

PROCESS FOR THE SYNTHESIS OF (1H)-BENZO[C]QUINOLIZIN-3-ONES DERIVATIVES

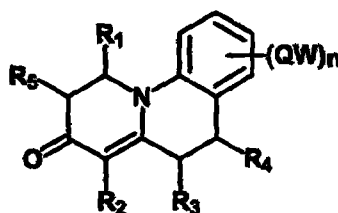
Summary of the invention

The present invention refers to a process for the preparation of (1H)-benzo[c]quinolizin-3-ones derivatives of general formula (I) which involves only three steps and the use, as starting products, of commercially available, or easily preparable, compounds. The compounds of formula (I) are useful as inhibitors of 5 α -reductases.

Field of the invention

The present invention refers to a process for the preparation of (1H)-benzo[c]quinolizin-3-ones derivatives of general formula (I)

wherein:



R_1 , R_2 , R_3 , R_4 , R_5 , 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 or different, are chosen in the group consisting of: H, C_{1-8} alkyl, cycloalkyl, aryl, heterocycle, aryl C_{1-8} alkyl;

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;

W is chosen in the group consisting of: H, C₁₋₈alkyl, C₂₋₈ alkenyl, C₂₋₈alkinyl, cycloalkyl, trifluoromethyl, C₁₋₈alkoxy, C₁₋₈ alkoxy-C₁₋₈alkyl, arylC₁₋₈alkyl, aryl, aryloxy, arylamino, C₁₋₈alkylcarbonyl, arylcarbonyl, arylcarboxyl, arylcarboxamide, halogen, CN, NRR', C₁₋₈alkylamino, heterocycle wherein the groups alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocycle, can be substituted;

n is an integer comprised between 1 and 4;

and their pharmaceutically acceptable salts or esters,

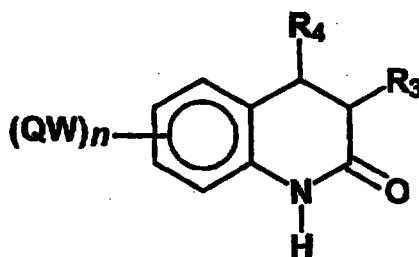
starting from commercially available, or easily preparable compounds, and involving only three steps.

10 State of the art

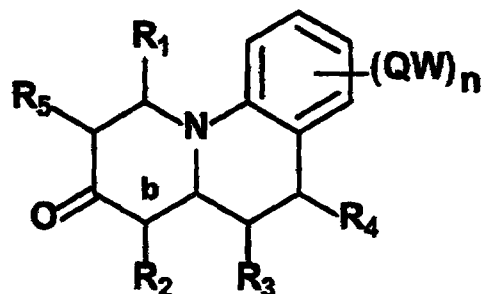
Compounds of general formula (I) as above defined are known 5 α -reductases inhibitors useful for the treatment of the pathologies mediated by the enzyme (for example acne, baldness, prostatic cancer and hypertrophy in men and hirsutism in women) (see International Application N° PCT/EP97/00552). They are also

15 active as plant growth regulators.

As it is described in the above said patent application, up to now the compounds of formula (I) are produced by a process involving various steps starting from a compound of formula II



According to the process the amide-group of compound II is protected as N-Boc derivative, the obtained compound is reduced, reacted with a silyloxydiene produced "in situ" and hydrolized to obtain a compound of formula III



(III)

Finally the introduction of the double bond in position b is performed by reaction with dichlorodicyanoquinone with the corresponding silylenolethers or by oxidation with mercuric acetate.

As it can be seen the above described process involves many steps which i.a. have a negative effect on the final yields of the desired compounds.

In view of the importance of these compounds as 5a-reductase inhibitors, it is evident the interest in making available new processes in order to prepare the desired compounds in a more efficient way.

Detailed description of the invention

The present invention allows to overcome the above said problems by a synthesis process that involves only three steps and moreover uses, as starting compounds, compounds which can be easily synthesized or are commercially available.

