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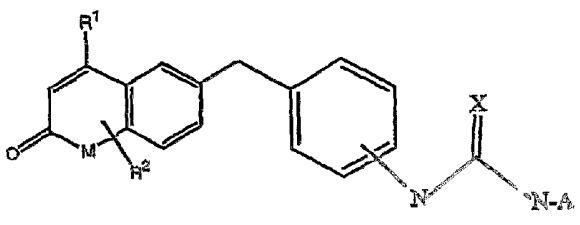
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(54) Title: BENZYL UREA AND THIOUREA DERIVATIVES USEFUL AS ANDROGEN ANTAGONISTS



(I)

(57) Abstract: The present invention is directed to a new class of 6-benzyl urea/thiourea-quinolin-2-one derivatives and 2-oxo-6-benzylurea/thiourea-chromene derivatives of the formula (I). These compound are androgen antagonists and are useful in the treatment of alopecia, acne and other conditions associated with inappropriate activation of the androgen receptor.

BENZYL UREA AND THIOUREA DERIVATIVES USEFUL AS ANDROGEN ANTAGONISTS

FIELD OF THE INVENTION

The present invention is directed to a new class of quinolin-2-ones and chromen-2-ones (hereinafter "quinolines and chromenes"), to their use as androgen receptor antagonists, to medicinals containing these compounds and to their use to alleviate conditions associated with inappropriate activation of the androgen receptor.

BACKGROUND OF THE INVENTION

The androgen receptor (AR) is a member of the steroid receptor (SR) family of transcriptional regulatory proteins that transduces the signaling information conveyed by androgens (Chang et al., 1995 and Wilson et al., 1991). Upon androgen binding, the androgen receptor is released from the repressive effects of an Hsp 90-based regulatory complex, allowing the receptor to either activate or inhibit transcription of target genes in a hormone-dependent manner (Suina et al., 1996; Fang et al., 1996; Fang et al., 1998; Picard et al., 1990; Segnitz et al., 1997; Jenster et al., 1991; and Jenster et al., 1992). In addition to the role the androgen receptor plays in male sex determination, its activation plays a critical role in the development and progression of benign prostate hyperplasia, prostate cancer, seborrhea, acne, premenstrual syndrome, lung cancer, ovarian polycyclic syndrome, hirsutism, and hair loss. Thus, the androgen receptor is an important target in multiple areas of drug discovery.

United States Patent No. 6,017,924 discloses a class of non-steroidal compounds, pyridinoquinolines that have affinity for the androgen receptor. The '924 patent describes these compounds as being agonists, partial agonists, antagonists, and partial antagonists, etc. The '924 patent provides no guidance on how to achieve a specific biological effect (i.e. agonist versus antagonist). Agonists have the ability to masculinize females, whereas antagonists feminize males. Such side effects limit the potential applicability of androgen therapy.

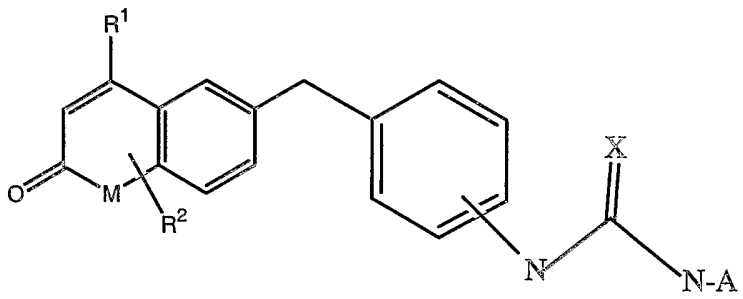
PCT applications WO 01/16133 and WO 01/16139 also disclose non-steroidal compounds that have affinity for the androgen receptor. Examples of such structures include pyrazinoquinolines, oxazinoquinolines, and pyridinoquinolines. The PCT application does not disclose any 6-benzylthiourea-quinolin-2-ones, 6-benzylurea-quinoline-2-ones, 6-benzylthiourea-chromen-2-ones or 6-benzylurea-chromen-2-ones.

PCT application WO 01 /16108 discloses non-steroidal compounds having affinity for the androgen receptor. Like the '924 patent described above, the compounds are described as having both agonist and antagonist effects. Some of the compounds of the PCT application are quinolin-2-one derivatives. The PCT application does not disclose any 6-benzylthiourea-quinolin-2-ones, 6-benzylurea-quinoline-2-ones, 6-benzylthiourea-chromen-2-ones or 6-benzylurea-chromen-2-ones.

While the prior art describes compounds having affinity for the androgen receptor, it does not describe how to achieve selectivity with respect to this affinity (i.e. agonist or antagonist). The physiological impact of this affinity is often an undesirable side effect, depending upon the gender of the patient. Thus a need exists in the art for androgen receptor antagonists.

SUMMARY OF THE INVENTION

In accordance with the present invention, a new class of androgen receptor antagonists has been discovered. These compounds may be represented by the following formula:



in which;

a. M is NZ or O;

b. Z is represented by H or C_1- C_4 alkyl;

c. R^1 is represented by hydrogen, (C_1-C_2)alkyl, optionally substituted with one or more halogens, or (C_1-C_2)alkoxy, optionally substituted with one or more halogens;

d. R^2 is absent, or may represent up to 2 substituents selected from the group consisting of halogen, nitrile, hydroxy, (C_1-C_4)alkyl, (C_2-C_4)alkenyl, (C_2-

C_4)alkynyl, (C_1-C_4)alkoxy, (C_1-C_2)alkyl substituted with one or more halogens, (C_1-C_2)alkoxy substituted with one or more halogens, SR^4, and NR^4R^5;

e. X is represented by O or S;

f. A is represented by hydrogen, (C_1- C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, -$[CH_2]_m$-D-$[CH_2]_n$-(CH_3), -$[CH_2]_m$C(O)OR^4, -$[CH_2]_m$C(O)R^4, -$[CH_2]_m$C(O)NR^4R^5, or $(CH_2)_n$-R^3-R^6;

g. m is an integer selected from 1 to 8;

h. n is an integer from 0 to 8;

i. D is represented by O or S;

j. R^3 is represented by optionally substituted phenyl, optionally substituted naphthyl, C_3-C_8 cycloalkyl, optionally substituted heteroaryl, or optionally substituted heterocyclic;

k. R^4 and R^5 are each independently represented by hydrogen, (C_1-C_4)alkyl, optionally substituted benzyl or optionally substituted phenyl, and;

l. R^6 is absent, or is represented by a substituent selected from the group consisting of optionally substituted phenyl, optionally substituted naphthyl, optionally substituted phenoxy, C_3-C_8cycloalkyl, optionally substituted heterocyclic, and optionally substituted heteroaryl.

The compounds of Formula I are androgen receptor antagonists. The compounds will inhibit, or decrease, activation of the androgen receptor by androgens. The compounds can be used to treat, or alleviate, conditions associated with inappropriate activation of the androgen receptor. Examples of such conditions include, but are not limited to, acne, excess seborrhea secretion, alopecia, prostrate cancer, hirsutism, etc.

The invention is also directed to pharmaceutical compositions containing at least one of the compounds of Formula I, in an amount effective to decrease activation of the androgen receptor. In a further embodiment, the invention is directed to an article of manufacture containing a compound of Formula I, packaged for retail distribution, in association with instructions advising the consumer on how to use the compound to alleviate a condition associated with inappropriate activation of the androgen receptor. An additional embodiment is

directed to the use of a compound of Formula I as a diagnostic agent to detect inappropriate activation of the androgen receptor.

In a further embodiment, the compounds of Formula I are used topically to induce and/or stimulate hair growth and/or to slow down hair loss. The compounds may also be used topically in the treatment of hyperseborrhoea and/or of acne.

DETAILED DESCRIPTION OF THE INVENTION

The headings within this document are only being utilized expediate its review by the reader. They should not be construed as limiting the invention or claims in any manner.

As used throughout this application, including the claims, the following terms have the meanings defined below, unless specifically indicated otherwise. The plural and singular should be treated as interchangeable, other than the indication of number:

a. "C_1- C_4alkyl" refers to a branched or straight chained alkyl group containing from 1 to 4 carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, etc.

b. "C_1- C_8alkyl" refers to a branched or straight chained alkyl group containing from 1 to 8 carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, n-pentane, neopentane, isopentane, n-hexyl, n-octyl, etc

c. "C_1- C_4 alkoxy" refers to a straight or branched chain alkoxy group containing from 1 to 4 carbon atoms, such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, etc

d. "halogen" refers to a chlorine, fluorine or bromine atom.

e. "C_1- C_2 alkyl substituted with one or more halogen atoms" refers to a straight chained alkyl group containing 1 or 2 carbon atoms, i.e. methyl or ethyl, in which at least one hydrogen atom is replaced with a halogen. Examples include chloromethyl, difluoromethyl, trifluoromethyl, etc.

f. "C_1-C_2 alkoxy substituted with one or more halogen atoms" refers to a straight chained alkoxy group containing 1 or 2 carbon atoms, ie, methoxy or ethoxy in which at least one hydrogen atom is replaced with a halogen.

