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(54) Title: EPIHERMS OF (22RS)-N-(1,1,1-TRIFLUORO-2-PHENYLPROP-2-YL)-3-OXO-4-AZA-5α-ANDROST-1-ENE-17β-CARBOXAMIDE

(57) Abstract

The present invention relates to the epimers: (22R)-N-(1,1,1-trifluoro-2-phenylprop-2-yl)-3-oxo-4-aza-5α-androst-1-ene-17β-carboxamide and (22S)-N-(1,1,1-trifluoro-2-phenylprop-2-yl)-3-oxo-4-aza-5α-androst-1-ene-17β-carboxamide useful as inhibitors of testosterone 5α-reductase enzyme, to a process for their preparation and to pharmaceutical compositions containing them.
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EPIMERS OF (22RS)-N-(1,1,1-TRIFLUORO-2-PHENYLPROP-2-YL)-3-OXO-4-AZA-5α-ANDROST-1-ENE-17β-CARBOXAMIDE

The present invention relates to two epimers of formula (I) and (II)

![Chemical Structures]

namely (22R)-N-(1,1,1-trifluoro-2-phenylprop-2-yl)-3-oxo-4-aza-5α-androst-1-ene-17β-carboxamide [compound of formula (I)] and (22S)-N-(1,1,1-trifluoro-2-phenylprop-2-yl)-3-oxo-4-aza-5α-androst-1-ene-17β-carboxamide [compound of formula (II)].

In the formulas of the present description the dashed line (-----) indicates a substituent in α configuration, i.e. below the plane of the ring, and the wedged line (-) indicates a substituent in β configuration, i.e. above the plane of the ring.
Metabolites and metabolic precursors of the compounds of formula (I) and (II) are within the scope of the present invention. The mixture of the epimers of formula (I) and (II) in ratio 1:1, namely the compound (2RS)-N-(1,1,1-trifluoro-2-phenylprop-2-yl)-3-oxo-4-aza-5α-androst-1-ene-17β-carboxamide (laboratory code FCE 28260), has already been described in our previous International Patent Application WO 94/03475 (see compound 41 at page 15 and Example 5, page 45), whereas the single epimer (22R) or (22S) has never been specifically mentioned therein.

The epimer mixture proved to be a potent inhibitor of testosterone 5α-reductase enzyme both in vitro and in vivo (see data reported in Table (I), page 33 of WO 94/03475) and therefore useful in those cases in which a reduction of androgenic activity is desired, for example, in treating benign prostatic hyperplasia, breast and prostate cancer and certain skin-hair alterations, for example, in treating acne, seborrhea, female hirsutism and male pattern baldness.

We have now separated the two epimers from their epimeric mixture and evaluated their activity as inhibitors of testosterone 5α-reductase enzyme.

The two epimers can be obtained, for example, following the method described in WO 94/03475 and subsequent separation of the epimer mixture thereof. Said separation can be carried out, for example, by means of high pressure liquid chromatography (HPLC).

Alternatively, the single epimers can be obtained, independently from each other, by reacting 3-oxo-4-aza-5α-androst-1-ene-17β-carboxylic acid with each single enantiomer of 1,1,1-trifluoro-2-phenylprop-2-yl amine previously resolved.
Additionally, as the corresponding epimeric amides obtained reacting 3-oxo-androst-4-ene-17β-carboxylic acid with (+)-1,1,1-trifluoro-2-phenylprop-2-yl amine are more easily separable than the corresponding 3-oxo-4-aza-5α-androst-1-ene-17β-carboxamide epimers, the single pure epimers can be advantageously obtained by:

a) reacting 3-oxo-androst-4-ene-17β-carboxylic acid, or a derivative thereof, with (+)-1,1,1-trifluoro-2-phenylprop-2-yl amine;

b) separating the two epimers of the so obtained (22RS)-N-(1,1,1-trifluoro-2-phenylprop-2-yl)-3-oxo-androst-4-ene-17β-carboxamide (e.g. by flash chromatography on silica gel);

c) converting the so obtained epimers separately into the final epimers of formulas (I) and (II), according to known reactions.

