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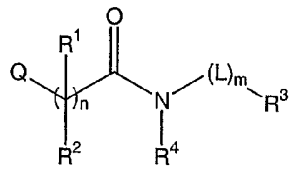
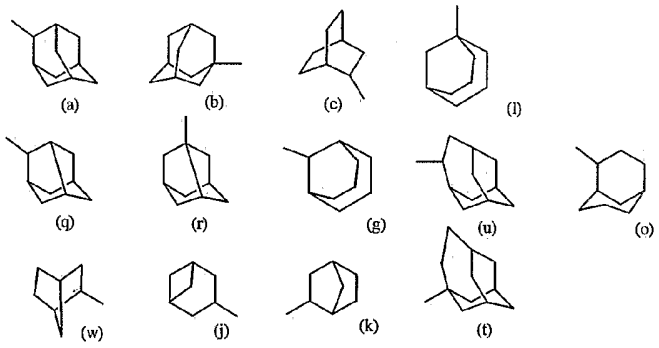


(I)



(57) Abstract: formulae (I)the N-oxide forms, the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof, wherein n represents an integer being 1 or 2; R_1 and R_2 each independently represents hydrogen C_{1-4}alkyl, NR^9R^{10}, C_{1-4}alkyloxy; or R^1 and R^2 taken together with the carbon atom with which they are attached form a C_{3-6}cycloalkyl; and where n is 2, either R^1 or R^2 may be absent to form an unsaturated bond; R^3 represents a C_{6-12}cycloalkyl, preferably selected from cylo-octanyl and cyclohexyl or R^3 represents a monovalent radical having one of the following formulae(a) (b) (c) (l) (q) (r) (g) (u) (o) (w) (j) (k) (t) wherein said C_{6-12}cycloalkyl or monovalent radical may optionally be substituted with one, or where possible two, three or more substituents selected from the group consisting of C_{1-4}alkyl, C_{1-4}alkyloxy, halo or hydroxy; Q represents Het^1 or Ar^2 wherein said C_{3-8}cycloalkyl, Het^1 or Ar^2 are optionally substituted with one or where possible two or more substituents selected from halo, C_{1-4}alkyl, C_{1-4}alkyloxy, hydroxy, nitro, NR^5R^6, C_{1-4}alkyloxy substituted with one or where possible two, three or more substituents each independently selected from hydroxycarbonyl, Het^2 and NR^7R^8, and C_{1-4}alkyl substituted with one or where possible two or three halo substituents, preferably trifluoromethyl; R^5 and R^6 each independently represent hydrogen, C_{1-4}alkyl, or C_{1-4}alkyl substituted with phenyl; R^7 and R^8 each independently represent hydrogen or C_{1-4}alkyl; R^9 and R^{10}? each independently represent hydrogen, C_{1-4}alkyl or C_{1-4}alkyloxycarbonyl; L represents C_{1-4}alkyl; Het^1 represents a heterocycle selected from pyridinyl, thiophenyl, or 1,3-benzodioxolyl; Het^2 represents piperidinyl, pyrrolidinyl or morpholinyl; Ar^2 represents phenyl, naphtyl or indenyl.

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

ADAMANTYL ACETAMIDES AS HYDROXYSTEROID DEHYDROGENASE INHIBITORS

The metabolic syndrome is a disease with increasing prevalence not only in the Western world but also in Asia and developing countries. It is characterised by obesity in particular central or visceral obesity, type 2 diabetes, hyperlipidemia, hypertension, arteriosclerosis, coronary heart diseases and eventually chronic renal failure (C.T. Montague et al. (2000), Diabetes, **49**, 883-888).

Glucocorticoids and 11β-HSD1 are known to be important factors in differentiation of adipose stromal cells into mature adipocytes. In the visceral stromal cells of obese patients, 11β-HSD1 mRNA level is increased compared with subcutaneous tissue. Further, adipose tissue over-expression of 11β-HSD1 in transgenic mice is associated with increased corticosterone levels in the adipose tissue, visceral obesity, insulin sensitivity, Type 2 diabetes, hyperlipidemia and hyperphagia (H. Masuzaki et al (2001), Science, **294**, 2166-2170). Therefore, 11β-HSD1 is most likely be involved in the development of visceral obesity and the metabolic syndrome.

Inhibition of 11β-HSD1 results in a decrease in differentiation and an increase in proliferation of adipose stromal cells. Moreover, glucocorticoid deficiency (adrenalectomy) enhances the ability of insulin and leptin to promote anorexia and weight loss, and this effect is reversed by glucocorticoid administration (P.M. Stewart et al (2002), Trends Endocrin. Metabol, **13**, 94-96). These data suggest that enhanced reactivation of cortisone by 11β-HSD1 may exacerbate obesity and it may be beneficial to inhibit this enzyme in adipose tissue of obese patients.

