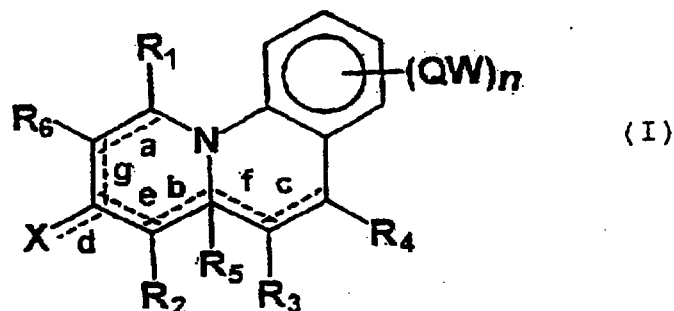


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Benzo[c]quinolizine derivatives, their preparation and use as 5 α -reductases inhibitors.

Field of the invention

The present invention refers to benzo[c]quinolizine derivatives of
5 general formula (I)



wherein:

R_1 , R_2 , R_3 , R_4 , R_6 , same or different, are chosen in the group consisting of: H, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkinyl, cycloalkyl, aryl, heterocycle, halogen, CN, azide, NRR' , C_{1-8} alkylamino, arylamino, C_{1-8} alkyloxy, aryloxy, COOR, CONRR' wherein R and R', same
10 or different, are chosen in the group consisting of: H, C_{1-8} alkyl, cycloalkyl, aryl, heterocycle, aryl C_{1-8} alkyl;

R_5 is chosen in the group consisting of: H, C_{1-8} alkyl, COOR, CN, aryl, heterocycle;

15 X is chosen in the group consisting of: O, $C(=O)R$, COOR, NO_2 , CONR'R wherein R and R' are as above defined;

Q is chosen in the group consisting of: simple bond, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkinyl, cycloalkyl, CO, CONR, NR, wherein R is as above defined;

20 W is chosen in the group consisting of: H, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkinyl, cycloalkyl, trifluoromethyl, C_{1-8} alkoxy, C_{1-8} alkoxy- C_{1-}

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galkyl, arylC₁₋₈galkyl, aryl, aryloxy, arylamino, C₁₋₈galkylcarbonyl, arylcarbonyl, halogen, CN, NRR', C₁₋₈galkylamino, heterocycle wherein the groups alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocycle, can be substituted;

5 n is an integer comprised between 1 and 4;

the symbol ----- means that the corresponding bonds a, b, c, d e, f, and g can be simple or double bonds;

with the proviso that when b or f are a double bond then the group R₅ is absent;

10 their pharmaceutically acceptable salts or esters, their process of preparation and their use as inhibitors of steroid 5 α -reductases (hereinafter indicated as 5 α -reductases).

State of the art

The enzyme known as steroid 5 α -reductase is a system formed by two
15 iso-enzymes (type I and type II or 5 α R-I and 5 α R-II respectively)) which converts testosterone into dihydrotestosterone, the most powerful androgen circulating in the body.

The type I iso-enzyme (5 α R-I) is mainly present in liver and skin while the type II iso-enzyme (5 α R-II) is mainly present in the
20 prostate tissue and in the male sexual organs and its activity is essential in the fetal developping process for the differentiation of the external sexual organs.

The production of dihydrotestosterone is associated with some pathologies which are widely diffused as for example benign prostate
25 hypertrophy, prostate cancer, baldness and acne in men and hirsutism in women. More particularly iso-enzyme I plays a role in the pathologies regarding the skin while iso-enzyme-II is involved in

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prostate pathologies.

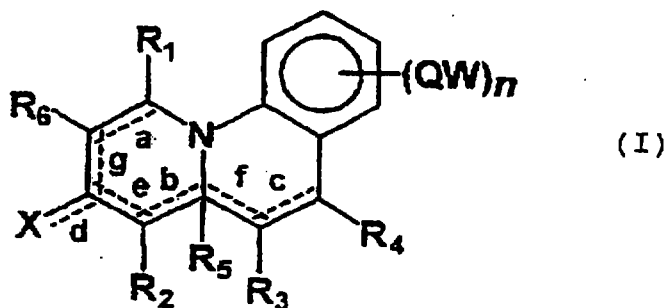
In the recent years a lot of international searchers have tried to isolate new compounds capable of inhibiting the 5 α -reductase enzyme in order to treat the above said pathologies, especially, if possible, acting selectively on only one of the two iso-enzymes.

Inhibitors of 5 α -reductase, and also of the iso-enzymes 5 α R-I and 5 α R-II were already described, for example finasteride used with success in the treatment of benign prostate hypertrophy [see for example J.Med.Chem. 36, 4313-15 (1993), J.Med.Chem. 37, 3871-74 (1994)]. It is therefore evident the importance of developing new compounds capable of inhibiting the action of the 5 α -reductase enzyme and in particular capable of acting selectively on 5 α R-I iso-enzyme which, as said, is responsible, of widely diffused pathologies having an high impact as baldness in men and hirsutism in women.

15 Detailed description of the invention

The present invention refers to new compounds capable of inhibiting the 5 α -reductase enzyme, either selectively in respect of 5 α R-I and 5 α R-II or on both the iso-enzymes, useful for the treatment of the pathologies mediated by the enzyme.

20 The products according to the invention have general formula (I)



- 4 -

wherein the substituents R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , X, Q, W, n and the symbol ----- are as above defined.

According to the present invention with group C_{1-8} alkyl, C_{2-8} alkenyl and C_{2-8} alkinyl are indicated linear or branched alkyl radicals as for
5 example: methyl, ethyl, propyl, isopropyl, butyl, pentyl, hexyl, heptyl, octyl, ethylene, propene, butene, isobutene, acetylene, propine, butine ecc.

With cycloalkyl are indicated: cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane, cyclooctane, norbornane,
10 canphane, adamantane.

With aryl are indicated: phenyl and naphtyl.

Heterocycle means in particular: saturated or aromatic heterocycles containing one or more N atoms, more particularly: piridine, imidazole, pyrrole, indole, triazoles, pyrrolidine, piperidine.

15 Halogen means: fluorine, chlorine, bromine, iodine.

The substituents of the above said group W are preferably: halogen, OR, phenyl, NRR' , CN, COOR, CONRR', C_{1-8} alkyl (wherein R and R' are as above defined).

In particular, according to the present invention compounds of formula
20 (I) are preferred wherein:

R_5 = H, heterocycle

X = O

Q = simple bond, CO, CONR, NR (wherein R is as above defined)

W = H, F, Cl, Br, Me, t-butyl, C_{1-8} alkoxy, 2,5-dimethylhexyl,
25 trifluoromethyl, 2,5-(di-trifluoromethyl)-phenyl, 4-methoxy-phenyl, 4-fluoro-phenyl, phenyl, phenyl- C_{1-8} alkyl, C_{1-8} alkylcarbonyl, phenylcarbonyl.

n = 1 and 2

R₁, R₂, R₃, R₄, R₆ = H, Me, CN, phenyl, COOR, CONRR' (wherein R and R' are as above defined).