This synthetic route is reported in the following reaction Scheme I (the absolute configurations at C(22) are tentative):
SCHEME I

\[ \text{III} \xrightarrow{d} \text{IV} \xrightarrow{e} \]

\[ \text{V} \xrightarrow{f} \text{VI} \xrightarrow{g} \]

\[ \text{VIa} \quad \text{Rf inf} \]

\[ \text{[\(\alpha\)_D} +126^\circ \text{ (c 1, abs. EtOH)} \]

\[ \text{VIb} \quad \text{Rf sup} \]

\[ \text{[\(\alpha\)_D} +187^\circ \text{ (c 1, abs. EtOH)} \]

\[ \xrightarrow{h} \]

\[ \text{d) NaOH, H}_2\text{O, Dioxane / reflux / 3h} \]
\[ \text{e) (COCl)}_2, \text{Toluene / RT / 3h} \]
\[ \text{f) (+)-PhCF}_3\text{(CH}_3\text{)CNH}_2, \text{Pyridine, CHCl}_3 / \text{reflux / 5h} \]
\[ \text{g) Chromatographic separation} \]
\[ \text{h) KMnO}_4, \text{NaIO}_4, \text{tBuOH / 35-40 °C / 2h} \]
SCHEME 1 (cont'd)

\[
\begin{align*}
\text{[\(\alpha\)]}_D & \quad +108^\circ \text{ (c 1, abs. EtOH)} \\
\text{(VIIa)} & \quad \text{i} \\
\text{[\(\alpha\)]}_D & \quad +48^\circ \text{ (c 1, abs. EtOH)} \\
\text{(VIIIa)} & \quad \text{l} \\
\text{[\(\alpha\)]}_D & \quad +12^\circ \text{ (c 1, abs. EtOH)} \\
\text{(IXa)} & \quad \text{m} \\
\text{[\(\alpha\)]}_D & \quad +46^\circ \text{ (c 1, CHCl}_3) \\
\text{Rf inf} & \\
\text{(FCE 29331)} & \\
\text{[\(\alpha\)]}_D & \quad +62^\circ \text{ (c 1, abs. EtOH)} \\
\text{(IXb)} & \quad \text{m} \\
\text{[\(\alpha\)]}_D & \quad +21^\circ \text{ (c 1, CHCl}_3) \\
\text{Rf sup} & \\
\text{(FCE 29330)} & \\
\end{align*}
\]

i) \(\text{NH}_3, (\text{CH}_2\text{OH})_2\) / 0 - 180 °C / 2h
l) \(\text{H}_2/\text{PtO}_2, \text{AcOH} / 40 - 50 \text{ psi} / 45 - 50^\circ \)
m) \((\text{PhSeO})_2\text{O}, \text{PhCl} / \text{reflux/ 5h}\)
As reported hereinbelow, \textit{in vitro} biological tests for inhibition of human prostatic testosterone 5α-reductase enzyme unexpectedly showed that one of the two epimers, tested separately, is approximately two-fold more potent than the other, while the epimeric mixture, as expected, has intermediate activity.

Therefore, object of the present invention are the two epimers of formula (I) and (II) as reported above, and their use as 5α-reductase inhibitors.

These epimers are useful in those cases in which a reduction of androgenic activity is desired, for example, in the treatment and/or chemoprevention of benign prostatic hyperplasia and prostatic cancer. Moreover, these epimers can be used in the treatment of breast cancer and certain skin-hair alterations, for example, in the treatment of acne, seborrhea, female hirsutism and male pattern baldness.

Furthermore, the present invention relates to pharmaceutical compositions comprising one of the epimers of formula (I) or (II), or a mixture thereof, wherein one of the epimers is present in a prevailing amount with respect to the other epimer, in combination with one or more pharmaceutically acceptable carriers and/or diluents.

The pharmaceutical compositions containing the compounds of the invention are usually prepared according to conventional methods and are administered in a suitable pharmaceutical form, such as, for example, one of those described in WO 94/03475.

The following examples further illustrate the invention.

\textbf{Example 1}

\((22\text{RS})-N-(1,1,1\text{-trifluoro-2-phenylprop-2-yl})-3\text{-oxo-4-aza-5\text{$\alpha$}-androst-1-ene-17\text{$\beta$}-carboxamide}\)
To a suspension of 3-oxo-4-aza-5α-androstane-17β-carboxylic acid (7 g) in chloroform (100 mL), a solution of thionyl chloride (SOCl₂) (35 mL) in chloroform (15 mL) was added dropwise, under nitrogen, over 30 minutes, keeping the reaction mixture at about +3°C in an ice-water bath. The suspension was stirred at room temperature for 1 h, and then the volatile compounds were evaporated under vacuum. A white solid was obtained.