g. "C_2- C_4 alkenyl" refers to a straight-chain or branched-chain hydrocarbon radical containing from 2 to 4 carbon atoms and 1, or more, carbon-carbon double bonds. Examples of alkenyl radicals include ethyenyl, propenyl, 1,4-butadienyl and the like

h. C_2- C_8 alkenyl" refers to a straight-chain or branched-chain hydrocarbon radical containing from 2 to 8 carbon atoms and 1, or more, carbon-carbon double bonds. Examples of alkenyl radicals include ethyenyl, propenyl, 1,4-butadienyl, 1-hexene, 2-hexene, 1,4-hexadiene, and the like.

i. "C_2- C_4 alkynyl" refers to a straight-chain or branched-chain hydrocarbon radical containing from 2 to 4 carbon atoms and having 1, or more, carbon-carbon triple bonds. Examples of alkynyl radicals include ethynyl, propynyl, butynyl and the like.

j. "C_2- C_8 alkynyl" refers to a straight-chain or branched-chain hydrocarbon radical containing from 2 to 8 carbon atoms and having 1, or more, carbon-carbon triple bonds. Examples of alkynyl radicals include ethynyl, propynyl, butynyl, 1-pentynyl, 2-pentynyl, 1-hexynyl, 2-hexynyl, 4-octynyl, and the like

k. "optionally substituted phenyl" refers to a phenyl (-C_6H_5) which may be substituted with up to 2 substituents, each substituent is independently selected from the group consisting of halogen, nitrile, hydroxy, (C_1-C_4)alkyl, (C_1-C_4)alkoxy, (C_1-C_2)alkyl substituted with one or more halogens, (C_1-C_2)alkoxy substituted with one or more halogens, SR^4, and NR^4R^5. These substituents may be the same or different and may be located at any of the ortho, meta, or para positions.

l. "optionally substituted phenoxy" refers to a phenoxy (-O-C_6H_5) which may be substituted with up to 2 substituents, each substituent is independently selected from the group consisting of halogen, nitrile, hydroxy, (C_1-C_4)alkyl, (C_1-C_4)alkoxy, (C_1-C_2)alkyl substituted with one or more halogens, (C_1-C_2)alkoxy substituted with one or more halogens, SR^4, and NR^4R^5. These substituents may be the same or different and may be located at any of the ortho, meta, or para positions.

m. "optionally substituted benzyl" refers to a benzyl, $-CH_2-(C_6H_5)$, which may be substituted with up to 2 substituents, each substituent is independently selected from the group consisting of halogen, nitrile, hydroxy, (C_1-C_4)alkyl, (C_1-C_4)alkoxy, (C_1-C_2)alkyl substituted with one or more halogens, (C_1-C_2)alkoxy substituted with one or more halogens, SR^4, and NR^4R^5. These substituents may be the same or different and may be located at any of the ortho, meta, or para positions.

n. "optionally substituted naphthyl" refers to a naphthalene ring system, which may be substituted with up to 2 substituents, each substituent is independently selected from the group consisting of halogen, nitrile, hydroxy, (C_1-C_4)alkyl, (C_1-C_4)alkoxy, (C_1-C_2)alkyl substituted with one or more halogens, (C_1-C_2)alkoxy substituted with one or more halogens, SR^4, and NR^4R^5. These substituents may be located at any of positions 2 thru 8 on the naphthalene ring (position 1 of the naphthelene ring is the point of attachment to the rest of the chemical structure).

o. "heteroaryl" refers to aromatic ring having one, or more, heteroatoms selected from oxygen, nitrogen and sulfur. More specifically, it refers to a 5-, or 6-, membered ring containing 1, 2, or 3 nitrogen atoms; 1 oxygen atom; 1 sulfur atom; 1 nitrogen and 1 sulfur atom; 1 nitrogen and 1 oxygen atom; 2 nitrogen atoms and 1 oxygen atom; or 2 nitrogen atoms and 1 sulfur atom. The 5-membered ring has 2 double bonds and the 6-membered ring has 3 double bonds. The term heteroaryl also includes bicyclic groups in which the heteroaryl ring is fused to a benzene ring, heterocyclic ring, a cycloalkyl ring, or another heteroaryl ring. Examples of such heteroaryl ring systems include, but is not limited to pyrrolyl, furanyl, thienyl, imidazolyl, oxazolyl, indolyl, thiazolyl, pyrazolyl, pyridinyl, pyrimidinyl, purinyl, quinolinyl, isoquinolinyl.

p. "optionally substituted heteroaryl" refers to a heteroaryl moiety as defined immediately above, in which up to 2 carbon atoms of the heteroaryl moiety may be substituted with a substituent, each substituent is independently selected from the group consisting of halogen, nitrile, hydroxy, (C_1-C_4)alkyl, (C_1-C_4)alkoxy, (C_1-C_2)alkyl substituted with one

or more halogens, (C_1-C_2)alkoxy substituted with one or more halogens, SR^4, and NR^4R^5.

q. "heterocycle" or "heterocyclic ring" refers to any 3- or 4-membered ring containing a heteroatom selected from oxygen, nitrogen and sulfur; or a 5-, 6-, 7-, 8-, 9-, or 10- membered ring containing 1, 2, or 3 nitrogen atoms; 1 oxygen atom; 1 sulfur atom; 1 nitrogen and 1 sulfur atom; 1 nitrogen and 1 oxygen atom; 2 oxygen atoms in non-adjacent positions; 1 oxygen and 1 sulfur atom in non-adjacent positions; or 2 sulfur atoms in non-adjacent positions. The 5-membered ring has 0 to 1 double bonds, the 6- and 7-membered rings have 0 to 2 double bonds, and the 8, 9, or 10 membered rings may have 0, 1, 2, or 3 double bonds. The term "heterocyclic" also includes bicyclic groups in which any of the above heterocyclic rings is fused to a benzene ring, a cyclohexane or cyclopentane ring or another heterocyclic ring (for example, indolyl, quinolyl, isoquinolyl, tetrahydroquinolyl, benzofuryl, dihydrobenzofuryl or benzothienyl and the like). Heterocyclics include: pyrrolidinyl, tetrahydrofuranyl, tetrahydrothienyl, piperidinyl, piperazinyl, azepane, azocane, morpholinyl, quinolinyl,

r. "optionally substituted heterocyclic" refers to a heterocyclic moiety as defined immediately above, in which up to 2 carbon atoms of the heterocycle moiety may be substituted with a substituent, each substituent is independently selected from the group consisting of halogen, nitrile, hydroxy, (C_1-C_4)alkyl, (C_1-C_4)alkoxy, (C_1-C_2)alkyl substituted with one or more halogens, (C_1-C_2)alkoxy substituted with 1 or more halogens, SR^4, and NR^4R^5.

s. "C_3- C_8 cycloalkyl" refers to a saturated or partially saturated monocyclic, bicyclic or tricyclic alkyl radical wherein each cyclic moiety has about 3 to about 8 carbon atoms. Examples of cycloalkyl radicals include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, and the like.

t. "androgen" refers to testosterone and its precursors and metabolites, and 5-alpha reduced androgens, including but not limited to dihydrotestosterone. Androgen refers to androgens from the testis, adrenal

gland, and ovaries, as well as all forms of natural, synthetic and substituted or modified androgens.

u. "pharmaceutically acceptable salts" is intended to refer to either pharmaceutically acceptable acid addition salts" or "pharmaceutically acceptable basic addition salts" depending upon actual structure of the compound.

v. "pharmaceutically acceptable acid addition salts" is intended to apply to any non-toxic organic or inorganic acid addition salt of the base compounds represented by Formula I or any of its intermediates. Illustrative inorganic acids which form suitable salts include hydrochloric, hydrobromic, sulphuric, and phosphoric acid and acid metal salts such as sodium monohydrogen orthophosphate, and potassium hydrogen sulfate. Illustrative organic acids, which form suitable salts include the mono-, di-, and tricarboxylic acids. Illustrative of such acids are for example, acetic, glycolic, lactic, pyruvic, malonic, succinic, glutaric, fumaric, malic, tartaric, citric, ascorbic, maleic, hydroxymaleic, benzoic, hydroxy-benzoic, phenylacetic, cinnamic, salicylic, 2-phenoxybenzoic, p-toluenesulfonic acid, and sulfonic acids such as methane sulfonic acid and 2-hydroxyethane sulfonic acid. Such salts can exist in either a hydrated or substantially anhydrous form. In general, the acid addition salts of these compounds are soluble in water and various hydrophilic organic solvents, and which in comparison to their free base forms, generally demonstrate higher melting points.

w. "pharmaceutically acceptable basic addition salts" is intended to apply to any non-toxic organic or inorganic basic addition salts of the compounds represented by Formula I, or any of its intermediates. Illustrative bases which form suitable salts include alkali metal or alkaline-earth metal hydroxides such as sodium, potassium, calcium, magnesium, or barium hydroxides; ammonia, and aliphatic, alicyclic, or aromatic organic amines such as methylamine, dimethylamine, trimethylamine, and picoline.

x. "prodrug" refers to compounds that are rapidly transformed in vivo to yield the parent compound of the above formulas, for example, by hydrolysis in blood. A thorough discussion is provided in T. Higuchi and V. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A.C.S.

Symposium Series, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference.

y. "compound of Formula I" "compounds of the invention" and "compounds" are used interchangeably throughout the application and should be treated as synonoms.