Among the pharmaceutically acceptable esters and salts according to
5 the present invention the following can be mentioned: hydrochloride, sulphate, citrate, formate, phosphate.

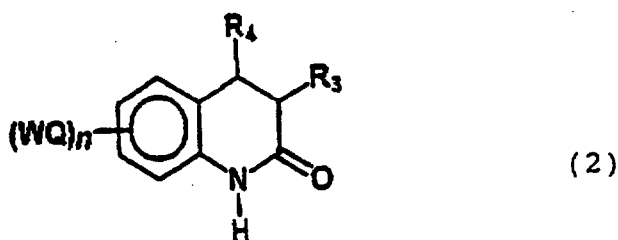
Preferred compounds according to the present invention are:

- 1,2,4,4a,5,6 hexahydro-(11H)-benzo[c]quinolizine-3-one;
- 8-chloro-1,2,4,4a,5,6 hexahydro-(11H)-benzo[c]quinolizine-3-one;
- 10 1,2,4,4a,5,6 hexahydro-8-methyl-(11H)-benzo[c]quinolizine-3-one;
- 1,2,4,4a,5,6 hexahydro-4-methyl-(11H)-benzo[c]quinolizine-3-one;
- 1,2,4,4a,5,6 hexahydro-1-methyl-(11H)-benzo[c]quinolizine-3-one;
- 1,2,5,6 tetrahydro-(11H)-benzo[c]quinolizine-3-one;
- 8-chloro-1,2,5,6 tetrahydro-(11H)-benzo[c]quinolizine-3-one;
- 15 8-methyl-1,2,5,6 tetrahydro-(11H)-benzo[c]quinolizine-3-one;
- 4-methyl-1,2,5,6 tetrahydro-(11H)-benzo[c]quinolizine-3-one;
- 1-methyl-1,2,5,6 tetrahydro-(11H)-benzo[c]quinolizine-3-one;
- 4,4a,5,6 tetrahydro-(11H)-benzo[c]quinolizine-3-one;
- 5,6-dihydro-(11H)-benzo[c]quinolizine-3-one;
- 20 8-chloro-4,4a,5,6 tetrahydro-(11H)-benzo[c]quinolizine-3-one;
- 8-chloro-1-methyl-4,4a,5,6-tetrahydro-(11H)-benzo[c]quinolizine-3-one;
- 8-methyl-4,4a,5,6 tetrahydro-(11H)-benzo[c]quinolizine-3-one;
- 4-methyl-4,4a,5,6 tetrahydro-(11H)-benzo[c]quinolizine-3-one (cis) and (trans);
- 25 8-chloro-4-methyl-1,2,5,6 tetrahydro-(11H)-benzo[c]quinolizine-3-one;
- 4,8-dimethyl-1,2,5,6 tetrahydro-(11H)-benzo[c]quinolizine-3-one;
- 4,8-dimethyl-4,4a,5,6 tetrahydro-(11H)-benzo[c]quinolizine-3-one (cis)

and (trans);

8-chloro-4-methyl-4,4a,5,6-tetrahydro-(11H)-benzo[c]quinolizine-3-one
(cis) and (trans).

The compounds according to the present invention can be prepared for
5 example starting from compounds of formula 2



(2)

wherein R_3 , R_4 , W, Q and n are as above defined, following the reaction Scheme reported hereinafter.

The compounds 2 are commercially available or can be prepared according to known techniques.

- 10 As it can be seen from the Scheme the preparation of the compounds according to the invention involves the protection of the amide-group in compound 2 by the protecting group Z, for example tert-butoxycarbonyl (t-Boc), to give compound 3; compound 3 is reduced to compound 4, for example (when R_5 is H) with sodium borohydride in
15 ethanol (pH 3), which is reacted with a silylether 6, produced "in situ" starting from vinyl-ketones 5 (wherein R_1 , R_2 and R_6 are as above defined) with a silylating agent as trimethylsilyltrifluoromethanesulphonic anhydride (TMSOTf) and thereafter hydrolyzed, for example in sodium hydrogencarbonate, to
20 give the compounds of formula (I) wherein $X = O$. The possible introduction of the double bonds and the transformation of the group X

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in one of the other groups mentioned above can be easily performed according to known techniques starting from the corresponding compound of formula (I) obtained as indicated. For example the introduction of the double bonds in position a or b, can be performed by reaction of
5 dichlorodicyanoquinone (DDQ) with the corresponding silylenolethers or by oxidation with mercuric acetate of the saturated corresponding compound obtained as described above. The transformation of group X can be performed via the corresponding enoltriflates and their carbonylation in the presence of palladium diacetate,
10 triphenylphosphine and the suitable nucleophilic reagent (alcohol, amine, nitro-group).

Example 1

Preparation of N-(t-butoxycarbonyl)-3,4-dihydroquinolin-2(1H)-one

[compound 3 wherein $(QW)_n = H$, $R_3 = R_4 = H$]

15 5 g (34 mmol) of 3,4-dihydroquinolin-2(1H)-one [compound 2 wherein $(QW)_2 = H$, $R_3 = R_4 = H$] and 111 ml of CH_2Cl_2 are charged, under nitrogen, in a 250 ml round bottom flask, equipped with magnetic stirrer.

To the above said mixture 4.7 ml (34 mmol) of triethylamine
20 (distilled on KOH), 8.9 g (40.8 mmol) of di-butyl dicarbonate and 1 g (8.2 mmol) of 4-dimethylaminopyridine are added. The mixture is stirred under reflux for 5 h, then for one night at room temperature and thereafter the solvent is removed and 200 ml of water are added. The aqueous phase is extracted with diethylether and the organic phase
25 is neutralized with an aqueous solution of $KHSO_4$ (1 M). The organic phase is washed with a saturated solution of NaCl and dried on Na_2SO_4 . After filtration and removal of the solvent 8.23 g of the desired

- 8 -

product are obtained (white crystals). M.p.: 68 - 69°C. Yield: 98%.

Example 2

Preparation of N-(t-butoxycarbonyl)-2-ethoxy-1,2,3,4-tetrahydroquinoline [compound 4 wherein $(QW)_n = H$, $R_3 = R_4 = R_5 = H$].

5 4.35 g (17.6 mmoles) of the compound obtained from example 1 and 136 ml of absolute ethanol are charged in a 500 ml round bottom flask equipped with magnetic stirrer.

The solution is cooled at -25°C and 2.66 g (70.4 mmoles) of $NaBH_4$ (subdivided in 6 portions) are added to the mixture in 1 h. After 4 h
10 a solution of HCl 2N in absolute ethanol is added to the mixture, up to pH 3, and the mixture is stirred at 0°C for 1,5 h. 100 ml of water are added, the aqueous phase is extracted with methylene chloride, the organic phase is washed with a saturated solution of $NaHCO_3$ and a saturated solution of NaCl and the mixture is dried on Na_2SO_4 . After
15 filtration the solvent is removed and 4,74 g of the expected product are obtained (dense yellow liquid); yield 96%.