The solid was suspended in chloroform (330 mL) and the suspension was cooled to +3°C; pyridine (1.78 mL) and then (±)-1,1,1-trifluoro-2-phenylprop-2-yl amine (7.1 g) were added and the reaction mixture heated to 60°C for 4 h and then stirred at room temperature overnight. The reaction mixture was poured into an ammonium chloride saturated aqueous solution (500 mL), the organic layer was separated and the aqueous layer extracted with methylene chloride (2 x 100 mL). The combined organic extracts were washed with water, dried over sodium sulfate and the solvent was removed under vacuum. The crude was purified by flash chromatography on silica gel (eluant: methylene chloride/acetone 70:30) to yield 7.036 g of (22RS)-N-(1,1,1-trifluoro-2-phenylprop-2-yl)-3-oxo-4-aza-5α-androst-1-ene-17β-carboxamide [(epimeric ratio 50:50 by HPLC (column: Partisphere C8, 4.6 x 250 mm; eluant: acetonitrile/water 50:50; flow: 1 mL/min; detector: UV at 210 nm)].

Example 2

Separation of the mixture into the single epimers by preparative HPLC.

Apparatus: PrepLC/System 500 (Water Associates)
Columns: 2 PrepPAK-500/SILICA
Eluant: Toluene/Acetic acid/methanol  100:3:3
Flow: 150 mL/min
Detector: Refractive index

As the absolute configuration of the single epimers was not established by X-ray crystallography, they were identified by laboratory code numbers FCE 29330 for the first eluted epimer (Rf sup.) and FCE 29331 for the second eluted compound (Rf inf.).

**FCE 29330**

NMR (CDCl₃) δ: 7.50-7.33 (m, 5H, Ph), 6.78 (d, 1H, H(1)), 5.87 (bs, 1H, NH(21)), 5.82 (dd, 1H, H(2)), 5.48 (bs, 1H, NH(4)), 3.33 (dd, 1H, H(5a)), 2.07 (s, 3H, C(CF₃)CH₂Ph), 0.98 (s, 3H, Me(19)), 0.72 (s, 3H, Me(18)).

[α]₀D +46.7° (c 0.89, abs. EtOH)

**FCE 29331**

NMR (CDCl₃) δ: 7.50-7.33 (m, 5H, Ph), 6.78 (d, 1H, H(1)), 5.90 (bs, 1H, NH(21)), 5.82 (dd, 1H, H(2)), 5.48 (bs, 1H, NH(4)), 3.33 (dd, 1H, H(5a)), 2.04 (s, 3H, C(CF₃)CH₂Ph), 0.98 (s, 3H, Me(19)), 0.68 (s, 3H, Me(18)).

[α]₀D +58.3° (c 0.061, abs. EtOH)

**Example 3**

Resolution of racemic (+)-1,1,1-trifluoro-2-phenylprop-2-yl amine into the single enantiomers

The racemic (+)-1,1,1-trifluoro-2-phenylprop-2-yl amine was treated with (+)-O,0′-dibenzoyl-D-tartaric acid; the
diastereomeric salts were crystallized from isopropanol. After 5 crystallizations a partially resolved amine was obtained, in which the (+)-enantiomer prevailed [enantiomeric ratio: (+)/(-) = 88/12].

Analogously, after 5 crystallizations of the diastereomeric salts of the racemic amine with (-)-O,O'-dibenzoyl-L-tartaric acid from isopropanol, an amine enriched in the (-)-enantiomer was obtained [enantiomeric ratio: (+)/(-) = 12/88].

Example 4

Reacting 3-oxo-4-aza-5α-androstane-17β-carboxylic acid with an amine enriched in the (+)-enantiomer [enantiomeric ratio (+)/(-) = 88/12], a mixture of FCE 29331 and FCE 29330 was obtained, in which the epimer ratio was FCE 29331/FCE 29330 = 88/12 (determined by HPLC).