According to the present invention in the compounds of formula (I) group C₁₋₈ alkyl, C₂₋₈ alkenyl and C₂₋₈ alkynyl represent linear or branched alkyl radicals as for

example: methyl, ethyl, propyl, isopropyl, butyl, pentyl, hexyl, heptyl, octyl, ethylene, propene, butene, isobutene, acetylene, propine, butine ecc.

The term cycloalkyl represents: cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane, cyclooctane, norbornane, canphane, adamantane.

5 The term aryl represents: phenyl and naphthyl.

The term heterocycle represents in particular: saturated or aromatic heterocycles containing one or more N atoms, more particularly: pyridine, imidazole, pyrrole, indole, triazoles, pyrrolidine, piperidine.

Halogen means: fluorine, chlorine, bromine, iodine.

10 The substituents of the above said group W are preferably: halogen, OR, phenyl, NRR', CN, COOR, CONRR', C₁₋₈alkyl (wherein R and R' are as above defined).

In particular, the process according to the present invention allows the preparation of the compounds of formula (I) wherein:

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, C₁₋₈ alkylcarbonyl, phenylcarbonyl.

n = 1 or 2

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

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

Specific compounds prepared according to the process of the invention are:

25 2,3,5,6-tetrahydro-(1H)-benzo[c]quinolizin-3-one;

- 8-chloro-2,3,5,6-tetrahydro-(1*H*)-benzo[c]quinolizin-3-one;
2,3,5,6-tetrahydro-8-methyl-(1*H*)-benzo[c]quinolizin-3-one;
2,3,5,6-tetrahydro-4-methyl-(1*H*)-benzo[c]quinolizin-3-one;
2,3,5,6-tetrahydro-1-methyl-(1*H*)-benzo[c]quinolizin-3-one;
5 8-chloro-2,3,5,6-tetrahydro-4-methyl-(1*H*)-benzo[c]quinolizin-3-one;
2,3,5,6-tetrahydro-4,8-dimethyl-(1*H*)-benzo[c]quinolizin-3-one;
8-chloro-2,3,5,6-tetrahydro-1-methyl-(1*H*)-benzo[c]quinolizin-3-one;
2,3,5,6-tetrahydro-1,4-dimethyl-(1*H*)-benzo[c]quinolizin-3-one;
2,3,5,6-tetrahydro-6-methyl-(1*H*)-benzo[c]quinolizin-3-one;
10 8-chloro-2,3,5,6-tetrahydro-6-methyl-(1*H*)-benzo[c]quinolizin-3-one;
2,3,5,6-tetrahydro-6,8-dimethyl-(1*H*)-benzo[c]quinolizin-3-one;
2,3,5,6-tetrahydro-4,6-dimethyl-(1*H*)-benzo[c]quinolizin-3-one;
2,3,5,6-tetrahydro-1,6-dimethyl-(1*H*)-benzo[c]quinolizin-3-one;
8-chloro-2,3,5,6-tetrahydro-4,6-dimethyl-(1*H*)-benzo[c]quinolizin-3-one;
15 2,3,5,6-tetrahydro-4,6,8-trimethyl-(1*H*)-benzo[c]quinolizin-3-one;
8-chloro-2,3,5,6-tetrahydro-1,6-dimethyl-(1*H*)-benzo[c]quinolizin-3-one;
2,3,5,6-tetrahydro-1,4,6-trimethyl-(1*H*)-benzo[c]quinolizin-3-one;
2,3,5,6-tetrahydro-5-methyl-(1*H*)-benzo[c]quinolizin-3-one;
8-chloro-2,3,5,6-tetrahydro-5-methyl-(1*H*)-benzo[c]quinolizin-3-one;
20 2,3,5,6-tetrahydro-5,8-dimethyl-(1*H*)-benzo[c]quinolizin-3-one;
2,3,5,6-tetrahydro-4,5-dimethyl-(1*H*)-benzo[c]quinolizin-3-one;
2,3,5,6-tetrahydro-1,5-dimethyl-(1*H*)-benzo[c]quinolizin-3-one;
8-chloro-2,3,5,6-tetrahydro-4,5-dimethyl-(1*H*)-benzo[c]quinolizin-3-one;
2,3,5,6-tetrahydro-4,5,8-trimethyl-(1*H*)-benzo[c]quinolizin-3-one;
25 8-chloro-2,3,5,6-tetrahydro-1,5-dimethyl-(1*H*)-benzo[c]quinolizin-3-one;