Operating as above said other compounds 4 wherein the substituents can not be reduced by $NaBH_4$ are obtained; if substituents which could be reduced by $NaBH_4$ are present these must be previously protected.

20 Example 3

Preparation of 1,2,4,4a,5,6-hexahydro-(11H)-benzo[c]quinolizin-3-one [compound of formula (I) wherein $X = O$; $(QW)_n = H$; $R_1 = R_2 = R_3 = R_4 = R_5 = R_6 = H$; a,b,c,e,f,g = simple bond]

70 μ l (0.86 mmoles) of 3-buten-2-one [compound of formula 5 wherein R_1
25 = $R_2 = R_6 = H$] and 2 ml of anhydrous CH_2Cl_2 are charged, at 0°C under argon in a two-necked round bottom flask equipped with magnetic stirrer and dropping funnel.

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170 μ l (1.22 mmoles) of triethylamine (distilled on KOH) and 209 μ l (1.08 mmoles) of trimethylsilyltrifluoromethanesulphonate (TMDOTf) (drop by drop) are added to the mixture. In this conditions 2-(trimethylsilyloxy)-1,3-butadiene [compound 6 wherein $R_1 = R_2 = R_6 =$
5 H] is formed "in situ". The mixture is stirred for 45 minutes and thereafter a solution of 100 mg (0.36 mmoles) of the product from Example 2 in 2 ml of anhydrous CH_2Cl_2 is added therein, drop by drop, together with 69 μ l (0.36 mmoles) of TMSOTf. The mixture is brought to room temperature and after 30 minutes 4 ml of a saturated solution of
10 NaHCO_3 are added and the mixture is stirred vigorously for 36 h.

4 ml of water are added to the mixture and the aqueous phase is extracted with methylene chloride, the organic phase is washed with a saturated solution of NaHCO_3 , water, a saturated solution of NaCl and is dried on Na_2SO_4 . After filtration the solvent is removed and 59 mg
15 of crude product are obtained. The product is purified by flash chromatography on silica gel column (FCC) eluting with methylene chloride and triethylamine 1%. 18 mg of the wanted product are obtained (crystals). M.p.: 53 - 54°C. Yield 25%.

Using various vinyl-ketones 5, or using directly the various
20 silylenolethers 6 (when available), it is possible to prepare the corresponding derivatives of formula (I).

In particular when 1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene (compound 6 wherein $R_1 = \text{MeO}$, $R_2 = \text{H}$, $R_6 = \text{H}$) was used, 4,4a,5,6-tetrahydro-(11H)-benzo[c]quinolizin-3-one (compound I wherein $X = \text{O}$,
25 $(\text{QW})_n = \text{H}$, $R_1 = R_2 = R_3 = R_4 = R_5 = R_6 = \text{H}$, a = double bond; b,c,e,f,g = single bond] was directly obtained according to the synthesis described in the following Example 4.

- 10 -

Example 4

Preparation of 4,4a,5,6-tetrahydro-(11H)-benzo[c]quinolizin-3-one
[compound I wherein $X = O$, $(QW)_n = H$; $R_1 = R_2 = R_3 = R_4 = R_5 = R_6 = H$;
 $a = \text{double bond}$; $b, c, e, f, g = \text{single bond}$].

- 5 To a stirred solution of compound 4 [$(QW)_n = H$, $R_3 = R_4 = H$] (4 g, 14.42 mmol) of the example 3, in 75 ml of anhydrous CH_2Cl_2 under argon at $-10^\circ C$ is added, dropwise in 7 min, 28.84 ml of a 1M solution of $TiCl_4$ in CH_2Cl_2 maintaining the temperature below $-5^\circ C$. Then 1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene (compound 6, $R_1 = MeO$, $R_2 = H$, $R_6 = H$) (3.29 ml, 17.3 mmol) is added by syringe at $0^\circ C$, and the reaction was left aside at room temperature for 1 h. The reaction mixture is added, cautiously, with 100 ml of $NaHCO_3$ saturated solution, and then stirred for 30 min. The organic layer is separated, washed with water, filtered on Celite and dried over Na_2SO_4 . After removal of
- 15 the solvent the crude product is purified by flash column chromatography (eluant light-petroleum ether/ethyl acetate 1:4) affording 0.72 g (25% yield) of the expected product (white crystals, m.p.: $135-137^\circ C$).

Example 5

- 20 a) Preparation of 4-methyl-4,4a,5,6-tetrahydro-(11H)-benzo[c]quinolizine-3-one [compound of formula (I) wherein $X = O$; $(QW)_n = H$; $R_1 = R_3 = R_4 = R_5 = R_6 = H$; $R_2 = Me$; $a = \text{double bond}$; $b, c, e, f, g = \text{single bonds}$], 4-methyl-1,2,5,6-tetrahydro-(11H)-benzo[c]quinolizine-3-one [compound of formula (I) wherein $X = O$;
- 25 $(QW)_n = H$; $R_1 = R_3 = R_4 = R_6 = H$; $R_2 = Me$; $b = \text{double bond}$; $a, c, e, f, g = \text{single bonds}$] and 4-methyl-5,6-dihydro-(11H)-benzo[c]quinolizine-3-one [compound of formula (I) wherein $X = O$; $(QW)_2 = H$; $R_1 = R_3 = R_4 =$

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$R_6 = H$; $R_2 = Me$; a,b = double bonds; c,e,f,g = single bonds].

- 1 g (4.64 mmol) of 4-methyl-1,2,4,4a,5,6-hexahydro-(11H)-benzo[c]quinolizine-3-one [compound of formula (I), wherein $X = O$; $(QW)_n = H$; $R_1 = R_3 = R_4 = R_5 = R_6 = H$; $R_2 = Me$; a,b,c,e,f,g = single bonds; obtained according to example 3 by reaction of compound 4 (wherein $(QW)_n = H$; $R_3 = R_4 = R_5 = H$) of example 2 and ethylvinylketone (compound 5 wherein $R_1 = R_6 = H$; $R_2 = Me$] and 120 ml of 5% solution (v/v) of glacial acetic acid in water are charged under nitrogen in a two-necked round bottom flask, equipped with magnetic stirrer, refrigerator and dropping funnel. Under vigorous stirring, 7.27 g (18.56 mmol) of tetrasodic salt EDTA and 5.92 g (18.56 mmol) of $(CH_3CO_2)_2Hg$ are added and the reaction mixture is heated at 90°C for 2h. After cooling at room temperature the reaction mixture is added with 120 ml of water and extracted with methylene chloride (4x70 ml).
- 15 The separated organic phase is washed with a saturated solution of $NaHCO_3$, with a saturated solution of $NaCl$ then dried over Na_2SO_4 . After removal of the solvent the crude product is purified by flash chromatography on silica gel by elution with ethylacetate/light petroleum ether 2:1 affording:
- 20 83 mg (10%) (gummy solid) of cis-4-methyl-4,4a,5,6-tetrahydro-(11H)-benzo[c]quinolizine-3-one [compound of formula (I) wherein $X = O$; $(QW)_n = H$; $R_1 = R_3 = R_4 = R_5 = R_6 = H$; $R_2 = Me$; a = double bond; b,c,e,f,g = single bonds]
- 350 mg (40%) (crystals, m.p.: 148-150°C) of 4 methyl-1,2,5,6-tetrahydro-(11H)-benzo[c]quinolizine-3-one [compound of formula (I) wherein $X = O$; $(QW)_n = H$; $R_1 = R_3 = R_4 = R_6 = H$; $R_2 = Me$; b = double bond; a,c,e,f,g = single bonds] and
- 25

- 12 -

107 mg (12%) (gummy solid) of 4-methyl-5,6-dihydro-(11H)-benzo[c]quinolizine-3-one [compound of formula (I) wherein $X = O$; $(QW)_n = H$; $R_1 = R_3 = R_4 = R_6 = H$; $R_2 = Me$; a,b=double bonds; c,e,f,g = single bonds].