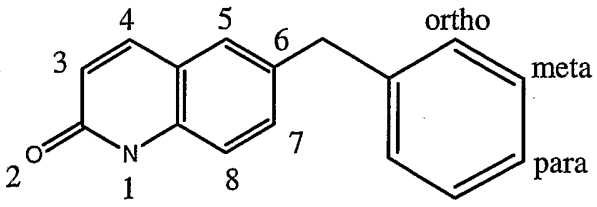
z. "patient" refers to warm blooded animals such as, for example, guinea pigs, mice, rats, gerbils, cats, rabbits, dogs, monkeys, chimpanzees, and humans.

aa. "treat" refers to the ability of the compounds to either relieve, alleviate, or slow the progression of the patient's disease (or condition) or any tissue damage associated with the disease.

Some of the compounds of Formula I will exist as optical isomers. Any reference in this application to one of the compounds represented by Formula I is meant to encompass either a specific optical isomer or a mixture of optical isomers (unless it is expressly excluded). The specific optical isomers can be separated and recovered by techniques known in the art such as chromatography on chiral stationary phases or resolution via chiral salt formation and subsequent separation by selective crystallization. Alternatively utilization of a specific optical isomer as the starting material will produce the corresponding isomer as the final product.

In addition, the compounds of the present invention can exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the present invention.

Some of the compounds of Formula I are based upon a 6-benzylurea/thiourea -quinolin-2-one nucleus. To further exemplify the invention this ring is depicted below along with its numbering system:

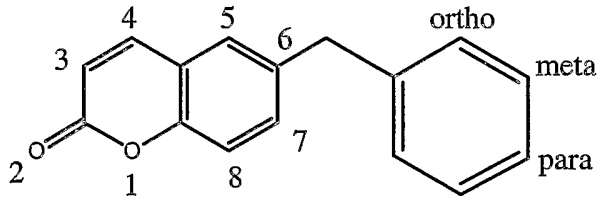


Ia

Position 1 of the quinoline nucleus contains a nitrogen atom. This nitrogen atom may be substituted with a lower alkyl group as described above. Position 6 of the quinoline ring will always be substituted with a benzyl moiety as depicted in Figure Ia. Any of positions 3, 5, 7, or 8 of the quinoline nucleus may optionally be substituted with a substituent from the list described for R^2. Up to two of these positions may be substituted. Position 4 of the quinoline nucleus may optionally be substituted with one of the halogenated lower alkyl or alkoxy moieties described for R^1 above. Typically, Position 4 will be substituted with a trifluoromethyl function.

The benzyl moiety adjacent to position 6 will be further substituted with a thiourea or urea moiety (-N-C(X)-N-A). The urea/thiourea moiety may be attached to either the ortho or para position of the benzyl ring. Adjacent to the urea or thiourea moiety is the substituent represented by A. One of the possible substituents that A may be represented by is a heterocyclic or heteroaryl ring. These hetero rings will be attached to the urea or thiourea via a carbon atom. They will not be bonded to the urea or thiourea moiety via a hetero atom.

The remaining compounds of Formula I are based upon a 6-urea/thiourea-2-oxo-chromene nucleus. To further exemplify the invention, this ring is depicted below along with its numbering system:



Ib

Position 1 of the chromene nucleus contains an oxygen atom. Position 6 of the chromene ring will always be substituted with a benzyl moiety as depicted in Figure 1. Any of Positions 3, 5, 7, or 8 of the chromene nucleus may optionally be substituted with a substituent from the list described for R_2. Up to two of these positions may be substituted. Position 4 of the chromene nucleus may optionally be substituted with one of the halogenated lower alkyl or alkoxy moieties described for R^1 above. Typically, Position 4 will be substituted with a trifluoromethyl function.

The benzyl moiety adjacent to position 6 will be further substituted with a thiourea or urea moiety (-N-C(X)-N-A). The urea/thiourea moiety may be attached to either the ortho or para position of the benzyl ring. Adjacent to the urea or thiourea moiety is the substituent

represented by A. One of the possible substituents that A may be represented by is a heterocyclic or heteroaryl ring. These hetero rings will be attached to the urea or thiourea via a carbon atom. They will not be bonded to the urea or thiourea moiety via a hetero.

More specific embodiments of the invention are directed to compounds of Formula I in which:

a) M is represented by NZ, in which Z is hydrogen, R^1 is trifluoromethyl, R^2 is absent, X is O, and A is bonded to the para position of the benzyl ring and is as in Formula I;

b) M is represented by NZ, in which Z is hydrogen, R^1 is trifluoromethyl, R^2 is absent, X is O, and A is bonded to the ortho position of the benzyl ring and is as in Formula I;

c) M is represented by NZ, in which Z is hydrogen, R^1 is trifluoromethyl, R^2 is absent, X is S, and A is bonded to the para position of the benzyl ring and is as in Formula I;

d) M is represented by NZ, in which Z is hydrogen, R^1 is trifluoromethyl, R^2 is absent, X is S, and A is bonded to the ortho position of the benzyl ring and is as in Formula I;

e) M is represented by NZ, in which Z is hydrogen, R^1 is trifluoromethyl, R^2 is absent, X is S, and A is bonded to the para position of the benzyl ring and is represented by optionally substituted phenyl;

f) M is represented by NZ, in which Z is hydrogen, R^1 is trifluoromethyl, R^2 is absent, X is S, and A is bonded to the ortho position of the benzyl ring and is represented by optionally substituted phenyl;

g) M is represented by NZ, in which Z is hydrogen, R^1 is trifluoromethyl, R^2 is absent, X is O, and A is bonded to the para position of the benzyl ring and is represented by optionally substituted phenyl, and;

h) M is represented by NZ, in which Z is hydrogen, R^1 is trifluoromethyl, R^2 is absent, X is O, and A is bonded to the ortho position of the benzyl ring and is represented by optionally substituted phenyl.

More Specific Examples of compounds encompassed by Formula I includes:

a) 1-[2-(2-Oxo-4-trifluoromethyl-1,2-dihydroquinolin-6-ylmethyl)phenyl]-3-phenylthiourea;

b) 1-(2-Morpholin-4-ylphenyl)-3-[2-(2-oxo-4-trifluoromethyl-1,2-dihydroquinolin-6-ylmethyl)phenyl]thiourea;

c) 1-(4-Methylbenzyl)-3-[2-(2-oxo-4-trifluoromethyl-1,2-dihydroquinolin-6-ylmethyl)phenyl]thiourea;

d) 1-(4-Methoxy-2-methylphenyl)-3-[2-(2-oxo-4-trifluoromethyl-1,2-dihydroquinolin-6-ylmethyl)phenyl]thiourea;

e) 1-[2-(2-Oxo-4-trifluoromethyl-1,2-dihydroquinolin-6-ylmethyl)phenyl]-3-phenethylthiourea;

f) 1-(4-Methoxyphenyl)-3-[2-(2-oxo-4-trifluoromethyl-1,2-dihydroquinolin-6-ylmethyl)phenyl]thiourea;

g) {3-[2-(2-Oxo-4-trifluoromethyl-1,2-dihydroquinolin-6-ylmethyl)phenyl]ureido}acetic acid ethyl ester;

h) 1-(4-Fluorophenyl)-3-[2-(2-oxo-4-trifluoromethyl-1,2-dihydroquinolin-6-ylmethyl)phenyl]thiourea;

i) 1-Benzo[1,3]dioxol-5-ylmethyl-3-[2-(2-oxo-4-trifluoromethyl-1,2-dihydroquinolin-6-ylmethyl)phenyl]thiourea;

j) 1-(3,5-Dimethoxyphenyl)-3-[2-(2-oxo-4-trifluoromethyl-1,2-dihydroquinolin-6-ylmethyl)phenyl]urea;

k) 1-(4-Methoxybenzyl)-3-[2-(2-oxo-4-trifluoromethyl-1,2-dihydroquinolin-6-ylmethyl)phenyl]thiourea;

l) 1-(2,3-Dimethoxybenzyl)-3-[2-(2-oxo-4-trifluoromethyl-1,2-dihydroquinolin-6-ylmethyl)phenyl]thiourea;

m) 1-Hexyl-3-[4-(2-oxo-4-trifluoromethyl-1,2-dihydroquinolin-6-ylmethyl)phenyl]urea;

n) 1-(4-Methylbenzyl)-3-[4-(2-oxo-4-trifluoromethyl-1,2-dihydroquinolin-6-ylmethyl)phenyl]thiourea;

o) 1-[2-(4-Chlorophenyl)ethyl]-3-[4-(2-oxo-4-trifluoromethyl-1,2-dihydroquinolin-6-ylmethyl)phenyl]thiourea;

p) 1-[4-(2-Oxo-4-trifluoromethyl-1,2-dihydroquinolin-6-ylmethyl)phenyl]-3-phenethylthiourea;

q) 1-Methyl-3-[4-(2-oxo-4-trifluoromethyl-1,2-dihydroquinolin-6-ylmethyl)phenyl]thiourea;

r) 1-(2,3-Dimethoxybenzyl)-3-[4-(2-oxo-4-trifluoromethyl-1,2-dihydroquinolin-6-ylmethyl)phenyl]thiourea;

s) 1-[4-(2-Oxo-4-trifluoromethyl-1,2-dihydroquinolin-6-ylmethyl)phenyl]-3-(2-p-tolylethyl)thiourea;

t) {3-[4-(2-Oxo-4-trifluoromethyl-1,2-dihydroquinolin-6-ylmethyl)phenyl]ureido}acetic acid ethyl ester;

u) 1-Allyl-3-[4-(2-oxo-4-trifluoromethyl-1,2-dihydroquinolin-6-ylmethyl)phenyl]thiourea;

v) 1-(2-Morpholin-4-ylethyl)-3-[4-(2-oxo-4-trifluoromethyl-1,2-dihydroquinolin-6-ylmethyl)phenyl]thiourea;

w) 1-Naphthalen-1-yl-3-[4-(2-oxo-4-trifluoromethyl-1,2-dihydroquinolin-6-ylmethyl)phenyl]urea;