2,3,5,6-tetrahydro-1,4,5-trimethyl-(1*H*)-benzo[c]quinolizin-3-one;

2,3,5,6-tetrahydro-5,6-dimethyl-(1*H*)-benzo[c]quinolizin-3-one;

8-chloro-2,3,5,6-tetrahydro-5,6-dimethyl-(1*H*)-benzo[c]quinolizin-3-one;

2,3,5,6-tetrahydro-5,6,8-trimethyl-(1*H*)-benzo[c]quinolizin-3-one;

5 2,3,5,6-tetrahydro-4,5,6-trimethyl-(1*H*)-benzo[c]quinolizin-3-one;

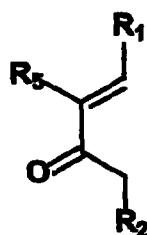
8-chloro-2,3,5,6-tetrahydro-4,5,6-trimethyl-(1*H*)-benzo[c]quinolizin-3-one;

2,3,5,6-tetrahydro-1,5,6-trimethyl-(1*H*)-benzo[c]quinolizin-3-one;

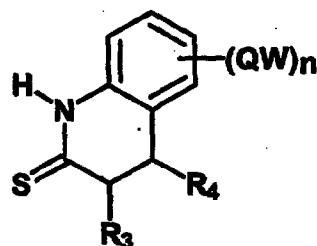
8-chloro-2,3,5,6-tetrahydro-1,5,6-trimethyl-(1*H*)-benzo[c]quinolizin-3-one;

2,3,5,6-tetrahydro-4,5,6,8-tetramethyl-(1*H*)-benzo[c]quinolizin-3-one.

- 10 According to the invention the above defined compounds of formula (I) can be prepared starting from compounds of general formula 2 and 3:



2



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wherein R_1 , R_2 , R_3 , R_4 , R_5 , W , Q and n are as above defined.

The compounds 2 and 3 are commercially available or can be prepared according
15 to known techniques.

As it can be seen from the Scheme 1 the preparation of the compounds I according to the invention involves the *N*-alkylation of the thioamide 3 with the vinyl ketone 2 to give the *N*-alkylated thioamide 4 in the presence of a strong, but not nucleophilic, base. Preferably the reaction is performed in an organic solvent
20 (for example THF) at a temperature comprised between 0°C - 30°C for a time

comprised between two and four hours. More preferably the vinyl ketone is added to the thioamide intermittently.

The characteristics of the base are crucial for the effectiveness of the reaction : indeed strong nucleophilic bases cause the polymerization of the vinylketone, whereas with mild bases the reaction does not occur. Preferred bases having the above said characteristics are: K_2CO_3 /18-crown-6 or diazabicycloundecene (DBU). The *N*-alkylated thioamide 4 is then methylated at sulfur atom, to give the salt 5, which is not usually isolated, but left to react with a base to give the final compound I. Also for this step the reaction conditions (temperature and time) and the type of base are important.

The best results were obtained using dimethyl sulfate as methylating agent, a strong but not nucleophilic base (for example DBU) and performing the reaction at refluxing temperature in an organic solvent (for example toluene) for a time comprised between half - and one hour.

The synthesis of two compounds of formula (I) is reported in the following examples in order to better illustrate the invention.