5 Activity Test

The inhibition potency of the prepared compounds in respect of the iso-enzymes 1 and 2 of 5 α -reductase was determined using tissue samples (for example prostate human tissue) or human cellular systems (for example DU 145 cells) expressing iso-enzymes 2 and 1
10 respectively.

The samples are incubated in the presence of testosterone labelled with tritium and thereafter the quantity of labelled dihydrotestosterone formed in the absence and in the presence of the inhibitor is measured.

15 The compounds showed high inhibiting power of 5 α -reductase enzyme (in particular of iso-enzyme 1) with an inhibition higher than 50% at the concentration of 10 - 100 nM.

For the therapeutical administration the compounds according to the invention are prepared in the form of pharmaceutical compositions
20 containing the active principle and the organic or inorganic excipients suitable for the oral, parenteral or topic administration of the compositions. The pharmaceutical compositions can therefore be in the solid form (dragees, suppositories, creams, ointments), liquid form (solutions, suspensions, emulsions) and can possibly contain the
25 stabilizers, conservatives, humectants, emulsifier, buffers or salts used for equilibrating the osmotic pressure which are commonly used in the art.

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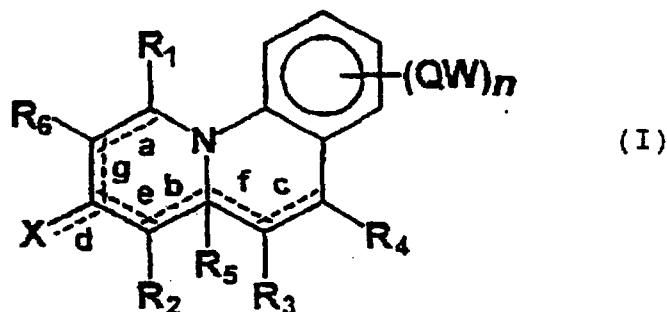
Generally the administration of the compounds is performed according to the modalities and quantities observed for the known agents used for the same purposes and taking into consideration the age and conditions of the patients.



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Claims

- 1 1. Benzo[c]-quinolizine compounds of formula (I)



- 2 wherein:

- 3 R_1, R_2, R_3, R_4, R_6 , same or different, are chosen in the group
 4 consisting of: H, C_{1-8} alkyl, C_2 -galkenyl, C_2 -galkinyl, cycloalkyl,
 5 aryl, heterocycle, halogen, CN, azide, NRR' , C_{1-8} alkylamino,
 6 arylamino, C_{1-8} alkyloxy, aryloxy, COOR, CONRR' wherein R and R', same
 7 or different, are chosen in the group consisting of: H, C_{1-8} alkyl,
 8 cycloalkyl, aryl, heterocycle, aryl C_{1-8} alkyl;
 9 R_5 is chosen in the group consisting of: H, C_{1-8} alkyl, COOR, CN, aryl,
 10 heterocycle;
 11 X is chosen in the group consisting of: O, $C(=O)R$, COOR, NO_2 , CONR'R
 12 wherein R and R' are as above defined;
 13 Q is chosen in the group consisting of: simple bond, C_{1-8} alkyl, C_2 -
 14 galkenyl, C_2 -galkinyl, cycloalkyl, CO, CONR, NR, wherein R is as above
 15 defined;
 16 W is chosen in the group consisting of: H, C_{1-8} alkyl, C_2 -galkenyl, C_2 -
 17 galkinyl, cycloalkyl, trifluoromethyl, C_{1-8} alkoxy, C_{1-8} alkoxy- C_{1-8}
 18 alkyl, aryl C_{1-8} alkyl, aryl, aryloxy, arylamino, C_{1-8} alkylcarbonyl,
 19 arylcarbonyl, halogen, CN, NRR' , C_{1-8} alkylamino, heterocycle wherein
 20 the groups alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocycle, can





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21 be substituted;
22 n is an integer comprised between 1 and 4;
23 the symbol ----- means that the corresponding bonds a, b, c, d e, f,
24 and g can be simple or double bonds;
25 with the proviso that when b or f are a double bond then the group R₅
26 is absent;
27 their pharmaceutically acceptable salts or esters.

1 2. Benzo[c]-quinolizine compounds of formula (I)

2 R₅ = H, heterocycle

3 X = O

4 Q = simple bond, CO, CONR, NR (wherein R is as above defined)

5 W = H, F, Cl, Br, Me, t-butyl, C₁₋₈alkoxy, 2,5-dimethylhexyl,
6 trifluoromethyl, 2,5-(di-trifluoromethyl)-phenyl, 4-methoxy-phenyl, 4-
7 fluoro-phenyl, phenyl, phenyl-C₁₋₈alkyl, C₁₋₈alkylcarbonyl,
8 phenylcarbonyl.

9 n = 1 and 2

10 R₁, R₂, R₃, R₄, R₅, R₆ = H, Me, CN, phenyl, COOR, CONRR' (wherein R
11 and R' are as above defined).

1 3. Benzo[c]-quinolizine compounds according to Claim 1 of formula

2 1,2,4,4a,5,6 hexahydro-(11H)-benzo[c]quinolizine-3-one;

3 8-chloro-1,2,4,4a,5,6 hexahydro-(11H)-benzo[c]quinolizine-3-one;

4 1,2,4,4a,5,6 hexahydro-8-methyl-(11H)-benzo[c]quinolizine-3-one;

5 1,2,4,4a,5,6 hexahydro-4-methyl-(11H)-benzo[c]quinolizine-3-one;

6 1,2,4,4a,5,6 hexahydro-1-methyl-(11H)-benzo[c]quinolizine-3-one;

7 1,2,5,6 tetrahydro-(11H)-benzo[c]quinolizine-3-one;

8 8-chloro-1,2,5,6 tetrahydro-(11H)-benzo[c]quinolizine-3-one;

9 8-methyl-1,2,5,6 tetrahydro-(11H)-benzo[c]quinolizine-3-one;

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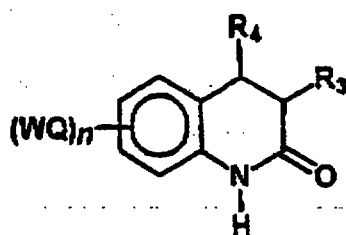