Reacting 3-oxo-4-aza-5α-androstane-17β-carboxylic acid with an amine enriched in the (-)-enantiomer [enantiomeric ratio (+)/(-) = 12/88], a mixture of FCE 29331 and FCE 29330 was obtained, in which the epimer ratio was FCE 29331/FCE 29330 = 12/88 (determined by HPLC).

Example 5

(22RS)-N-(1,1,1-trifluoro-2-phenylprop-2-yl)-3-oxo-androst-4-ene-17β-carboxamide (compound (VI))

To a suspension of 3-oxo-androst-4-ene-17β-carboxylic acid (compound (IV)) (2.00 g) in toluene (28 mL) and pyridine (0.640 mL), cooled to 10°C, a solution of oxalyl chloride (0.68 mL) in toluene (4 mL) was added over 10 minutes. The
cooling bath was removed and the mixture was stirred at room temperature for 1.5 h. The volatile compounds were removed under reduced pressure at a temperature below 40°C. The acyl chloride so obtained (compound (V)) was dissolved in chloroform (100 mL), cooled in an ice-water bath; triethylamine (0.876 mL), and then a solution of (±)-1,1,1-trifluoro-2-phenylprop-2-yl amine (2.375 g) in chloroform (4 mL) were added. The reaction mixture was heated to reflux for 4 h. The reaction mixture was poured into a chilled saturated sodium chloride aqueous solution of (200 mL) and extracted with methylene chloride (3 × 100 mL); the organic extracts were washed with water, dried over sodium sulfate and the solvent was removed under reduced pressure. 2.150 g of the title compound were obtained.

The two epimers were separated by flash chromatography on silica gel (eluant: n-hexane/ethyl acetate 70:30) to yield 770 mg of the less retained (R_f sup.) epimer and 700 mg of the most retained (R_f inf.) epimer.

Following an analogous procedure, using a (+)-enantiomerically enriched amine [enantiomeric ratio (+)/(-) = 88/12] a final compound with the same epimeric ratio between the R_f inf. and R_f sup. epimers was obtained. This fact shows that the (+)-amine yields the R_f inf. epimer.

Analogously, using the (-)-enriched amine a final compound enriched in the R_f sup. epimer was obtained.

**Compound (VIb) (R_f sup.)**

NMR (CDCl_3) δ: 7.50-7.30 (m, 5H, Ph), 5.86 (bs, 1H, NH(21)), 5.75 (m, 1H, H(4)), 2.08 (s, 3H, C(CF_3)CH_3Ph), 1.20 (s, 3H, Me(19)), 0.76 (s, 3H, Me(18)).

[α]_D +187° (c 1, abs. EtOH)
Compound (VIA) (R_f inf.)

NMR (CDCl₃) δ: 7.50-7.30 (m, 5H, Ph), 5.90 (bs, 1H, NH(21)), 5.75 (m, 1H, H(4)), 2.04 (s, 3H, C(CF₃)CH₂Ph), 1.20 (s, 3H, Me(19)), 0.72 (s, 3H, Me(18)).

[α]_D +126° (c 1, abs. EtOH)

17β-[N-(1,1,1-trifluoro-2-phenylprop-2-yl)carbamoyl]-5-oxo-4-nor-3,5-secoandrostan-3-oic acid (R_f inf.) (compound (VIIA))

To a solution of N-(1,1,1-trifluoro-2-phenylprop-2-yl)-3-oxo-androst-4-ene-17β-carboxamide (R_f inf.) (compound (VIA)) (1.70 g; 3.486 mmol) in tert-butanol (40 mL) and 2M aqueous sodium carbonate (2.09 mL), a 2% potassium permanganate aqueous solution (1.8 mL) and a 0.75M sodium metaperiodate aqueous solution (30 mL) were added dropwise simultaneously, over about 5 minutes, at about 40°C, at such a rate that the colour of the reaction mixture remained always pink. After stirring at 40°C for 1 h and 15 minutes, the reaction mixture was cooled to room temperature, filtered and tert-butanol removed from the filtrate by evaporation under vacuum (40 mL of solvent were collected). Then the solution was cooled to about 0°C, diluted with water, acidified with 1N hydrochloric acid and extracted with ethyl acetate (4 x 30 mL) and with methylene chloride (2 x 30 mL); the collected organic extracts were washed with water (2 x 30 mL), brine (20 mL) and anhydrified over sodium sulfate. Evaporation of the solvent yielded a solid foam, that was purified by flash chromatography (eluant: n-hexane/ethyl acetate 50:50) to yield 1.656 g of white solid compound.