EXAMPLE 1

Preparation of 6-chloro-1-(3-oxo-1-pentyl)-(1*H*)-3,4-dihydroquinolin-2-thione [compound 4 wherein (QW)_n = Cl, R₁ = R₃ = R₄ = R₅ = H, R₂ = Me]

Under nitrogen atmosphere, ethyl vinyl ketone (compound 2, wherein R₁ = R₅ = H, R₂ = Me) (340 ml, 3.42 mmol) is added to a stirred suspension of 6-chloro-(1*H*)-3,4-dihydroquinolin-2-thione (compound 3 wherein (QW)_n = Cl, R₃ = R₄ = H) (450 mg, 2.28 mmol), anhydrous K_2CO_3 (692 mg, 5.01 mmol), and 18-crown-6 (60 mg, 0.23 mmol) in anhydrous THF (41 ml), while cooling at 0 °C. The suspension is then allowed to warm to room temperature and, after 30 min of stirring, the

suspension is cooled at 0 °C and a further amount of ethyl vinyl ketone (3.42 mmol) is added. After 1 h at room temperature the suspension is cooled again at 0 °C and the last amount of ethyl vinyl ketone (3.42 mmol) is added. After 1 h at room temperature the reaction is thus complete. The reaction mixture is filtered
5 through a short pad of anhydrous Na₂SO₄ and the solvent evaporated. The residual oil is chromatographed (ethyl acetate: light petroleum ether, 1:9, R_f = 0.29) affording pure 6-chloro-1-(3-oxo-1-pentyl)-(1*H*)-3,4-dihydroquinolin-2-thione [compound 4 wherein (QW)_n = Cl, R₁ = R₃ = R₄ = R₅ = H, R₂ = Me] (277 mg, 45%) as a pale yellow solid (mp. 68-70 °C).

10 As an alternative, thioamide 3 (450 mg, 2.28 mmol) is dissolved in 5 ml of anhydrous THF, DBU (69 ml, 0.46 mmol) is added and, while cooling at 0 °C, ethylvinylketone 2 (275 ml, 2.76 mmol) is added dropwise under stirring and nitrogen atmosphere. After 2.5 h at 0 °C a further amount of ethyl vinyl ketone (113 ml, 1.38 mmol) is added, the reaction is left another hour at 0 °C and then
15 the solvent is evaporated, the residual oil diluted with CH₂Cl₂ (30 ml), washed with 5% citric acid, NaHCO₃ (satd) and water. The organic layer is dried over Na₂SO₄, filtered and evaporated, obtaining a crude oil which is chromatographed as reported above. Compound 4 is thus obtained as a 1.6 : 1 mixture with unreacted thioamide 3. Calculated yield on 4: 35%.

20 EXAMPLE 2

Preparation of 8-chloro-2,3,5,6-tetrahydro-4-methyl-(1*H*)-benzo[c]quinolizin-3-one [compound I wherein (QW)_n = Cl, R₁ = R₃ = R₄ = R₅ = H and R₂ = Me].

To a solution of 6-chloro-1-(3-oxo-1-pentyl)-(1*H*)-3,4-dihydroquinolin-2-thione [compound 4 wherein (QW)_n = Cl, R₁ = R₃ = R₄ = R₅ = H, R₂ = Me], (250 mg, 0.93
25 mmol) in anhydrous toluene (3 ml) is added Me₂SO₄ (149 ml, 1.57 mmol) under

stirring and nitrogen atmosphere. The solution is heated at reflux and after 5 min a red oil begins to separate. After further 10 min, DBU (235 ml, 1.57 mmol) is added dropwise to the refluxing two-phase reaction mixture, causing after a few minutes, a darkening of the mixture. The reflux is maintained for 20 min, then the solution is cooled at room temperature, diluted with dichloromethane (50 ml), washed with water (50 ml) and dried over Na_2SO_4 . After filtration and evaporation of the solvent the dark residual oil is chromatographed (ethyl acetate : light petroleum ether, 1:1, $R_f = 0.28$) affording pure 8-chloro-2,3,5,6-tetrahydro-4-methyl-(1*H*)-benzo[*c*]quinolizin-3-one [compound 1 wherein $(\text{QW})_n = \text{Cl}$, $R_1 = R_3 = R_4 = R_5 = \text{H}$ and $R_2 = \text{Me}$] (90 mg, 41%) as an oil which solidify on standing (mp 112-114 °C).