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- 10 4-methyl-1,2,5,6 tetrahydro-(11H)-benzo[c]quinolizine-3-one;
- 11 1-methyl-1,2,4,6 tetrahydro-(11H)-benzo[c]quinolizine-3-one;
- 12 4,4a,5,6 tetrahydro-(11H)-benzo[c]quinolizine-3-one;
- 13 5,6-dihydro-(11H)-benzo[c]quinolizine-3-one;
- 14 8-chloro-4,4a,5,6 tetrahydro-(11H)-benzo[c]quinolizine-3-one;
- 15 8-chloro-1-methyl-4,4a,5,6-tetrahydro-(11H)-benzo[c]quinolizine-3-one;
- 16 8-methyl-4,4a,5,6 tetrahydro-(11H)-benzo[c]quinolizine-3-one;
- 17 4-methyl-4,4a,5,6 tetrahydro-(11H)-benzo[c]quinolizine-3-one (cis) and
- 18 (trans);
- 19 8-chloro-4-methyl-1,2,5,6 tetrahydro-(11H)-benzo[c]quinolizine-3-one;
- 20 4,8-dimethyl-1,2,5,6 tetrahydro-(11H)-benzo[c]quinolizine-3-one;
- 21 4,8-dimethyl-4,4a,5,6 tetrahydro-(11H)-benzo[c]quinolizine-3-one (cis)
- 22 and (trans);
- 23 8-chloro-4-methyl-4,4a,5,6-tetrahydro-(11H)-benzo[c]quinolizine-3-one
- 24 (cis) and (trans).

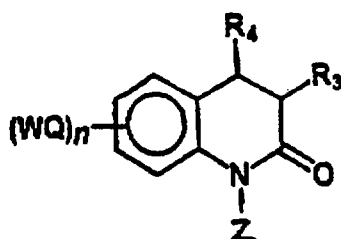
1 4. Process for the preparation of compounds according to Claim 1
2 wherein:

3 the amide-group of a compound of formula (2)



(2)

4 is protected with a protecting group Z to give the compound (3)



(3)

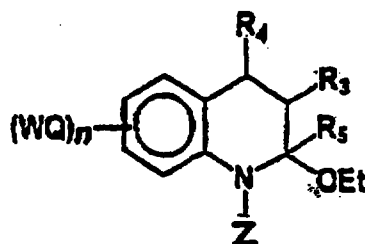




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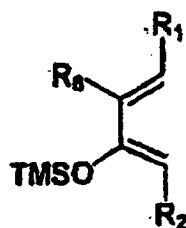
5 the above said compound (3) is reduced to compound (4), for example
6 with sodium borohydride in ethanol (pH3)

(4)



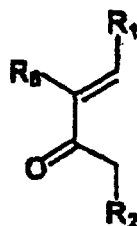
7 and compound (4) is reacted with a silylether (6)

(6)



8 prepared "in situ" by reacting a vinyl-ketone (5)

(5)



9 (wherein R_1 , R_2 , R_6 are as above defined) with a silylating agent as
10 trimethylsilyltrifluoromethanesulphonic anhydride (TMSOTf) and are
11 finally hydrolyzed, for example with sodium hydrogencarbonate, to give
12 the final compound of formula (I) wherein $X = O$.

1 5. Process according to claim 4 wherein the possible introduction of
2 the double bonds in position a or b is performed by reaction of
3 dichlorodicyanoquinone (DDQ) with the corresponding silylenolethers or
4 by oxidation with quicksilver acetate of the saturated compound
5 obtained as claimed above and the possible transformation of the group
6 X is performed via the corresponding enoltriflates and following
7 carbonylation in the presence of palladium diacetate.

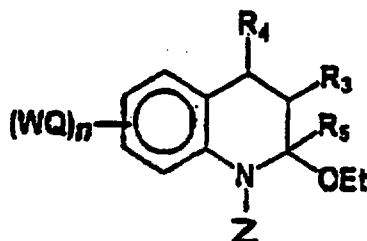




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8 triphenylphosphine and the suitable nucleophilic reagent.

1 6. Compound of formula (4)



(4)

2 wherein W, Q, n, R₃, R₄, R₅ are as defined in claim 1 and Z is a
3 protecting group for the amide-group.

1 7. Pharmaceutical composition wherein the active principle is a
2 compound of formula (I) according to Claim 1 or mixtures thereof in
3 combination with the suitable pharmaceutical acceptable excipients.

1 8. Pharmaceutical composition according to Claim 7 for use in the
2 inhibition of the 5αR-I and/or 5αR-II iso-enzymes.

1 9. Pharmaceutical composition according to claims 7 and 8 in the form
2 suitable for topic use.

1 10. Use of a compound of formula (I) according to Claim 1 as a
2 medicament.

1 11. Use of a compound of formula (I) according to Claim 1 for the
2 preparation of a pharmaceutical composition for the treatment of acne,
3 baldness, prostatic cancer and prostatic hypertrophy in men and
4 hirsutism in women.

1 12. Method for the treatment of pathologies related to 5α-reductase
2 enzymes by administration to the patient of a pharmaceutically active
3 amount of a pharmaceutical composition according to Claims 7.

1 13. Method for treatment of acne, baldness, prostatic cancer and
2 prostatic hypertrophy in men and hirsutism in women, by administration