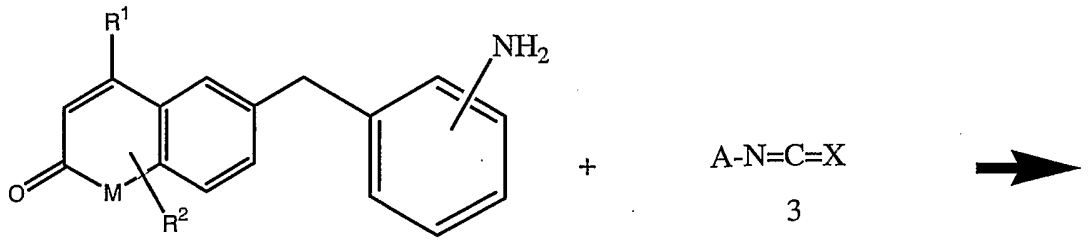
x) 1-Benzo[1,3]dioxol-5-ylmethyl-3-[4-(2-oxo-4-trifluoromethyl-1,2-dihydroquinolin-6-ylmethyl)phenyl]thiourea;

y) 1-(4-Methoxybenzyl)-3-[4-(2-oxo-4-trifluoromethyl-1,2-dihydroquinolin-6-ylmethyl)phenyl]thiourea, and;

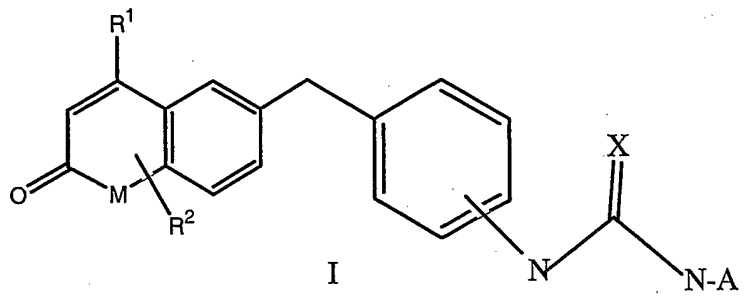
z) 1-Benzyl-3-[4-(2-oxo-4-trifluoromethyl-1,2-dihydroquinolin-6-ylmethyl)phenyl]thiourea.

SYNTHESIS

The compounds of Formula I can be prepared using methods analogous to those known in the art for the preparation of ureas and thioureas. The reader's attention is directed to J. March, Advanced Organic Chemistry, 3rd edition, pages 802-803, John Wiley & Sons (1985) for a review of such reactions. Scheme I below provides a general overview:



2 3



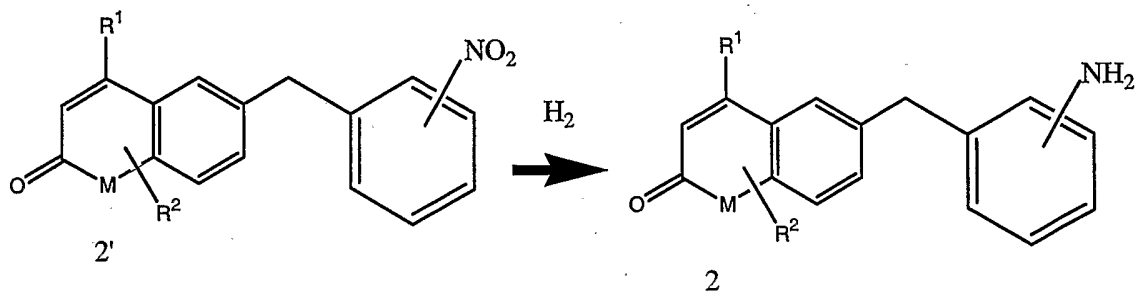
I

As depicted by Formula 2, one of the starting materials is an appropriately substituted quinolin-2-one or 2-oxo-chromene (i.e. R^1, R^2, and M are as in desired final product). The structure depicted by Formula 2 is substituted at the 6-position with an ortho or para amino benzyl moiety as desired in the final product. The other starting material, as described by Formula 3, is an appropriately substituted isocyanate or isothiocyanate (i.e. A and X are as in final product).

The amine of Formula 2 is contacted with about one equivalent of the isocyanate/isothiocyanate of Formula 3 in an anhydrous solvent such as tetrahydrofuran, n-methyl pyrrolidone, dimethylformamide, etc. The reaction is typically carried out in the presence of a catalyst, such as pyridine, at room temperature. The reaction is allowed to proceed to completion, which may be accomplished in from 5 minutes to 20 hours depending on the quantity of reactions. At the completion of the reaction, the compound is typically isolated and recovered using techniques known in the art such as extraction, precipitation, etc. If desired, the compounds may be purified by flash chromatography or other techniques known to those skilled in the art. Such reactions are described in greater detail in Examples 1-25 infra.

The isocyanates and isothiocyanates of Formula 3 are known in the art. They may be prepared as taught in the literature. More conveniently, they may be purchased from supply houses such as Aldrich, which has an office located in St. Louis, Mo. USA. Further information may be obtained from Aldrich at, www.sigmaaldrich.com.

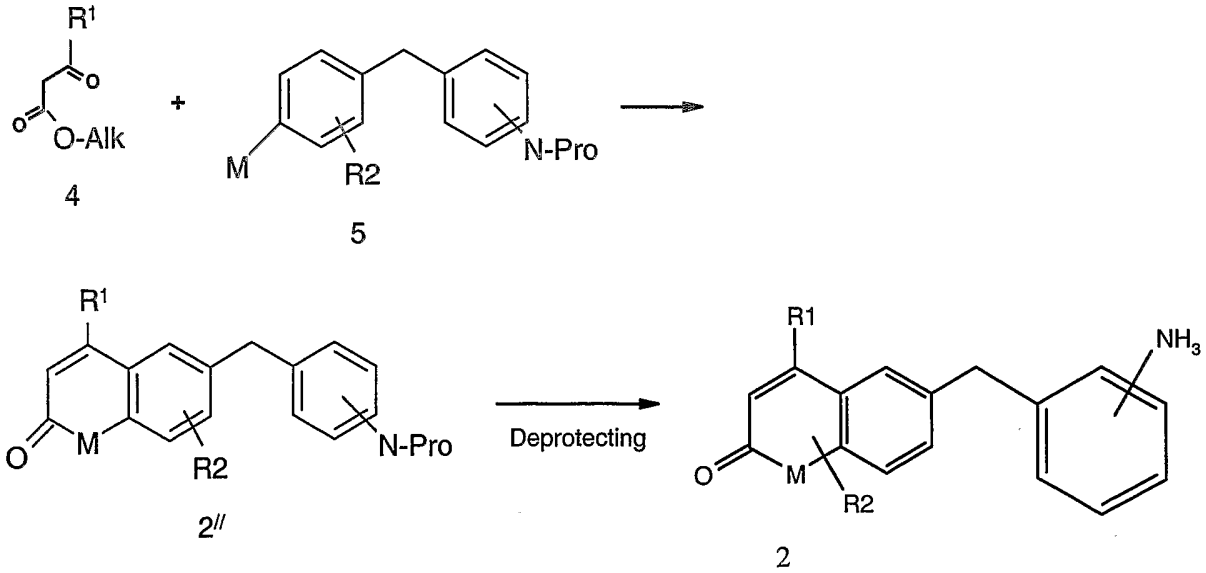
The amines of Formula 2 may be prepared by methods known in the art. One suitable method is depicted below in Scheme II:



2' 2

As shown in Scheme II, the corresponding 6-benzyl nitro derivative of Formula 2' is reduced to the corresponding amine of Formula 2. This may be accomplished as is known in the art. For example, the nitro derivative of Formula 2' may be contacted with an excess of hydrogen in the presence of a palladium catalyst. In Formula 2' R^1, R^2, and M should be represented by the same substituents desired in the final product and the nitro function should be located at the ortho or para postion as desired in the final product. As is known to those skilled in the art, protecting groups may be used as required. For further details, the reader's attention is directed to Preparation Number 2 where such a reaction is exemplified. Other appropriate reducing agents, as is known in the art, may also be utilized.

Alternatively, the amine of Formula 2, may be prepared as shown below in Reaction Scheme III



4 5 2// 2

As depicted in Scheme III, a Knorr cyclization may be carried out between an appropriately substituted aniline or phenol (i.e. Structure 5 in which M, R^2 and the location of the protected amine, N-Pro, are as in final product) and a β-ketoester as described by structure 4 (R^1/R^2 as are in final product and Alk is an easily removable leaving group). Examples of suitable protecting group include T-BOC, benzyl, etc. The use of protecting groups is well-known in the art, & is fully described, among other places, in: *Protecting Groups in Organic Chemistry*, J. W. F. McOmie, (ed.), 1973, Plenum Press; & in: *Protecting Groups in Organic Synthesis*, 2nd edition, T. W. Greene & P. G. M. Wutz, 1991, Wiley-Interscience, which are incorporated by reference in their entirety.