EXAMPLE 3

Preparation of 6-methyl-1-(3-oxo-1-pentyl)-(1*H*)-3,4-dihydroquinolin-2-thione

[compound 4 wherein $(\text{QW})_n = \text{Me}$, $R_1 = R_3 = R_4 = R_5 = \text{H}$, $R_2 = \text{Me}$]

Under nitrogen atmosphere, ethyl vinyl ketone (compound 2, wherein $R_1 = R_5 = \text{H}$, $R_2 = \text{Me}$) (380 ml, 3.81 mmol) is added to a stirred suspension of 6-methyl-(1*H*)-3,4-dihydroquinolin-2-thione (compound 3 wherein $(\text{QW})_n = \text{Me}$, $R_3 = R_4 = \text{H}$) (500 mg, 2.82 mmol), anhydrous K_2CO_3 (900 mg, 6.5 mmol), and 18-crown-6 (89 mg, 0.28 mmol) in anhydrous THF (47 ml), while cooling at 0 °C. The suspension is then allowed to warm to room temperature and, after 60 min of stirring, the suspension is cooled again at 0 °C and a further amount of ethyl vinyl ketone 2 (3.81 mmol) is added. After 2 h at room temperature the reaction is complete. The reaction mixture is filtered through a short pad of anhydrous Na_2SO_4 and the solvent evaporated. The residual oil is chromatographed (ethyl acetate: light petroleum ether, 1:9, $R_f = 0.23$) affording pure 6-methyl-1-(3-oxo-1-pentyl)-(1*H*)-

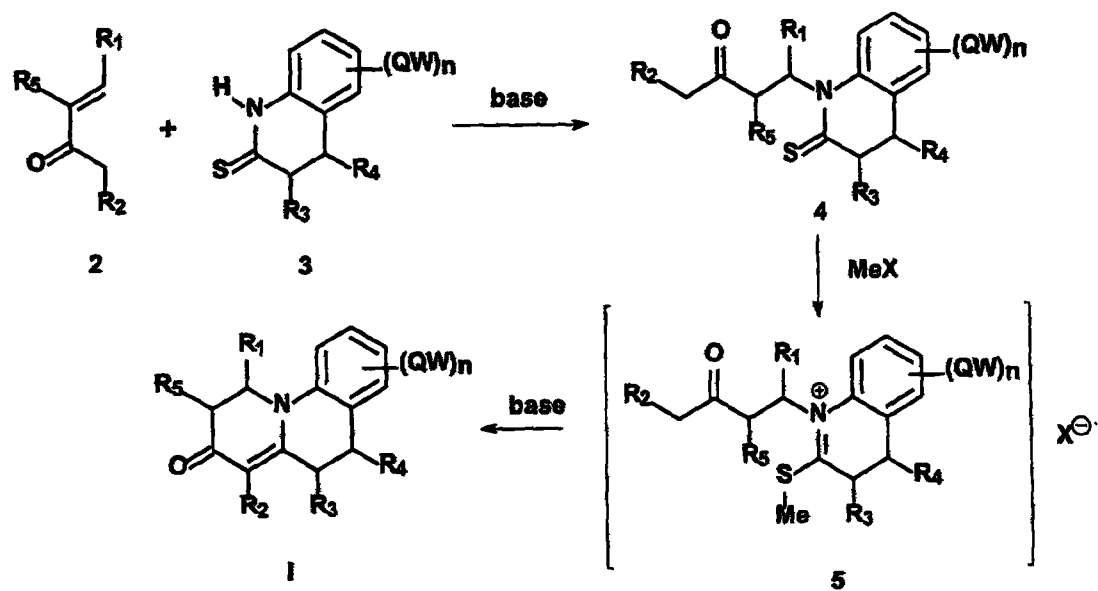
3,4-dihydroquinolin-2-thione [compound 4 wherein $(QW)_n = \text{Me}$, $R_1 = R_3 = R_4 = R_5 = \text{H}$, $R_2 = \text{Me}$] (500 mg, 68%) as a white solid (mp 70-71°C).

