 and B are as defined in claim 1
and cyclizing a compound of formula (IX) as
defined above, in the presence of a compound of
formula (X)



- 40 -

wherein R is as defined in claim 1, so obtaining a compound of formula (XI)



wherein R, R₁, R₂, R₃ and B are as defined in claim 1 and reducing a compound of formula (XI) as defined above, so obtaining a compound of formula (I) wherein the (X) bond and the (Y) bond are single bonds, A is an N-R group wherein R is as defined in claim 1 and R₁, R₂, R₃ and B are as defined in claim 1 and/or, if desired,

f) dehydrogenating a compound of formula (I) wherein A, B, R₁, R₂, R₃ are as defined in claim 1, the (X) bond is a single bond and (Y) is a single or a double bond, so obtaining a compound of formula (I) wherein A, B, R₁, R₂, R₃ are as defined in claim 1 and the (X) bond is a double bond and the (Y) bond is a single or double bond and, if desired, separating a mixture of isomers into the single isomers.

- 41 -

5. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and/or diluent and, as an active principle, a compound of formula (I) according to claim 1.
- 5 6. A compound of formula (I) according to claim 1 for use as a testosterone 5 α -reductase inhibitor.
7. Use of a compound of formula (I) according to claim 1 in the manufacture of a medicament for use as a testosterone 5 α -reductase inhibitor.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 93/02035

A. CLASSIFICATION OF SUBJECT MATTER

IPC 5 C07J73/00 C07J41/00 A61K31/56 A61K31/58

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 5 C07J A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO,A,91 12261 (FARMITALIA CARLO ERBA S.R.L.) 22 August 1991 see claims; examples ---	1,4,5
A	US,A,4 191 759 (D. B. R. JOHNSTON ET AL) 4 March 1980 see the whole document -----	1,5

☐ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

29 November 1993

Date of mailing of the international search report

21.12.93

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+31-70) 340-3016

Authorized officer

Moreno, C

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 93/02035

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9112261	22-08-91	AU-A- 7230791 EP-A- 0468012 JP-T- 4505462 US-A- 5155107	03-09-91 29-01-92 24-09-92 13-10-92
US-A-4191759	04-03-80	NONE	