Obesity is also linked to cardiovascular risks. There is a significant relationship between cortisol excretion rate and HDL cholesterol in both men and women, suggesting that glucocorticoids regulate key components of cardiovascular risk. In analogy, aortic stiffness is also associated with visceral adiposity in older adults.

Glucocorticoids and glaucoma

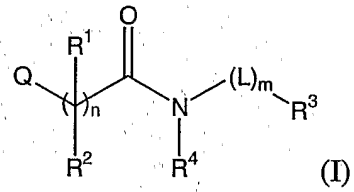
Glucocorticoids increase the risk of glaucoma by raising the intraocular pressure when administered exogenously and in certain conditions of increased production like in Cushing's syndrome. Corticosteroid-induced elevation of intra ocular pressure is caused by increased resistance to aqueous outflow due to glucocorticoid induced changes in the trabecular meshwork and its intracellular matrix. Zhou et al. (Int J Mol

Med (1998) **1**, 339-346) also reported that corticosteroids increase the amounts of fibronectin as well as collagen type I and type IV in the trabecular meshwork of organ-cultured bovine anterior segments.

11β-HSD1 is expressed in the basal cells of the corneal epithelium and the non-pigmented epithelial cells. Glucocorticoid receptor mRNA was only detected in the trabecular meshwork, whereas in the non-pigmented epithelial cells mRNA for the glucocorticoid-, mineralocorticoid receptor and 11β-HSD1 was present. Carbenoxolone administration to patients resulted in a significant decrease in intra-ocular pressure (S. Rauz et al. (2001), Invest. Ophtalmol. Vis. Science, **42**, 2037-2042), suggesting a role for HSD1-inhibitors in treating glaucoma.

Accordingly, the underlying problem to be solved by the present invention was to identify potent 11β-HSD inhibitors, with a high selectivity for 11β-HSD1, and the use thereof in treating pathologies associated with excess cortisol formation such as obesity, diabetes, obesity related cardiovascular diseases, and glaucoma.

This invention concerns compounds of formula (I)



(I)

the *N*-oxide forms, the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof, wherein

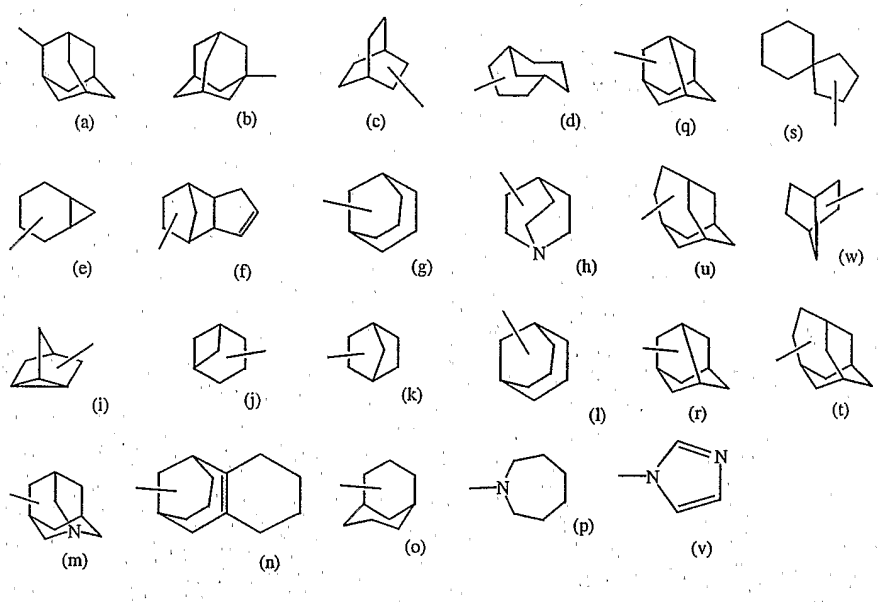
n represents an integer being 0, 1 or 2;

m represents an integer being 0 or 1;

R^1 and R^2 each independently represents hydrogen, C_{1-4}alkyl, NR^9R^{10}, C_{1-4}alkyloxy, Het^3-O-C_{1-4}alkyl; or

R^1 and R^2 taken together with the carbon atom with which they are attached form a carbonyl, or a C_{3-6}cycloalkyl; and where n is 2, either R^1 or R^2 may be absent to form an unsaturated bond;