The cyclization is carried out in the presence of a suitable acid catalyst, such as methanesulfonic acid, in an aprotic solvent such as toluene. A molar excess of the β-ketoester is typically utilized and the reaction is carried out at elevated temperatures (typically reflux). The amine of Formula 2'' may be recovered and the protecting group represented by Pro may be removed as is known in the art. For additional details, the readers' attention is directed to Preparation Numbers one and three, where such reactions are exemplified.

Medical and Cosmetic Uses

The compounds of Formula I are androgen receptor antagonists. They can be used to alleviate any condition associated with inappropriate activation of the androgen receptor. Examples of such conditions include prostate carcinomas, benign hyperplasia of the prostate, acne, hirsutism, seborrhoea, alopecia, premenstrual syndrome, lung cancer, and precocious puberty.

In order to exhibit the therapeutic properties described above, the compounds need to be administered in a quantity sufficient to inhibit activation of the androgen receptor. This antagonistic amount can vary depending upon the particular disease/condition being treated, the severity of the patient's disease/condition, the patient, the particular compound being administered, the route of administration, and the presence of other underlying disease states within the patient, etc. When administered systemically, the compounds typically exhibit their effect at a dosage range of from about 0.1 mg/kg/day to about 100 mg/kg/day for any of the diseases or conditions listed above. Repetitive daily administration may be desirable and will vary according to the conditions outlined above.

The compounds of the present invention may be administered by a variety of routes. They are effective if administered orally. The compounds may also be administered parenterally (i.e. subcutaneously, intravenously, intramuscularly, intraperitoneally, or intrathecally), rectally, or topically.

In a typical embodiment, the compounds are administered topically. Topical administration is especially appropriate for hirsutism, alopecia, acne and hyperseborhhea. The dose will vary, but as a general guideline, the compound will be present in a dermatologically acceptable carrier in an amount of from 0.1 to 10 w/w% and the dermatological preparation will be applied to the affected area from 1 to 4 times daily. "Dermatologically acceptable" refers to a carrier which may be applied to the skin or hair, and which will allow the drug to diffuse to the site of action. More specifically, it refers the site where inhibition of activation of an androgen receptor is desired. In a further embodiment, the compounds are used topically to relieve alopecia, especially androgenic alopecia. Androgens have a profound effect on both hair growth and hair loss. In most body sites, such as the beard and pubic skin, androgens stimulate hair growth by prolonging the growth phase of the hair cycle (anagen) and increasing follicle size. Hair growth on the scalp does not require androgens but, paradoxically, androgens are necessary for balding on the scalp in genetically predisposed individuals (androgeneic alopecia) where there is a progressive decline in the duration of anagen and in hair follicle size. Men castrated before puberty fail to grow beards and do not go bald. If subsequently treated with testosterone about one third of male castrates will show balding. Androgeneic alopecia is also common in women where it usually present as a diffuse hair loss rather than showing the patterning seen in men.

As used in this application "alopecia" refers to partial or complete hair loss on the scalp. The compounds will typically be used to alleviate androgenetic alopecia. This condition afflicts both men and women. In males, the hair loss begins in the lateral frontal areas or over the vertex. For females, it is typically associated with thinning of the hair in the frontal and parietal regions. Complete hair loss in females is rare.

While the compounds will most typically be used to alleviate androgenic alopecia, the invention is not limited to this specific condition. The compounds may be used to alleviate any type of alopecia. Examples of non-androgenic alopecia include alopecia areata, alopecia due to radiotherapy or chemotherapy, scarring alopecia, stress related alopecia, etc.

Thus, the compounds can be applied topically to the scalp and hair to prevent, or alleviate balding. Further, the compound can be applied topically in order to induce or promote the growth of hair on the scalp.

In a further embodiment of the invention, a compound of Formula I is applied topically in order to prevent the growth of hair in areas where such hair growth is not desired. One such use will be to alleviate hirsutism. Hirsutism is excessive hair growth in areas that typically do not have hair (i.e. a female face). Such inappriate hair growth occurs most commonly in women and is frequently seen at menopause. The topical administration of the compounds will alleviate this condition leading to a reduction, or elimination of this inappropriate, or undesired, hair growth.

The compounds may also be used topically to decrease seborrhea production and more specifically to alleviate hyperseborrhoea (oily skin). Likewise the compounds can be used topically alleviate acne.

Formulations

If desired, the compounds can be administered directly without any carrier. However, to ease administration, they will typically be formulated into pharmaceutical carriers. Likewise, they will most typically be formulated into dermatological, or cosmetic carriers. In this application the terms "dermatological carrier" and "cosmetic" carrier are being used interchangeably. They refer to formulations designed for administration directly to the skin or hair.

Pharmaceutical and cosmetic compositions can be manufactured utilizing techniques known in the art. Typically an antagonistic amount of the compound will be admixed with a pharmaceutically/cosmetically acceptable carrier.

For oral administration, the compounds can be formulated into solid or liquid preparations such as capsules, pills, tablets, lozenges, melts, powders, suspensions, or emulsions. Solid unit dosage forms can be capsules of the ordinary gelatin type containing, for example, surfactants, lubricants and inert fillers such as lactose, sucrose, and cornstarch or they can be sustained release preparations.

In another embodiment, the compounds of Formula I can be tableted with conventional tablet bases such as lactose, sucrose, and cornstarch in combination with binders, such as acacia, cornstarch, or gelatin, disintegrating agents such as potato starch or alginic acid, and a lubricant such as stearic acid or magnesium stearate. Liquid preparations are prepared by dissolving the

active ingredient in an aqueous or non-aqueous pharmaceutically acceptable solvent, which may also contain suspending agents, sweetening agents, flavoring agents, and preservative agents as are known in the art.

For parenteral administration the compounds may be dissolved in a physiologically acceptable pharmaceutical carrier and administered as either a solution or a suspension. Illustrative of suitable pharmaceutical carriers are water, saline, dextrose solutions, fructose solutions, ethanol, or oils of animal, vegetative, or synthetic origin. The pharmaceutical carrier may also contain preservatives, buffers, etc., as are known in the art. When the compounds are being administered intrathecally, they may also be dissolved in cerebrospinal fluid as is known in the art.

The compounds of this invention will typically be administered topically. As used herein, topical refers to application of the compounds (and optional carrier) directly the skin or hair. The topical composition according to the present invention can be in the form of solutions, lotions, salves, creams, ointments, liposomes, sprays, gels, roller sticks, or any other method using micelles and pharmaceutically acceptable penetration enhancers

Thus, a further embodiment relates to cosmetic or pharmaceutical compositions, in particular dermatological compositions, which comprise at least one of the compounds corresponding to Formula I above. Such dermatological compositions will contain from 0.001% to 10% w/w% of the compounds in admixture with a dermatologically acceptable carrier, and more typically, from 0.1 to 5 w/w% of the acompounds. Such compositions will typically be applied from 1 to 4 times daily.

The compositions according to the invention can also consist of solid preparations constituting cleansing soaps or bars. These compositions are prepared according to the usual methods.

The compounds can also be used for the hair in the form of aqueous, alcoholic or aqueous-alcoholic solutions, or in the form of creams, gels, emulsions or mousses, or alternatively in the form of aerosol compositions also comprising a propellant under pressure. The composition according to the invention can also be a hair care composition, and in particular a shampoo, a hair-setting lotion, a treating lotion, a styling cream or gel, a dye composition (in particular an oxidation dye composition) optionally in the form of coloring shampoos, restructuring lotions for the hair, a permanent-waving composition (in particular a composition for the first stage of a permanent-waving operation), a lotion or gel for preventing hair loss, etc. The amounts of the various constituents in the dermatological compositions according to the invention are those conventionally used in the fields considered.

The medicinals and cosmetics containing the compounds of the invention will typically be packaged for retail distribution (i.e. an article of manufacture). Such articles will be labeled and packaged in a manner to instruct the patient how to use the product. Such instructions will include the condition, which may be treated, duration of treatment, dosing schedule, etc.

The compounds of Formula I may also be admixed with any inert carrier and utilized in laboratory assays in order to determine the concentration of the compounds within the serum, urine, etc., of the patient as is known in the art. The compounds may also be used as a research tool.

While the invention has been described in connection with specific embodiments thereof, it will be understood that it is capable of further modifications and this application is intended to cover any variations, uses, or adaptations of the invention following, in general, the principles of the invention and including such departures from the present disclosure as come within known or customary practice within the art to which the invention. The following examples and biological data is being presented in order to further illustrate the invention. This disclosure should not be construed as limiting the invention in any manner.

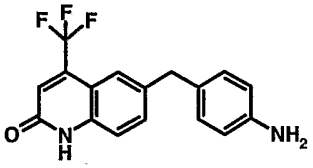
EXAMPLES

Materials & methods

Column chromatography was carried out on SiO_2 (40–63 mesh). LCMS data were obtained using a Phenomenex Mercury Luna 3μ C_{18} column (2 × 10 mm, flow rate = 1.5 mL min^{-1}) eluting with a 5% MeCN in H_2O–MeCN solution (4:1 to 1:4) containing 0.1% HCO_2H over 2.55 min & diode array detection. The mass spectra were obtained employing an electrospray ionisation source in the positive (ES^+) & negative (ES^-) ion modes. Preparative mass-directed liquid chromatographic purification was carried out utilising a Waters Xterra 5μ C_{18} column (19 × 50 mm, flow rate = 20 mL min^{-1}) eluting with a 5% MeCN in H_2O–MeCN solution (4:1 to 1:4) containing 0.1% HCO_2H over 7 min & diode array detection. ^1H NMR spectra were recorded at 400 MHz on a Varian Mercury spectrometer at 27 °C. The deuterated solvent was used as the lock, while the residual solvent peak was employed as internal reference. Acronyms: DMAP = 4-dimethylaminopyridine; HATU = *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate; NMP = 1-methyl-2-pyrrolidinone; PE = petroleum ether (B.p. = 60–80 °C); RT = retention time.