NMR (CDCl₃) δ: 7.30-7.50 (m, 5H, Ph), 5.90 (bs, 1H, NH), 2.04 (s, 3H, C(CF₃)CH₂Ph), 1.12 (s, 3H, Me(19)), 0.71 (s, 3H, Me(18)).
MS (FAB') (m/z): 508 [M+H]+, 490 [M-H2O+H]+, 336 [M-
C(CF3)CH3Ph+ 2H]+, 173 PhCH3(CF3)C
[α]D +108.2° (c 1, abs. Ethanol)

Following an analogous procedure starting from N-(1,1,1-
trifluoro-2-phenylprop-2-yl)-3-oxo-androst-4-ene-17β-
carboxamide (Rf sup.) (compound (VIb)), the epimeric compound
was obtained (compound VIIb):
NMR (CDCl3) δ: 7.30-7.50 (m, 5H, Ph), 5.88 (bs, 1H, NH), 2.08
(s, 3H, C(CF3)CH3Ph), 1.14 (s, 3H, Me(19)), 0.78 (s, 3H, Me(18)).
[α]D +80° (c 1, abs. Ethanol)

N-(1,1,1-trifluoro-2-phenylprop-2-yl)-3-oxo-4-aza-androst-5-
ene-17β-carboxamide (Rf inf.) (compound (VIIIa))

A suspension of 17β-[N-(1,1,1-trifluoro-2-phenylprop-2-
yl)carbamoyl]-5-oxo-4-nor-3,5-secoandrostan-3-oic acid (Rf
inf.) (compound (VIIa)) (1.540 g) in anhydrous ethylene
glycol (35 mL) was saturated at 0°C with anhydrous gaseous
ammonia: the secoacid dissolved completely. The solution so
obtained was heated slowly to 180°C over 1 hour and 10
minutes and maintained at this temperature for 20 minutes.
Then the temperature was allowed to reach room temperature
over 0.5 hour. The yellowish solution was cooled to about 0°C
under good stirring: the final compound began to
precipitate. After diluting with water (30 mL) the stirring
was continued for 0.5 hour at 0°C and the precipitate was
filtered and washed with water. 1.36 g of a pale brownish
solid were obtained, which was purified by flash
chromatography on silica gel (eluant: n-hexane/ethyl acetate
yielded 1.090 g of the title compound.

\[ \delta: 7.50-7.30 (m, 5H, Ph), 5.88 (bs, 1H, NH), 4.81 (m, 1H, H(6)), 2.06 (s, 3H, C(CF₃)CH₂Ph), 1.12 (s, 3H, Me(19)), 0.71 (s, 3H, Me(18)) \].

\[ \alpha_D = +48.5^\circ \text{ (c 1, abs. Ethanol)} \]

Following an analogous procedure starting from 17β-\[N-(1,1,1-trifluoro-2-phenylprop-2-yl)carbamoyl]-5-oxo-4-nor-3,5-secoandrostan-3-oic acid (R_s sup.) (compound (VIIb)) the epimeric compound was obtained (compound (VIIIb)):

\[ \delta: 7.50-7.30 (m, 5H, Ph), 5.88 (bs, 1H, NH), 4.78 (m, 1H, H(6)), 2.09 (s, 3H, C(CF₃)CH₂Ph), 1.12 (s, 3H, Me(19)), 0.74 (s, 3H, Me(18)) \].

\[ \alpha_D = -2^\circ \text{ (c 1, abs. Ethanol)} \]

\[ N-(1,1,1-trifluoro-2-phenylprop-2-yl)-3-oxo-4-aza-5\alpha-androstan-17\beta-carboxamide (R_f inf.) \text{ (compound (IXa))} \]

A solution of \[N-(1,1,1-trifluoro-2-phenylprop-2-yl)-3-oxo-4-aza-androstan-5-ene-17\beta-carboxamide (R_f inf.) \text{ (compound (VIIIa))} \text{ (700 mg) in glacial acetic acid (45 mL) was hydrogenated in the presence of PtO}_2 \text{ (Adams' catalyst) (140 mg) under a pressure of 45 psi of hydrogen at 45°C for 1h.} \]