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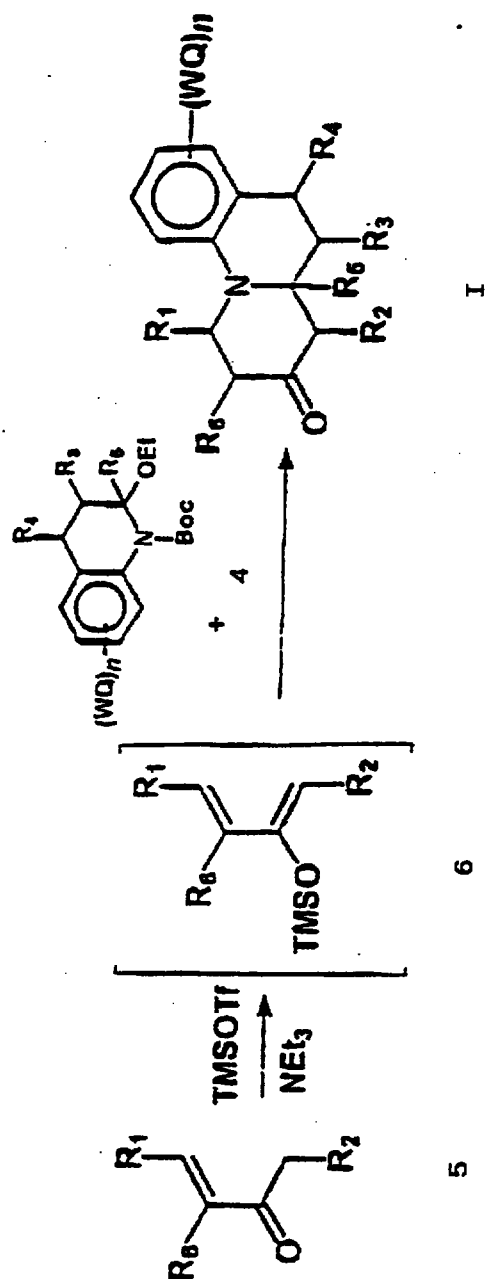
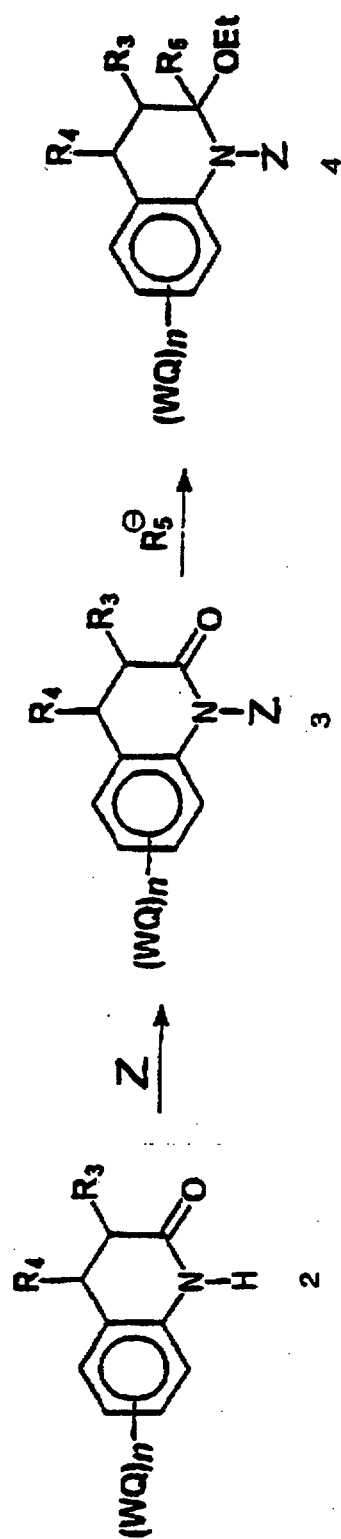
3 of a pharmaceutically active amount of a pharmaceutical composition
4 according to Claims 7.

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SCHEME



C_{1-8} alkyl, aryl C_{1-8} alkyl, aryl, aryloxy, arylamino, C_{1-8} alkylcarbonyl, arylcarbonyl, halogen, CN, NRR' , C_{1-8} alkylamino, heterocycle wherein the groups alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocycle, can be substituted;

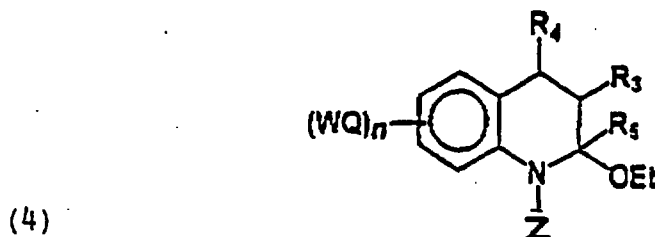
5 n is an integer comprised between 1 and 4;

the symbol ----- means that the corresponding bonds a, b, c, d e, f, and g can be simple or double bonds;

with the proviso that when b or f are a double bond then the group R_5 is absent; and with the proviso that the following two compounds are
10 excluded: 4-carbonitril-2,3-dihydro-(1H)-benzo[c]quinolizin-3-one and 3,4-dihydro-1-phenyl-4aH-benzo[c]quinolizin-3-one;

their pharmaceutically acceptable salts or esters, their process for preparation and their use as inhibitors of steroid Δ^5 -reductases (hereinafter indicated as Δ^5 -reductases).

15 The invention refers also to compounds of formula (4)



wherein W, Q, n, R_3 , R_4 , R_5 are as above defined and Z is a protecting group for the amide-group with the proviso that when $\text{R}_3 = \text{R}_4 = \text{R}_5 = (\text{WQ})_n = \text{H}$ than Z is not a group ethoxycarbonyl.

State of the art

20 The enzyme known as steroid Δ^5 -reductase is a system formed by two iso-enzymes (type I and type II or Δ^5 R-I and Δ^5 R-II respectively)) which converts testosterone into dihydrotestosterone,

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the most powerful androgen circulating in the body.

The type I iso-enzyme (5alphaR-I) is mainly present in liver and skin while the type II iso-enzyme (5alphaR-II) is mainly present in the prostate tissue and in the male sexual organs and its activity is
5 essential in the fetal developing process for the differentiation of the external sexual organs.

The production of dihydrotestosterone is associated with some pathologies which are widely diffused as for example benign prostate hypertrophy, prostate cancer, baldness and acne in men and hirsutism
10 in women. More particularly iso-enzyme I plays a role in the pathologies regarding the skin while iso-enzyme-II is involved in

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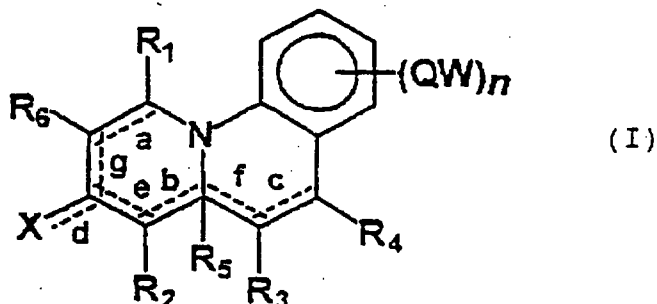
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Claims

1. Benzo[c]-quinolizine compounds of formula (I)



wherein:

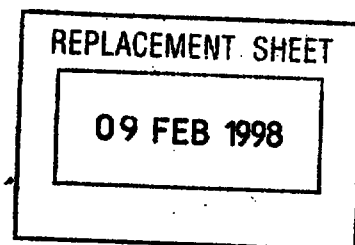
R_1, R_2, R_3, R_4, R_6 , same or different, are chosen in the group consisting of: H, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkinyl, cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane, cyclooctane, norbornane, canphane, adamantane, phenyl, naphtyl, saturated or aromatic heterocycle containing one or more N atoms, halogen, CN, azide, NRR' , C_{1-8} alkylamino, arylamino, C_{1-8} alkyloxy, aryloxy, COOR, CONRR' wherein R and R', same or different, are chosen in the group consisting of: H, C_{1-8} alkyl, cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane, cyclooctane, norbornane, canphane, adamantane, phenyl, naphtyl, saturated or aromatic heterocycle containing one or more N atoms, aryl C_{1-8} alkyl;

R_5 is chosen in the group consisting of: H, C_{1-8} alkyl, COOR, CN, phenyl, naphtyl, saturated or aromatic heterocycle containing one or more N atoms;

X is chosen in the group consisting of: O, $C(=O)R$, COOR, NO_2 , CONR'R wherein R and R' are as above defined;

Q is chosen in the group consisting of: simple bond, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkinyl, cyclopropane, cyclobutane, cyclopentane,

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cyclohexane, cycloheptane, cyclooctane, norbornane, canphane, adamantane, CO, CONR, NR, wherein R is as above defined;