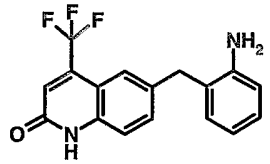
Preparation of Starting Materials

Preparation Number 1: 6-(4-Aminobenzyl)-4-trifluoromethyl-1*H*-quinolin-2-one



A solution of [4-(4-aminobenzyl)phenyl]carbamic acid *tert*-butyl ester (1.26 g, 4.2 mmol) in PhMe (15 mL) was treated with a PhMe (10 mL) solution of $CF_3COCH_2CO_2Et$ (0.79 g, 4.3 mmol), before being heated under reflux for 1 h. More $CF_3COCH_2CO_2Et$ (0.40 g, 2.2 mmol) was added, & the mixture was heated under reflux for 1.5 h. The precipitate generated when the mixture was cooled to –15 °C was collected to give {4-[4-(4,4,4-trifluoro-3-oxobutyrylamino)benzyl]phenyl}carbamic acid *tert*-butyl ester (1.62 g, 90%): *m/z* (ES^-) = 435.3 $[M - H]^-$. This compound (1.00 g, 2.3 mmol) was added portionwise with stirring to cold H_2SO_4 (5 mL) to generate a brown solution. This solution was heated at 90 °C for 1 h, then the cooled mixture was poured onto crushed ice. The aqueous phase was treated with solid NaOH until basic, & the mixture was extracted with Et_2O (200 mL). The Et_2O extracts were dried ($MgSO_4$), concentrated to a small volume, & triturated with PE to furnish the title compound (0.66 g, 91%): δ_H ($(CD_3)_2SO$) = 3.80 (s, 2H), 4.85 (s, 2H), 6.45 (d, 2H), 6.85 (d, 2H), 6.95 (s, 1H), 7.35 (d, 1H), 7.40–7.50 (m, 2H); *m/z* (ES^+) = 319.1 $[M + H]^+$.

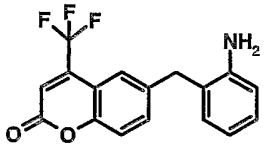
Preparation Number 2: 6-(2-Aminobenzyl)-4-trifluoromethyl-1*H*-quinolin-2-one



A solution of *N*-[2-(4-nitrobenzyl)phenyl]acetamide (6.80 g, 25.2 mmol) in EtOAc (700 mL) was treated with Pd (10% on C, 0.53 g, 0.5 mmol). The mixture was stirred under a H_2 atmosphere for 5 h. The reaction mixture was filtered through Celite, before being concentrated to yield *N*-[2-(4-aminobenzyl)phenyl]acetamide (6.00 g, 99%): δ_H ($(CD_3)_2SO$) = 2.00 (s, 3H), 3.75 (s, 2H), 4.80 (s, 2H), 6.45 (d, 2H), 6.80 (d, 2H), 7.00–

7.15 (m, 3H), 7.35 (d, 1H), 9.20 (s, 1H). A PhMe (75 mL) suspension of this aniline (5.00 g, 20.8 mmol) was treated with a solution of $CF_3COCH_2CO_2Et$ (3.83 g, 20.8 mmol) in PhMe (50 mL), before being heated under reflux for 1.5 h. The PhMe was evaporated off under reduced pressure, then the residue was dissolved in EtOAc (400 mL), before being washed with 0.2 M HCl (50 mL) & brine (50 mL). After drying ($MgSO_4$), the EtOAc solution was filtered & concentrated to give a foam that was dissolved in H_2SO_4 (40 mL). The mixture was heated at 90 °C for 1.5 h, before being cooled & poured onto crushed ice. H_2O was added to adjust the volume to 400 mL, then the off-white precipitate produced was collected by filtration & air-dried. The precipitate was treated with AcOH (8 mL) & 12 M HCl (40 mL), & the resulting suspension was heated under reflux. The solid gradually dissolved & heating was stopped after 4 h. The cooled reaction mixture was poured onto crushed ice (50 g), then H_2O (200 mL) was added. The aqueous phase was basicified with solid NaOH, then the mixture was extracted with EtOAc (200 mL). The EtOAc layer was dried ($MgSO_4$), filtered, & concentrated to provide the title compound (3.01 g, 45%): δ_H ($(CD_3)_2SO$) = 3.85 (s, 2H), 4.85 (s, 2H), 6.50 (t, 1H), 6.60 (d, 1H), 6.85 (d, 1H), 6.90–7.00 (m, 2H), 7.35 (d, 1H), 7.50 (d, 1H), 7.55 (s, 1H); *m/z* (ES^+) = 360.3 $[M + H + MeCN]^+$.

Preparation Number 3: 6-(2-Aminobenzyl)-4-trifluoromethylchromen-2-one

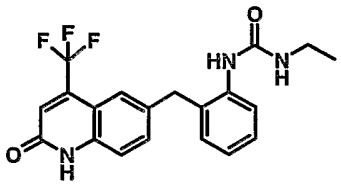


A solution of *N*-[2-(4-hydroxybenzyl)phenyl]acetamide (200 mg, 0.83 mmol) in $CF_3COCH_2CO_2Et$ (305 mg, 1.66 mmol) & $MeSO_3H$ (750 μL, 11.55 mmol) was heated at 75 °C for 2 d. On cooling to 20 °C, the mixture was treated with H_2O (20 mL), then the pH was adjusted to 12 with NaOH. The mixture was extracted with EtOAc (150 mL), then the extracts were washed with 0.5 M NaOH (2 × 50 mL), before being dried ($MgSO_4$). Filtration, solvent evaporation, & column chromatography (1:2 PE–EtOAc) yielded *N*-[2-(2-oxo-4-trifluoromethyl-2*H*-chromen-6-ylmethyl)-phenyl]acetamide (78 mg, 26%): *m/z* (ES^+) = 362.2 $[M + H]^+$. A solution of this

compound in AcOH–12 M HCl (1:6, 3.5 mL) was heated at 95 °C for 6 h. On cooling to 20 °C, H_2O (8 mL) was added, then the mixture was treated with NaOH then Na_2CO_3 to adjust the pH to 10. Extraction with EtOAc (10 mL) & solvent evaporation furnished a residue which was subjected to column chromatography (2:1 PE–EtOAc) to give the title compound (8 mg, 12%): δ_H ($CDCl_3$) = 3.50 (br s, 2H), 4.00 (s, 2H), 6.70 (d, 1H), 6.80 (m, 2H), 7.00 (d, 1H), 7.10 (t, 1H), 7.35 (d, 1H), 7.40 (d, 1H), 7.55 (s, 1H); *m/z* (ES^+) = 320.1 $[M + H]^+$.

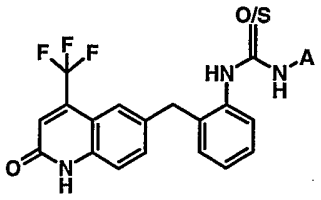
COMPOUNDS OF FORMULA I

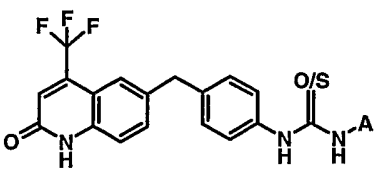
Example 1: 1-Ethyl-3-[2-(2-oxo-4-trifluoromethyl-1,2-dihydroquinolin-6-ylmethyl)phenyl]urea



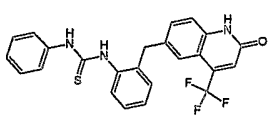
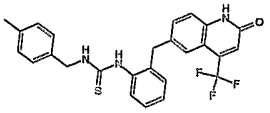
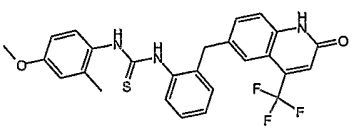
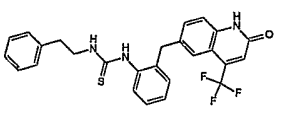
A stirred THF (5 mL) solution of 6-(2-aminobenzyl)-4-trifluoromethyl-1*H*-quinolin-2-one (Preparation #2, 50 mg, 157 μmol) was treated dropwise with a solution of EtNCO (78 μL, 985 μmol) in anhydrous THF (1 mL) at 0 °C. The reaction mixture was allowed to warm to 20 °C, before being stirred for 36 h. The precipitate formed was collected, washed with THF, & dried to give the title compound (38 mg, 62%): δ_H ($(CD_3)_2SO$) = 1.00 (t, 3H), 3.05 (q, 2H), 4.00 (s, 2H), 6.30 (t, 1H), 6.90–6.95 (m, 2H), 7.05 (d, 1H), 7.15 (t, 1H), 7.35 (d, 1H), 7.40 (d, 1H), 7.55 (s, 1H), 7.70–7.80 (m, 2H); *m/z* (ES^+) = 390.2 $[M + H]^+$.