R^3 represents hydrogen, Ar^1, C_{1-8}alkyl, C_{6-12}cycloalkyl or a monovalent radical having one of the following formulae



wherein said Ar^1, C_{6-12}cycloalkyl or monovalent radical may optionally be substituted with one, or where possible two or three substituents selected from the group consisting of C_{1-4}alkyl, C_{1-4}alkyloxy, phenyl, halo, oxo, carbonyl, 1,3-dioxolyl or hydroxy;

R^4 represents hydrogen or C_{1-4}alkyl;

Q represents C_{3-8}cycloalkyl, Het^1 or Ar^2, wherein said C_{3-8}cycloalkyl, Het^1 or Ar^2 are optionally substituted with one or where possible more substituents selected from halo, C_{1-4}alkyl, C_{1-4}alkyloxy, hydroxy, nitro, Het^4, phenyl, phenyloxy, C_{1-4}alkyloxycarbonyl, hydroxycarbonyl, NR^5R^6, C_{1-4}alkyloxy substituted with one or where possible two or three substituents each independently selected from hydroxycarbonyl, Het^2 and NR^7R^8, and

C_{1-4}alkyl substituted with one or where possible two or three halo substituents;

R^5 and R^6 are each independently selected from hydrogen, C_{1-4}alkyl, C_{1-4}alkyloxyC_{1-4}alkyl, C_{1-4}alkyloxycarbonyl, C_{1-4}alkylcarbonyl, C_{1-4}alkylcarbonyl substituted with one or where possible two or three substituents each independently selected from halo, C_{1-4}alkyl, and C_{1-4}alkyloxy or R^5 and R^6 each independently represent C_{1-4}alkyl substituted with phenyl;

R^7 and R^8 are each independently selected from hydrogen or C_{1-4}alkyl;

R^9 and R^{10} are each independently selected from hydrogen, C_{1-4}alkyl or C_{1-4}alkyloxycarbonyl;

L represents C_{1-4}alkyl optionally substituted with one or where possible more substituents selected from C_{1-4}alkyl or phenyl;

Het^1 represents a heterocycle selected from pyridinyl, piperinidyl, pyrimidinyl, pyrazinyl, piperazinyl, pyridazinyl, indolyl, isoindolyl, indolinyl, furanyl, benzofuranyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, benzothiophenyl,

thiophenyl, 1,8-naphthyridinyl, 1,6-naphthyridinyl, quinolinyl, isoquinolinyl, quinoxalinyl, quinazolinyl, phthalazinyl, or 1,3-benzodioxolyl.;

Het ^{2} represents a monocyclic heterocycle selected from piperidinyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, piperazinyl, 2H-pyrrolyl, pyrrolyl, 2-pyrrolinyl, 3-pyrrolinyl, pyrrolidinyl, or morpholinyl;

Het^{3} represents a monocyclic heterocycle selected from 2H-pyranyl, 4H-pyranyl, furanyl, tetrahydro-2H-pyranyl, pyridinyl, piperidinyl, or furanyl;

Het^{4} represents a monocyclic heterocycle selected from pyridazinyl, pyrimidinyl, pyrrolidinyl, pyrazinyl, piperazinyl or morpholinyl, said Het^{4} optionally being substituted with one or where possible two or more substituents each idependently selected from hydroxy, carbonyl, C_{1-4}alkyl or C_{1-4}alkyloxy;

Ar^{1} represents carbocyclic radicals containing one or more rings selected from the group consisting of phenyl, biphenyl, indenyl, 2,3-dihydroindenyl, fluorenyl, 5,6,7,8-tetrahydronaphtyl or naphtyl

Ar^{2} represents carbocyclic radicals containing one or more rings selected from the group consisting of phenyl, biphenyl, indenyl, 2,3-dihydroindenyl, fluorenyl, 5,6,7,8-tetrahydronaphtyl or naphtyl.

As used in the foregoing definitions and hereinafter, halo is generic to fluoro, chloro, bromo and iodo; C_{1-4}alkyl defines straight and branched chain saturated hydrocarbon radicals having from 1 to 4 carbon atoms such as, for example, methyl, ethyl, propyl, butyl, 1-methylethyl, 2-methylpropyl, 2,2-dimethylethyl and the like; C_{1-8}alkyl defines straight and branched chain saturated hydrocarbon radicals having from 1 to 8 carbon atoms such as the groups defined for $C_{(1-4)}$alkyl and pentyl, hexyl, octyl, 2-methylbutyl 2-methylpentyl, 2,2-dimethylpentyl and the like;C_{3-6}cycloalkyl is generic to cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl; C_{6-12}cycloalkyl is generic to cycloheptyl and cyclo-octanyl, cyclononane, cyclodecane, cycloundecane and cyclododecane; C_{1-4}alkyloxy defines straight or branched saturated hydrocarbon radicals such as methoxy, ethoxy, propyloxy, butyloxy, 1-methylethyloxy, 2-methylpropyloxy and the like.