EXAMPLE 4

Preparation of 8-methyl-2,3,5,6-tetrahydro-4-methyl-(1*H*)-benzo[*c*]quinolizin-3-one
5 [compound I wherein $(QW)_n = \text{Me}$, $R_1 = R_3 = R_4 = R_5 = \text{H}$ and $R_2 = \text{Me}$].

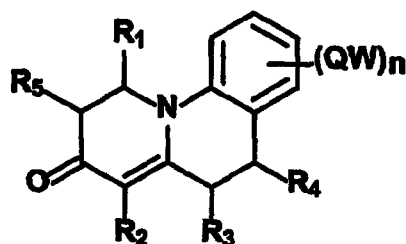
To a solution of 6-methyl-1-(3-oxo-1-pentyl)-(1*H*)-3,4-dihydroquinolin-2-thione
[compound 4 wherein $(QW)_n = \text{Me}$, $R_1 = R_3 = R_4 = R_5 = \text{H}$, $R_2 = \text{Me}$] (350 mg, 1.40
mmol) in anhydrous toluene (4 ml) is added Me_2SO_4 (227 ml, 2.40 mmol) under
stirring and nitrogen atmosphere. The solution is heated at reflux and after 5 min a
10 red oil begins to separate. After further 15 min, DBU (365 ml, 2.40 mmol) is added
dropwise to the refluxing two-phase reaction mixture, causing after a few minutes,
a darkening of the mixture. The reflux is maintained for 20 min, then the solution is
cooled at room temperature, diluted with dichloromethane (50 ml), washed with
water (50 ml) and dried over Na_2SO_4 . After filtration and evaporation of the
15 solvent, the dark residual oil is chromatographed (ethyl acetate : light petroleum
ether, 1:1, $R_f = 0.29$) affording pure 8-methyl-2,3,5,6-tetrahydro-4-methyl-(1*H*)-
benzo[*c*]quinolizin-3-one [compound I wherein $(QW)_n = \text{Me}$, $R_1 = R_3 = R_4 = R_5 = \text{H}$
and $R_2 = \text{Me}$] (152 mg, 50%) as an oil which became a solid on standing (mp 143-
145 °C)

SCHEME 1



CLAIMS

1. Process for the preparation of compounds of formula (I):



I

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3 wherein:

4 R_1, R_2, R_3, R_4, R_5 , same or different, are chosen in the group consisting of: H, C_{1-8}
 5 alkyl, C_{2-8} alkenyl, C_{2-8} alkinyl, cycloalkyl, aryl, heterocycle, halogen, CN, azide,
 6 NRR' , C_{1-8} alkylamino, arylamino, C_{1-8} alkyloxy, aryloxy, COOR, CONRR' wherein R
 7 and R', same or different, are chosen in the group consisting of: H, C_{1-8} alkyl,
 8 cycloalkyl, aryl, heterocycle, aryl C_{1-8} alkyl;