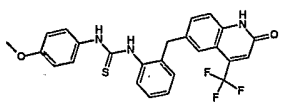
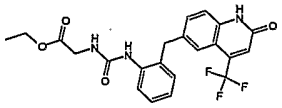
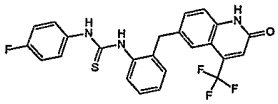
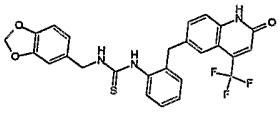
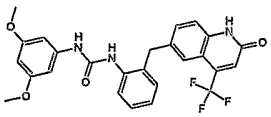
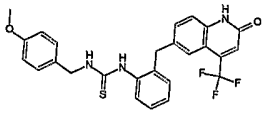
Examples 2-25 : [2-(2-Oxo-4-trifluoromethyl-1,2-dihydroquinolin-6-ylmethyl)-phenyl]ureas, [2-(2-oxo-4-trifluoromethyl-1,2-dihydroquinolin-6-ylmethyl)-phenyl]thioureas, [4-(2-oxo-4-trifluoromethyl-1,2-dihydroquinolin-6-ylmethyl)-phenyl]ureas, & [4-(2-oxo-4-trifluoromethyl-1,2-dihydroquinolin-6-ylmethyl)-phenyl]thioureas (Table 1)

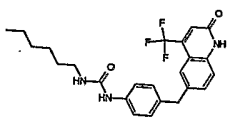
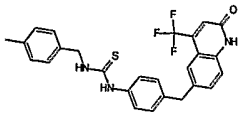
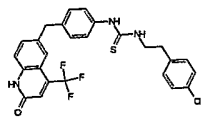
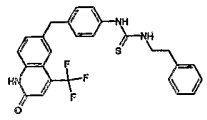
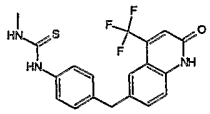
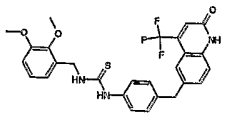
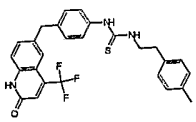


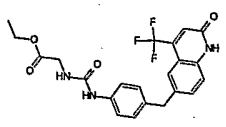
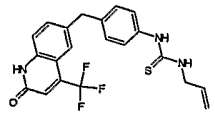
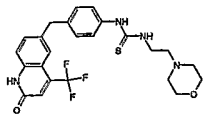
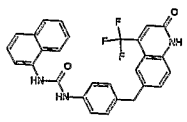
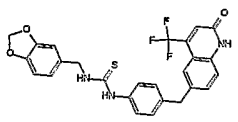
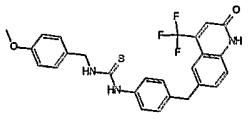
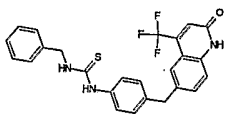


These compounds were prepared by solution phase parallel synthesis. The appropriate amine as described by Formula 2 above (100 μL of a 0.2 M solution in NMP, 20 μmol) was mixed with pyridine (10 μL of a 0.2 M solution in NMP, 2 μmol) & the appropriate isocyanate/ isothiocyanate of Formula 3 (120 μL of a 0.2 M solution in NMP, 24 μmol) in 1 well of a 96-well plate using an automated liquid handler. After agitating for 5 d, the solvents were evaporated off under reduced pressure, then the residues were dissolved in 1:1 DMF–THF (200 μL). A cation-exchanging sorbent for solid phase extraction (MCX, Waters, 10–15 mg of sorbent with loading = 0.85 μmol mg^{-1}) was added using a 96-well dispenser, then the plate was agitated for 2 d. Filtration & solvent evaporation furnished residues which were treated with MeCN (250 μL) to generate precipitates. These precipitates were pelleted by centrifugation, then the supernatants were separated, leaving the compounds displayed in Table 1.

Example	CHEMISTRY	Name	RT	Base Peak
2		1-[2-(2-Oxo-4-trifluoromethyl-1,2-dihydroquinolin-6-ylmethyl)phenyl]-3-phenylthiourea	1.75	454.2 $[M + H]^+$
3		1-(4-Methylbenzyl)-3-[2-(2-oxo-4-trifluoromethyl-1,2-dihydroquinolin-6-ylmethyl)phenyl]thiourea	1.90	482.2 $[M + H]^+$
4		1-(4-Methoxy-2-methylphenyl)-3-[2-(2-oxo-4-trifluoromethyl-1,2-dihydroquinolin-6-ylmethyl)phenyl]thiourea	1.76	498.2 $[M + H]^+$
5		1-[2-(2-Oxo-4-trifluoromethyl-1,2-dihydroquinolin-6-ylmethyl)phenyl]-3-phenethylthiourea	1.86	482.2 $[M + H]^+$

6		1-(4-Methoxyphenyl)-3-[2-(2-oxo-4-trifluoromethyl-1,2-dihydroquinolin-6-ylmethyl)phenyl]thiourea	1.76	484.2 $[M + H]^+$
7		{3-[2-(2-Oxo-4-trifluoromethyl-1,2-dihydroquinolin-6-ylmethyl)phenyl]ureido}acetic acid ethyl ester	1.58	448.2 $[M + H]^+$
8		1-(4-Fluorophenyl)-3-[2-(2-oxo-4-trifluoromethyl-1,2-dihydroquinolin-6-ylmethyl)phenyl]thiourea	1.77	472.1 $[M + H]^+$
9		1-Benzo[1,3]dioxol-5-ylmethyl-3-[2-(2-oxo-4-trifluoromethyl-1,2-dihydroquinolin-6-ylmethyl)phenyl]thiourea	1.80	512.1 $[M + H]^+$
10		1-(3,5-Dimethoxyphenyl)-3-[2-(2-oxo-4-trifluoromethyl-1,2-dihydroquinolin-6-ylmethyl)phenyl]urea	1.74	498.2 $[M + H]^+$
11		1-(4-Methoxybenzyl)-3-[2-(2-oxo-4-trifluoromethyl-1,2-dihydroquinolin-6-ylmethyl)phenyl]thiourea	1.81	498.2 $[M + H]^+$

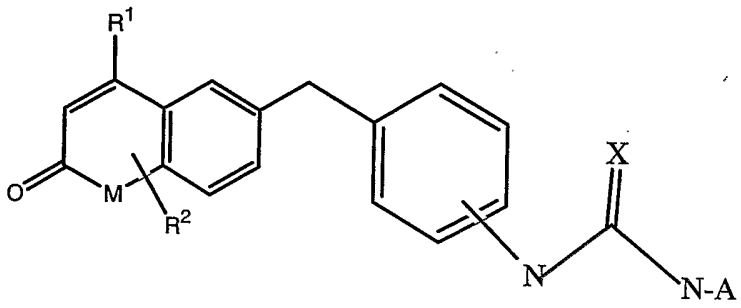
12		1-Hexyl-3-[4-(2-oxo-4-trifluoromethyl-1,2-dihydroquinolin-6-ylmethyl)phenyl]urea	1.93	446.2 $[M + H]^+$
13		1-(4-Methylbenzyl)-3-[4-(2-oxo-4-trifluoromethyl-1,2-dihydroquinolin-6-ylmethyl)phenyl]thiourea	1.95	482.2 $[M + H]^+$
14		1-[2-(4-Chlorophenyl)ethyl]-3-[4-(2-oxo-4-trifluoromethyl-1,2-dihydroquinolin-6-ylmethyl)phenyl]thiourea	2.00	516.2 $[M + H]^+$
15		1-[4-(2-Oxo-4-trifluoromethyl-1,2-dihydroquinolin-6-ylmethyl)phenyl]-3-phenethylthiourea	1.90	482.2 $[M + H]^+$
16		1-Methyl-3-[4-(2-oxo-4-trifluoromethyl-1,2-dihydroquinolin-6-ylmethyl)phenyl]thiourea	1.61	392.2 $[M + H]^+$
17		1-(2,3-Dimethoxybenzyl)-3-[4-(2-oxo-4-trifluoromethyl-1,2-dihydroquinolin-6-ylmethyl)phenyl]thiourea	1.86	528.2 $[M + H]^+$
18		1-[4-(2-Oxo-4-trifluoromethyl-1,2-dihydroquinolin-6-ylmethyl)phenyl]-3-(2-*p*-tolylethyl)thiourea	1.97	496.2 $[M + H]^+$

19		{3-[4-(2-Oxo-4-trifluoromethyl-1,2-dihydroquinolin-6-ylmethyl)phenyl]ureido}acetic acid ethyl ester	1.61	448.2 $[M + H]^+$
20		1-Allyl-3-[4-(2-oxo-4-trifluoromethyl-1,2-dihydroquinolin-6-ylmethyl)phenyl]thiourea	1.72	418.2 $[M + H]^+$
21		1-(2-Morpholin-4-ylethyl)-3-[4-(2-oxo-4-trifluoromethyl-1,2-dihydroquinolin-6-ylmethyl)phenyl]thiourea	1.30	491.2 $[M + H]^+$
22		1-Naphthalen-1-yl-3-[4-(2-oxo-4-trifluoromethyl-1,2-dihydroquinolin-6-ylmethyl)phenyl]urea	1.97	488.2 $[M + H]^+$
23		1-Benzo[1,3]dioxol-5-ylmethyl-3-[4-(2-oxo-4-trifluoromethyl-1,2-dihydroquinolin-6-ylmethyl)phenyl]thiourea	1.83	512.2 $[M + H]^+$
24		1-(4-Methoxybenzyl)-3-[4-(2-oxo-4-trifluoromethyl-1,2-dihydroquinolin-6-ylmethyl)phenyl]thiourea	1.88	498.2 $[M + H]^+$
25		1-Benzyl-3-[4-(2-oxo-4-trifluoromethyl-1,2-dihydroquinolin-6-ylmethyl)phenyl]thiourea	1.85	468.2 $[M + H]^+$