The reaction mixture was cooled to room temperature, the catalyst was filtered off and the solvent removed under reduced pressure. The residue was taken up with methylene chloride, washed with 1N sulfuric acid, with brine, with aqueous sodium carbonate, with brine, with water, dried over sodium sulfate and the solvent was removed under vacuum. The crude solid so obtained was purified by flash chromatography
on silica gel (eluant: toluene/ethyl acetate/methanol 75:20:5) to yield 420 mg of the title compound.

\[ \text{NMR (CDCl}_3\text{)} \delta: 7.50-7.30 (m, 5H, Ph), 5.88 (bs, 1H, NH(21)), 5.55 (bs, 1H, NH(4)), 3.06 (dd, 1H, H(5a)), 2.05 (s, 3H, C(CF}_3\text{)CH}_3\text{Ph}), 0.92 (s, 3H, Me(19)), 0.68 (s, 3H, Me(18)). \]
\[ [\alpha]_D^\circ +12^\circ \text{ (c 1, abs. Ethanol)} \]

Following an analogous procedure starting from \( N-(1,1,1\text{-trifluoro-2-phenylprop-2-yl})-3\text{-oxo-4-aza-5\alpha-androst-5-ene-17β-carboxamide (R}_f^\text{ sup.)} \) (compound (VIIIb)) the epimeric compound was obtained (compound (IXb)):

\[ \text{NMR (CDCl}_3\text{)} \delta: 7.50-7.30 (m, 5H, Ph), 5.88 (bs, 1H, NH(21)), 5.55 (bs, 1H, NH(4)), 3.06 (dd, 1H, H(5a)), 2.05 (s, 3H, C(CF}_3\text{)CH}_3\text{Ph}), 0.92 (s, 3H, Me(19)), 0.71 (s, 3H, Me(18)). \]
\[ [\alpha]_D^\circ +62^\circ \text{ (c 1, abs. Ethanol)} \]

\[ N-(1,1,1\text{-trifluoro-2-phenylprop-2-yl})-3\text{-oxo-4-aza-5\alpha-androst-1-ene-17β-carboxamide (R}_f^\text{ inf.}) \] (FCE 29331)

To a solution of \( N-(1,1,1\text{-trifluoro-2-phenylprop-2-yl})-3\text{-oxo-4 aza-5\alpha-androstane-17β-carboxamide (R}_f^\text{ inf.}) \) (compound (IXa)) (106 mg) in chlorobenzene (5 mL) phenylseleninic anhydride (108.3 mg) was added. The solution was refluxed for 5 h, while water was removed by a Marcusson device. The solution was evaporated and the residue dissolved in methylene chloride, washed with aqueous sodium carbonate, saturated sodium chloride solution, water and dried over sodium sulfate. After evaporating the solvent, the crude was purified by flash chromatography (eluant: toluene/ethyl acetate/methanol 75:20:5) to yield 70 mg of the title
compound.

NMR (CDCl₃) δ: 7.50-7.33 (m, 5H, Ph), 6.78 (d, 1H, H(1)), 5.90 (bs, 1H, NH(21)), 5.82 (dd, 1H, H(2)), 5.48 (bs, 1H, NH(4)), 3.33 (dd, 1H, H(5a)), 2.04 (s, 3H, C(CF₃)CH₂Ph), 0.98 (s, 3H, Me(19)), 0.68 (s, 3H, Me(18)).

[α]D +46° (c 1, CHCl₃)

Following an analogous procedure starting from N-(1,1,1-trifluoro-2-phenylprop-2-yl)-3-oxo-4-aza-5α-androstane-17β-carboxamide (R f sup.) (compound (IXb)) the epimeric compound FCE 29330 was obtained:

NMR (CDCl₃) δ: 7.50-7.33 (m, 5H, Ph), 6.78 (d, 1H, H(1)), 5.87 (bs, 1H, NH(21)), 5.82 (dd, 1H, H(2)), 5.48 (bs, 1H, NH(4)), 3.33 (dd, 1H, H(5a)), 2.07 (s, 3H, C(CF₃)CH₂Ph), 0.98 (s, 3H, Me(19)), 0.72 (s, 3H, Me(18)).