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

11 W is chosen in the group consisting of: H, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkinyl,
 12 cycloalkyl, trifluoromethyl, C_{1-8} alkoxy, C_{1-8} alkoxy- C_{1-8} alkyl, aryl C_{1-8} alkyl, aryl,
 13 aryloxy, arylamino, C_{1-8} alkylcarbonyl, arylcarbonyl, arylcarboxyl, arylcarboxamide,
 14 halogen, CN, NRR' , C_{1-8} alkylamino, heterocycle wherein the groups alkyl, alkenyl,
 15 alkyl, cycloalkyl, aryl, heterocycle, can be substituted;

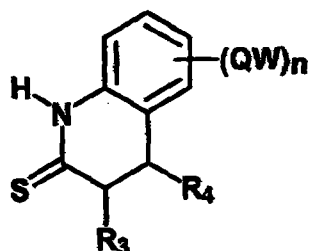
16 n is an integer comprised between 1 and 4;

17 and their pharmaceutically acceptable salts or esters,

18 wherein :

19 a thioamide 3

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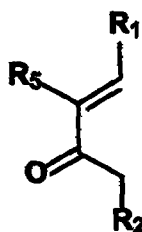


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21 (wherein R_3 and R_4 are as above defined)

22 is N-alkylated with a vinyl ketone of formula 2:

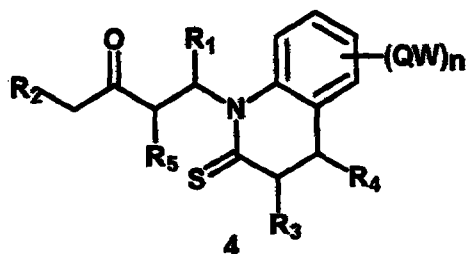


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24 (wherein R_1 , R_2 and R_5 are as above defined)

25 to give the corresponding compound 4:



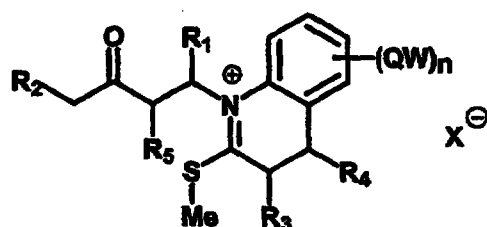
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26 (wherein all the substituents are as above defined)

27 which is methylated, at the sulfur atom to give the salt 5:

28





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This Sheet Has Been Replaced



- 29 (wherein all the substituents are as above defined)
- 30 which is directly reacted with a base to give the desired compound I.
- 1 2. Process according to claim 1 wherein the reaction between the compounds 2
 - 2 and 3 is conducted in an organic solvent, in the presence of a strong, but non
 - 3 nucleophilic, base.
 - 1 3. Process according to claim 1 wherein the final step of cyclization is conducted
 - 2 in an organic solvent in the presence of a strong, but not nucleophilic, base.
 - 1 4. Process according to claim 2 wherein the base is K_2CO_3 /18-crown-6 or
 - 2 diazabicycloundecene (DBU).
 - 1 5. Process according to claim 3 wherein the base is diazabicycloundecene (DBU).
 - 1 6. Process according to claim 2 wherein the solvent is THF.
 - 1 7. Process according to claims 1 and 3 wherein the methylating agent is
 - 2 dimethylsulfate and the solvent is toluene at refluxing temperature.
 - 1 8. Process according to claim 7 wherein the overall reaction time is comprised
 - 2 between half-hour to one hour.



1 9. Process according to claim 1 wherein the compound of formula (I) are:

2 2,3,5,6-tetrahydro-(1*H*)-benzo[c]quinolizin-3-one;

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

4 2,3,5,6-tetrahydro-8-methyl-(1*H*)-benzo[c]quinolizin-3-one;

5 2,3,5,6-tetrahydro-4-methyl-(1*H*)-benzo[c]quinolizin-3-one;

6 2,3,5,6-tetrahydro-1-methyl-(1*H*)-benzo[c]quinolizin-3-one;

7 8-chloro-2,3,5,6-tetrahydro-4-methyl-(1*H*)-benzo[c]quinolizin-3-one;