W is chosen in the group consisting of: H, C₁₋₈alkyl, C₂₋₈alkenyl, C₂₋₈alkinyl, cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane, cyclooctane, norbornane, canphane, adamantane, trifluoromethyl, C₁₋₈alkoxy, C₁₋₈alkoxy-C₁₋₈alkyl, arylC₁₋₈alkyl, phenyl, naphthyl aryloxy, arylamino, C₁₋₈alkylcarbonyl, arylcarbonyl, halogen, CN, NRR', C₁₋₈alkylamino, saturated or aromatic heterocycle containing one or more N atoms, wherein the groups alkyl, alkenyl, alkinyl, cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane, cyclooctane, norbornane, canphane, adamantane, phenyl, naphthyl, saturated or aromatic heterocycle containing one or more N atoms can be substituted by halogen, OR, phenyl, NRR', CN, COOR, CONRR', C₁₋₈alkyl (wherein R and R' are as above defined);

n is an integer comprised between 1 and 4;

the symbol ----- means that the corresponding bonds a, b, c, d e, f, and g can be simple or double bonds;

with the proviso that when b or f are a double bond then the group R₅ is absent; and with the proviso that the following two compounds are excluded from the Claim: 4-carbonitril-2,3-dihydro-(1H)-benzo[c]quinolizin-3-one and 3,4-dihydro-1-phenyl-4aH-benzo[c]quinolizin-3-one;

their pharmaceutically acceptable salts or esters.

2. Benzo[c]-quinolizine compounds of formula (I) according to Claim 1 wherein

R₅ = H, saturated or aromatic heterocycle containing one or more N atoms;

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X = O;

Q = simple bond, CO, CONR, NR (wherein R is as above defined);

W = H, F, Cl, Br, Me, t-butyl, C₁₋₈alkoxy, 2,5-dimethylhexyl, trifluoromethyl, 2,5-(di-trifluoromethyl)-phenyl, 4-methoxy-phenyl, 4-fluoro-phenyl, phenyl, phenyl-C₁₋₈alkyl, C₁₋₈alkylcarbonyl, phenylcarbonyl;

n = 1 and 2;

R₁, R₂, R₃, R₄, R₅, R₆ = H, Me, CN, phenyl, COOR, CONRR' (wherein R and R' are as above defined).

- 10 3. Benzo[c]-quinolizine compounds according to Claim 1 of formula
- 1,2,4,4a,5,6 hexahydro-(11H)-benzo[c]quinolizine-3-one;
- 8-chloro-1,2,4,4a,5,6 hexahydro-(11H)-benzo[c]quinolizine-3-one;
- 1,2,4,4a,5,6 hexahydro-8-methyl-(11H)-benzo[c]quinolizine-3-one;
- 1,2,4,4a,5,6 hexahydro-4-methyl-(11H)-benzo[c]quinolizine-3-one;
- 15 1,2,4,4a,5,6 hexahydro-1-methyl-(11H)-benzo[c]quinolizine-3-one;
- 1,2,5,6 tetrahydro-(11H)-benzo[c]quinolizine-3-one;
- 8-chloro-1,2,5,6 tetrahydro-(11H)-benzo[c]quinolizine-3-one;
- 8-methyl-1,2,5,6 tetrahydro-(11H)-benzo[c]quinolizine-3-one;
- 4-methyl-1,2,5,6 tetrahydro-(11H)-benzo[c]quinolizine-3-one;
- 20 1-methyl-1,2,4,6 tetrahydro-(11H)-benzo[c]quinolizine-3-one;
- 4,4a,5,6 tetrahydro-(11H)-benzo[c]quinolizine-3-one;
- 5,6-dihydro-(11H)-benzo[c]quinolizine-3-one;
- 8-chloro-4,4a,5,6 tetrahydro-(11H)-benzo[c]quinolizine-3-one;
- 8-chloro-1-methyl-4,4a,5,6-tetrahydro-(11H)-benzo[c]quinolizine-3-one;
- 25 8-methyl-4,4a,5,6 tetrahydro-(11H)-benzo[c]quinolizine-3-one;
- 4-methyl-4,4a,5,6 tetrahydro-(11H)-benzo[c]quinolizine-3-one (cis) and (trans);

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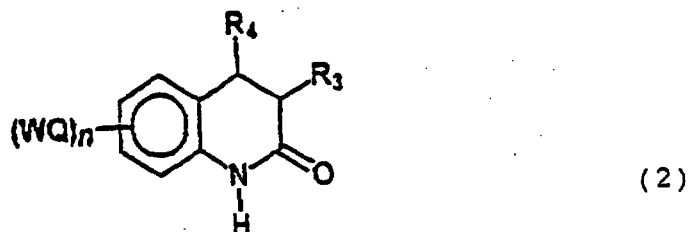
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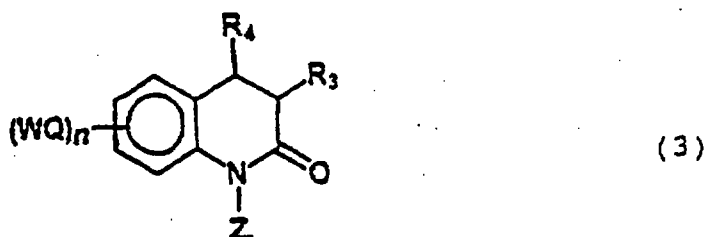
- 8-chloro-4-methyl-1,2,5,6 tetrahydro-(11H)-benzo[c]quinolizine-3-one;
4,8-dimethyl-1,2,5,6 tetrahydro-(11H)-benzo[c]quinolizine-3-one;
4,8-dimethyl-4,4a,5,6 tetrahydro-(11H)-benzo[c]quinolizine-3-one (cis)
and (trans);
- 5 8-chloro-4-methyl-4,4a,5,6-tetrahydro-(11H)-benzo[c]quinolizine-3-one
(cis) and (trans).

4. Process for the preparation of compounds according to Claim 1
wherein:

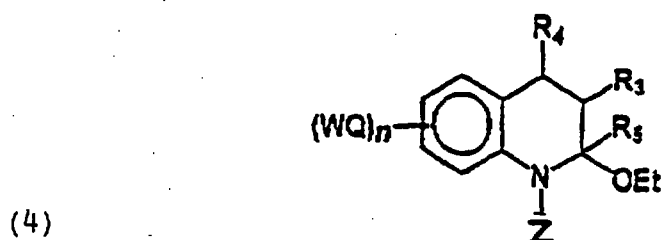
the amide-group of a compound of formula (2)



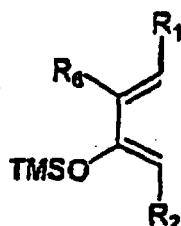
- 10 is protected with a protecting group Z to give the compound (3)



the above said compound (3) is reduced to compound (4), for example
with sodium borohydride in ethanol (pH3)



and compound (4) is reacted with a silylether (6)



(6)

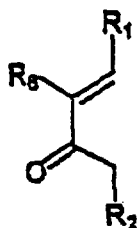
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prepared "in situ" by reacting a vinyl-ketone (5)

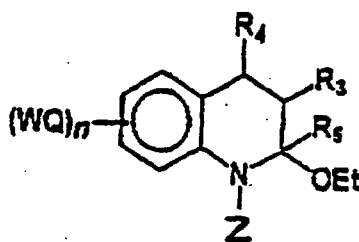


(5)

(wherein R_1 , R_2 , R_6 are as above defined) with a silylating agent as trimethylsilyltrifluoromethanesulphonic anhydride (TMSOTf) and are finally hydrolized, for example with sodium hydrogencarbonate, to give
5 the final compound of formula (I) wherein $X = O$.