[α]D +21° (c 1, CHCl₃)

As shown by this example, FCE 29331 was obtained from (+)-amine, whereas FCE 29330 was obtained from (-)-amine.

IN VITRO ASSAY OF 5α-REDUCTASE INHIBITION

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

The assay for 5α-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 μM [14C] testosterone, an aliquot of the enzyme preparation and various concentrations of the inhibitors. After 30 min. incubation 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 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). 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. The concentration of each compound required to reduce control 5α-reductase activity by 50% (IC₅₀) was determined by plotting % inhibition versus log of inhibitor concentration.

The results obtained on the single epimers FCE 29330 and FCE 29331, and on the racemic mixture FCE 28260 are reported in the following Table 1.

Table 1

In vitro inhibition of human prostatic 5α-reductase by stereoisomers of FCE 28260

<table>
<thead>
<tr>
<th>Compound</th>
<th>IC₅₀ (nM)</th>
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<tr>
<td>FCE 28260</td>
<td>12</td>
</tr>
<tr>
<td>FCE 29330</td>
<td>17</td>
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<td>FCE 29331</td>
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</table>
From the results reported in Table 1 it is evident that the epimer FCE 29331 is approximately two-fold more potent than the other epimer FCE 29330. The mixture FCE 28260, as expected, shows intermediate activity.
1. Epimers of formula (I) and (II):

\[
\text{(I)}
\]

\[
\text{(II)}
\]

i.e. (22R)-N-(1,1,1-trifluoro-2-phenylprop-2-yl)-3-oxo-4-aza-5α-androst-1-ene-17β-carboxamide [compound of formula (I)] and (22S)-N-(1,1,1-trifluoro-2-phenylprop-2-yl)-3-oxo-4-aza-5α-androst-1-ene-17β-carboxamide [compound of formula (II)].

2. A process for preparing an epimer of formula (I) or (II) according to claim 1, which comprises separating the single epimers from the corresponding epimer mixture.

3. A process for preparing an epimer of formula (I) or (II) according to claim 1, which comprises reacting 3-oxo-4-aza-5α-androst-1-ene-17β-carboxylic acid with each single enantiomer of 1,1,1-trifluoro-2-phenylprop-2-yl amine
previously resolved.

4. A process for preparing an epimer of formula (I) or (II) according to claim 1, which comprises:
   a) reacting 3-oxo-androst-4-ene-17β-carboxylic acid, or a derivative thereof, with (+)-1,1,1-trifluoro-2-phenylprop-2-yl amine;
   b) separating the two epimers of the so obtained (22RS)-N-(1,1,1-trifluoro-2-phenylprop-2-yl)-3-oxo-androst-4-ene-17β-carboxamide;
   c) converting the so obtained epimers separately into the final epimers of formulas (I) and (II), according to known reactions.

5. A pharmaceutical composition comprising one of the epimers of formula (I) or (II) according to claim 1, or a mixture thereof, wherein one of the epimers is present in a prevailing amount with respect to the other epimer, in combination with one or more pharmaceutically acceptable carriers and/or diluents.

6. A compound of formula (I) or (II) as defined in claim 1, for use as inhibitor of testosterone 5α-reductase enzyme.

7. A compound of formula (I) or (II) as defined in claim 1, for use as an anti-androgenic agent.

8. A compound of formula (I) or (II) according to claim 1, for use in the treatment and/or chemoprevention of benign prostatic hyperplasia or of prostatic cancer.

9. A compound of formula (I) or (II) according to claim 1,
for use in the treatment of breast cancer, acne, seborrhea, female hirsutism and/or male pattern baldness.
**INTERNATIONAL SEARCH REPORT**

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC 6 C07J/33/00 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 6 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**

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<td>X</td>
<td>JOURNAL OF STEROID BIOCHEMISTRY AND MOLECULAR BIOLOGY, vol. 49, no. 4-6, 1994, pages 289-294, XP082016863 E. DI SALLE ET AL: &quot;Novel Aromatase and 5.alpha.-Reductase Inhibitors&quot; see the whole document</td>
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Further documents are listed in the continuation of box C. Patent family members are listed in annex.

**Date of the actual completion of the international search**

25 October 1996

**Date of mailing of the international search report**

22.11.96

**Name and mailing address of the ISA**

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**Authorized officer**

Watchorn, P
## INTERNATIONAL SEARCH REPORT

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