8 2,3,5,6-tetrahydro-4,8-dimethyl-(1*H*)-benzo[c]quinolizin-3-one;

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

10 2,3,5,6-tetrahydro-1,4-dimethyl-(1*H*)-benzo[c]quinolizin-3-one;

11 2,3,5,6-tetrahydro-6-methyl-(1*H*)-benzo[c]quinolizin-3-one;

12 8-chloro-2,3,5,6-tetrahydro-6-methyl-(1*H*)-benzo[c]quinolizin-3-one;

13 2,3,5,6-tetrahydro-6,8-dimethyl-(1*H*)-benzo[c]quinolizin-3-one;

14 2,3,5,6-tetrahydro-4,6-dimethyl-(1*H*)-benzo[c]quinolizin-3-one;

15 2,3,5,6-tetrahydro-1,6-dimethyl-(1*H*)-benzo[c]quinolizin-3-one;

16 8-chloro-2,3,5,6-tetrahydro-4,6-dimethyl-(1*H*)-benzo[c]quinolizin-3-one;

17 2,3,5,6-tetrahydro-4,6,8-trimethyl-(1*H*)-benzo[c]quinolizin-3-one;

18 8-chloro-2,3,5,6-tetrahydro-1,6-dimethyl-(1*H*)-benzo[c]quinolizin-3-one;

19 2,3,5,6-tetrahydro-1,4,6-trimethyl-(1*H*)-benzo[c]quinolizin-3-one;

20 2,3,5,6-tetrahydro-5-methyl-(1*H*)-benzo[c]quinolizin-3-one;

21 8-chloro-2,3,5,6-tetrahydro-5-methyl-(1*H*)-benzo[c]quinolizin-3-one;

22 2,3,5,6-tetrahydro-5,8-dimethyl-(1*H*)-benzo[c]quinolizin-3-one;

23 2,3,5,6-tetrahydro-4,5-dimethyl-(1*H*)-benzo[c]quinolizin-3-one;

24 2,3,5,6-tetrahydro-1,5-dimethyl-(1*H*)-benzo[c]quinolizin-3-one;

25 8-chloro-2,3,5,6-tetrahydro-4,5-dimethyl-(1*H*)-benzo[c]quinolizin-3-one;

This Sheet Has Been Replaced



* C L H S *

- 26 2,3,5,6-tetrahydro-4,5,8-trimethyl-(1*H*)-benzo[c]quinolizin-3-one;
- 27 8-chloro-2,3,5,6-tetrahydro-1,5-dimethyl-(1*H*)-benzo[c]quinolizin-3-one;
- 28 2,3,5,6-tetrahydro-1,4,5-trimethyl-(1*H*)-benzo[c]quinolizin-3-one;
- 29 2,3,5,6-tetrahydro-5,6-dimethyl-(1*H*)-benzo[c]quinolizin-3-one;
- 30 8-chloro-2,3,5,6-tetrahydro-5,6-dimethyl-(1*H*)-benzo[c]quinolizin-3-one;
- 31 2,3,5,6-tetrahydro-5,6,8-trimethyl-(1*H*)-benzo[c]quinolizin-3-one;
- 32 2,3,5,6-tetrahydro-4,5,6-trimethyl-(1*H*)-benzo[c]quinolizin-3-one;
- 33 8-chloro-2,3,5,6-tetrahydro-4,5,6-trimethyl-(1*H*)-benzo[c]quinolizin-3-one;
- 34 2,3,5,6-tetrahydro-1,5,6-trimethyl-(1*H*)-benzo[c]quinolizin-3-one;
- 35 8-chloro-2,3,5,6-tetrahydro-1,5,6-trimethyl-(1*H*)-benzo[c]quinolizin-3-one;
- 36 2,3,5,6-tetrahydro-4,5,6,8-tetramethyl-(1*H*)-benzo[c]quinolizin-3-one.