5. Process according to claim 4 wherein the possible introduction of the double bonds in position a or b is performed by reaction of dichlorodicyanoquinone (DDQ) with the corresponding silylenolethers or by oxidation with quicksilver acetate of the saturated compound
10 obtained as claimed above and the possible transformation of the group X is performed via the corresponding enoltriflates and following carbonylation in the presence of palladium diacetate, triphenylphosphine and the suitable nucleophilic reagent.

6. Compound of formula (4)



(4)

15 wherein W, Q, n, R_3 , R_4 , R_5 are as defined in claim 1 and Z is a protecting group for the amide-group with the proviso that when $R_3 = R_4 = R_5 = (WQ)_n = H$ than Z is not a group ethoxycarbonyl.

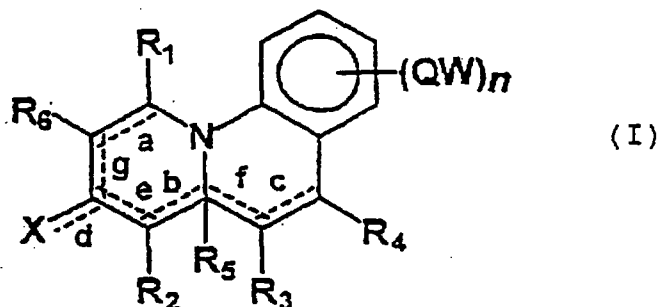
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7. Pharmaceutical composition wherein the active principle is a compound of formula (I)



wherein:

- R_1, R_2, R_3, R_4, R_6 , same or different, are chosen in the group consisting of: H, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkinyl, cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane, cyclooctane, norbornane, canphane, adamantane, phenyl, naphtyl, saturated or aromatic heterocycle containing one or more N atoms, halogen, CN, azide, NRR' , C_{1-8} alkylamino, arylamino, C_{1-8} alkyloxy, aryloxy, COOR, CONRR' wherein R and R', same or different, are chosen in the group consisting of: H, C_{1-8} alkyl, cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane, cyclooctane, norbornane, canphane, adamantane, phenyl, naphtyl, saturated or aromatic heterocycle containing one or more N atoms aryl C_{1-8} alkyl;
- R_5 is chosen in the group consisting of: H, C_{1-8} alkyl, COOR, CN, phenyl, naphtyl, saturated or aromatic heterocycle containing one or more N atoms;
- X is chosen in the group consisting of: O, $C(=O)R$, COOR, NO_2 , CONR' R wherein R and R' are as above defined;
- Q is chosen in the group consisting of: simple bond, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkinyl, cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane, cyclooctane, norbornane, canphane, adamantane, CO, CONR, NR, wherein R is as above defined;

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W is chosen in the group consisting of: H, C₁₋₈alkyl, C₂₋₈alkenyl, C₂₋₈alkinyl, cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane, cyclooctane, norbornane, canphane, adamantane, trifluoromethyl, C₁₋₈alkoxy, C₁₋₈alkoxy-C₁₋₈alkyl, arylC₁₋₈alkyl, 5 phenyl, naphthyl, aryloxy, arylamino, C₁₋₈alkylcarbonyl, arylcarbonyl, halogen, CN, NRR', C₁₋₈alkylamino, saturated or aromatic heterocycle containing one or more N atoms wherein the groups alkyl, alkenyl, alkynyl, cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane, cyclooctane, norbornane, canphane, adamantane, phenyl, 10 naphthyl, saturated or aromatic heterocycle containing one or more N atoms can be substituted by halogen, OR, phenyl, NRR', CN, COOR, CONRR', C₁₋₈alkyl (wherein R and R' are as above defined);

n is an integer comprised between 1 and 4;

the symbol ----- means that the corresponding bonds a, b, c, d e, f, 15 and g can be simple or double bonds;

with the proviso that when b or f are a double bond then the group R₅ is absent;

their pharmaceutically acceptable salts or esters
or mixtures thereof in combination with the suitable pharmaceutical
20 acceptable excipients.

8. Pharmaceutical composition according to Claim 7 for use in the inhibition of the 5αphar-I and/or 5αphar-II iso-enzymes.

9. Pharmaceutical composition according to claims 7 and 8 in the form suitable for topic use.

25 10. Use of a compound of formula (I) according to Claim 7 as a medicament.

11. Use of a compound of formula (I) according to Claim 7 for the

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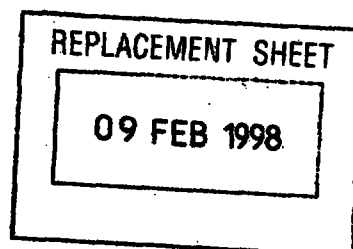


preparation of a pharmaceutical composition for the treatment of acne, baldness, prostatic cancer and prostatic hypertrophy in men and hirsutism in women.

12. Method for the treatment of pathologies related to 5alpha-
5 reductase enzymes by administration to the patient of a pharmaceutically active amount of a pharmaceutical composition according to Claims 7.

13. Method for treatment of acne, baldness, prostatic cancer and prostatic hypertrophy in men and hirsutism in women, by administration
10 of a pharmaceutically active amount of a pharmaceutical composition according to Claims 7.

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(21) International Application Number: ✓ PCT/EP97/00552 (22) International Filing Date: ✓ 7 February 1997 (07.02.97) (30) Priority Data: ✓ FI96A000019 ✓ 9 February 1996 (09.02.96) ✓ IT (71) Applicant (for all designated States except US): APPLIED RESEARCH SYSTEMS ARS HOLDING N.V. [NL/NL]; John B. Gorsiraweg 14, Curaçao (AN). (72) Inventors; and (75) Inventors/Applicants (for US only): GUARNA, Antonio [IT/IT]; Via Pistoiese, 158, I-50040 Seano (IT). SERIO, Mario [IT/IT]; Via Roma, 41, I-52010 Subbiano (IT). (74) Agent: GERVASI, Gemma; Notarbartolo & Gervasi, Corso di Porta Vittoria, 9, I-20122 Milan (IT).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.
(54) Title: BENZO[C]QUINOLIZINE DERIVATIVES, THEIR PREPARATION AND USE AS 5α-REDUCTASES INHIBITORS (57) Abstract The present invention refers to benzo[c]quinolizine derivatives of general formula (I), their pharmaceutically acceptable salts or esters, processes for their preparation and pharmaceutical compositions containing them. (I)		