CLAIMS

What is claimed is:

1. A compound of the formula:



in which;

a. M is NZ or O;

b. Z is represented by H or C_1- C_4 alkyl;

c. R^1 is represented by hydrogen, (C_1-C_2)alkyl, optionally substituted with one or more halogens, or (C_1-C_2)alkoxy, optionally substituted with one or more halogens;

d. R^2 is absent, or may represent up to 2 substituents selected from the group consisting of halogen, nitrile, hydroxy, (C_1-C_4)alkyl, (C_2-C_4)alkenyl, (C_2-C_4)alkynyl, (C_1-C_4)alkoxy, (C_1-C_2)alkyl substituted with one or more halogens, (C_1-C_2)alkoxy substituted with one or more halogens, SR^4, and NR^4R^5;

e. X is represented by O or S;

f. A is represented by hydrogen, (C_1- C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, -$[CH_2]_m$-D-$[CH_2]_n$-(CH_3), -$[CH_2]_m C(O)OR^4$, -$[CH_2]_m C(O)R^4$, -$[CH_2]_m C(O)NR^4R^5$, or $(CH_2)_n$-R^3-R^6;

g. m is an integer selected from 1 to 8;

h. n is an integer from 0 to 8;

i. D is represented by O or S;

j. R^3 is represented by optionally substituted phenyl, optionally substituted naphthyl, C_3-C_8 cycloalkyl, optionally substituted heteroaryl, or optionally substituted heterocyclic;

k. R^4 and R^5 are each independently represented by hydrogen, (C_1-C_4)alkyl, optionally substituted benzyl or optionally substituted phenyl, and;

l. R^6 is absent, or is represented by a substituent selected from the group consisting of optionally substituted phenyl, optionally substituted naphthyl, optionally substituted phenoxy, C_3-C_8cycloalkyl, optionally substituted heterocyclic, and optionally substituted heteroaryl.

2. The compound according to claim 1 in which NC(X)N-A is bonded to the para-position of the benzyl ring, M is represented by NZ in which Z is hydrogen, R^1 is trifluoromethyl, R^2 is absent, X is S or O, and A is represented by optionally substituted phenyl.

3. The compound according to claim 1 in which NC(X)N-A is bonded to the ortho-position of the benzyl ring, M is represented by NZ in which Z is hydrogen, R^1 is trifluoromethyl, R^2 is absent, X is S or O, and A is represented by optionally substituted phenyl.

4. A compound selected from the group consisting of

aa) 1-[2-(2-Oxo-4-trifluoromethyl-1,2-dihydroquinolin-6-ylmethyl)phenyl]-3-phenylthiourea;

bb) 1-(2-Morpholin-4-ylphenyl)-3-[2-(2-oxo-4-trifluoromethyl-1,2-dihydroquinolin-6-ylmethyl)phenyl]thiourea;

cc) 1-(4-Methylbenzyl)-3-[2-(2-oxo-4-trifluoromethyl-1,2-dihydroquinolin-6-ylmethyl)phenyl]thiourea;

dd) 1-(4-Methoxy-2-methylphenyl)-3-[2-(2-oxo-4-trifluoromethyl-1,2-dihydroquinolin-6-ylmethyl)phenyl]thiourea;

ee) 1-[2-(2-Oxo-4-trifluoromethyl-1,2-dihydroquinolin-6-ylmethyl)phenyl]-3-phenethylthiourea;

ff) 1-(4-Methoxyphenyl)-3-[2-(2-oxo-4-trifluoromethyl-1,2-dihydroquinolin-6-ylmethyl)phenyl]thiourea;

gg) {3-[2-(2-Oxo-4-trifluoromethyl-1,2-dihydroquinolin-6-ylmethyl)phenyl]ureido}acetic acid ethyl ester;

hh) 1-(4-Fluorophenyl)-3-[2-(2-oxo-4-trifluoromethyl-1,2-dihydroquinolin-6-ylmethyl)phenyl]thiourea;

ii) 1-Benzo[1,3]dioxol-5-ylmethyl-3-[2-(2-oxo-4-trifluoromethyl-1,2-dihydroquinolin-6-ylmethyl)phenyl]thiourea;

jj) 1-(3,5-Dimethoxyphenyl)-3-[2-(2-oxo-4-trifluoromethyl-1,2-dihydroquinolin-6-ylmethyl)phenyl]urea;

kk) 1-(4-Methoxybenzyl)-3-[2-(2-oxo-4-trifluoromethyl-1,2-dihydroquinolin-6-ylmethyl)phenyl]thiourea;

ll) 1-(2,3-Dimethoxybenzyl)-3-[2-(2-oxo-4-trifluoromethyl-1,2-dihydroquinolin-6-ylmethyl)phenyl]thiourea;

mm) 1-Hexyl-3-[4-(2-oxo-4-trifluoromethyl-1,2-dihydroquinolin-6-ylmethyl)phenyl]urea;

nn) 1-(4-Methylbenzyl)-3-[4-(2-oxo-4-trifluoromethyl-1,2-dihydroquinolin-6-ylmethyl)phenyl]thiourea;

oo) 1-[2-(4-Chlorophenyl)ethyl]-3-[4-(2-oxo-4-trifluoromethyl-1,2-dihydroquinolin-6-ylmethyl)phenyl]thiourea;

pp) 1-[4-(2-Oxo-4-trifluoromethyl-1,2-dihydroquinolin-6-ylmethyl)phenyl]-3-phenethylthiourea;

qq) 1-Methyl-3-[4-(2-oxo-4-trifluoromethyl-1,2-dihydroquinolin-6-ylmethyl)phenyl]thiourea;

rr) 1-(2,3-Dimethoxybenzyl)-3-[4-(2-oxo-4-trifluoromethyl-1,2-dihydroquinolin-6-ylmethyl)phenyl]thiourea;

ss) 1-[4-(2-Oxo-4-trifluoromethyl-1,2-dihydroquinolin-6-ylmethyl)phenyl]-3-(2-p-tolylethyl)thiourea;

tt) {3-[4-(2-Oxo-4-trifluoromethyl-1,2-dihydroquinolin-6-ylmethyl)phenyl]ureido}acetic acid ethyl ester;

uu) 1-Allyl-3-[4-(2-oxo-4-trifluoromethyl-1,2-dihydroquinolin-6-ylmethyl)phenyl]thiourea;

vv) 1-(2-Morpholin-4-ylethyl)-3-[4-(2-oxo-4-trifluoromethyl-1,2-dihydroquinolin-6-ylmethyl)phenyl]thiourea;

ww) 1-Naphthalen-1-yl-3-[4-(2-oxo-4-trifluoromethyl-1,2-dihydroquinolin-6-ylmethyl)phenyl]urea;

xx) 1-Benzo[1,3]dioxol-5-ylmethyl-3-[4-(2-oxo-4-trifluoromethyl-1,2-dihydroquinolin-6-ylmethyl)phenyl]thiourea;

yy) 1-(4-Methoxybenzyl)-3-[4-(2-oxo-4-trifluoromethyl-1,2-dihydroquinolin-6-ylmethyl)phenyl]thiourea, and;

zz) 1-Benzyl-3-[4-(2-oxo-4-trifluoromethyl-1,2-dihydroquinolin-6-ylmethyl)phenyl]thiourea.

5. Use of a compound according to any one of claims 1, 2, 3, or 4 as a medicine.

6. Use of a compound according to any one of claims 1, 2, 3, or 4 in the manufacture of a medicament for inhibiting activation of the androgen receptor.

7. Use of a compound according to any one of claims 1, 2, 3, or 4 in the manufacture of a medicament for at least one condition selected from alopecia, acne, oily skin, prostrate cancer, hirsutism, or benign prostate hyperplasia.

8. A pharmaceutical composition comprising a compound according to any one of claims 1, 2, 3, or 4 in admixture with one, or more, pharmaceutically acceptable excipients.

9 A topical pharmaceutical formulation comprising a compound according to anyone of claims 1,2 3, or 4 in admixture with one, or more, pharmaceutically acceptable excipients suitable for dermal application.

INTERNATIONAL SEARCH REPORT

I ional Application No	PCT/IB2004/000317

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D215/22 C07D311/08 C07D311/14 C07D405/12 A61K31/4704
A61K31/4709 A61K31/352 A61P17/00 A61P13/08

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 7 C07D A61K A61P

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)

CHEM ABS Data, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 01/16108 A (ZHI LIN ;ARJAN VAN OEVEREN CORNELIS (CA); PIO BARBARA (US); FARMER) 8 March 2001 (2001-03-08) cited in the application the whole document	1,5-9

☐ 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

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"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	Date of mailing of the international search report
13 May 2004	24/05/2004

Name and mailing address of the ISA	Authorized officer
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	Bosma, P

INTERNATIONAL SEARCH REPORT

Information on patent family members

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PCT/IB2004/000317

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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