As used herein before, the terms oxo or carbonyl refers to (=O) that forms a carbonyl moiety with the carbon atom to which it is attached.

The pharmaceutically acceptable addition salts as mentioned hereinabove are meant to comprise the therapeutically active non-toxic acid addition salt forms, which the compounds of formula (I), are able to form. The latter can conveniently be obtained by

treating the base form with such appropriate acid. Appropriate acids comprise, for example, inorganic acids such as hydrohalic acids, e.g. hydrochloric or hydrobromic acid; sulfuric; nitric; phosphoric and the like acids; or organic acids such as, for example, acetic, propanoic, hydroxyacetic, lactic, pyruvic, oxalic, malonic, succinic (i.e. butanedioic acid), maleic, fumaric, malic, tartaric, citric, methanesulfonic, ethanesulfonic, benzenesulfonic, *p*-toluenesulfonic, cyclamic, salicylic, *p*-aminosalicylic, pamoic and the like acids.

The pharmaceutically acceptable addition salts as mentioned hereinabove are meant to comprise the therapeutically active non-toxic base addition salt forms which the compounds of formula (I), are able to form. Examples of such base addition salt forms are, for example, the sodium, potassium, calcium salts, and also the salts with pharmaceutically acceptable amines such as, for example, ammonia, alkylamines, benzathine, *N*-methyl-D-glucamine, hydrabamine, amino acids, e.g. arginine, lysine.

Conversely said salt forms can be converted by treatment with an appropriate base or acid into the free acid or base form.

The term addition salt as used hereinabove also comprises the solvates which the compounds of formula (I), as well as the salts thereof, are able to form. Such solvates are for example hydrates, alcoholates and the like.

The term stereochemically isomeric forms as used hereinbefore defines the possible different isomeric as well as conformational forms which the compounds of formula (I), may possess. Unless otherwise mentioned or indicated, the chemical designation of compounds denotes the mixture of all possible stereochemically and conformationally isomeric forms, said mixtures containing all diastereomers, enantiomers and/or conformers of the basic molecular structure. All stereochemically isomeric forms of the compounds of formula (I), both in pure form or in admixture with each other are intended to be embraced within the scope of the present invention.

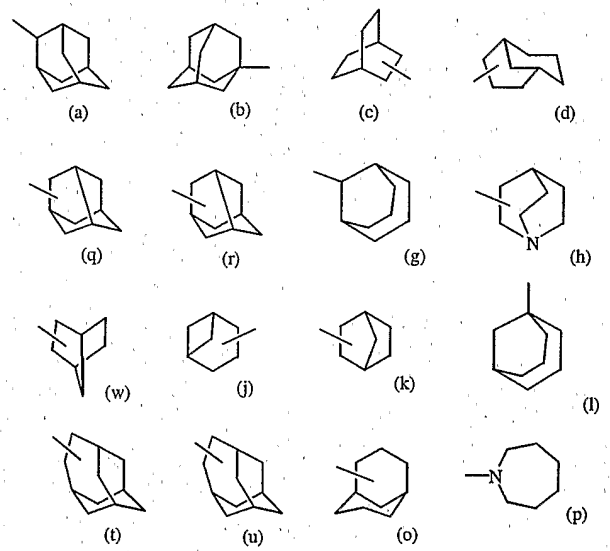
The *N*-oxide forms of the compounds of formula (I), are meant to comprise those compounds of formula (I) wherein one or several nitrogen atoms are oxidized to the so-called *N*-oxide.

An interesting group of compounds consists of those compounds of formula (I) wherein one or more of the following restrictions apply :

(i) n represents an integer being 1 or 2 provided that when n represents 2, Q represents Het^1 or Ar^2, wherein said Het^1 or Ar^2 are optionally substituted with one or where possible more substituents selected from halo, C_{1-4}alkyl, C_{1-4}alkyloxy, hydroxy, nitro, Het^4, phenyl, phenyloxy, hydroxycarbonyl, NR^5R^6, C_{1-4}alkyloxy substituted with one or where possible two or three substituents each independently selected from hydroxycarbonyl, Het^2 and NR^7R^8, and C_{1-4}alkyl substituted with one or where possible two or three halo substituents;

(ii) R^1 and R^2 each independently represents hydrogen, C_{1-4}alkyl, NR^9R^{10}, C_{1-4}alkyloxy, Het^3-O-C_{1-4}alkyl; or R^1 and R^2 taken together with the carbon atom with which they are attached form a carbonyl, or a C_{3-6}cycloalkyl;

(iii) R^3 represents phenyl, C_{6-12}cycloalkyl or a monovalent radical having one of the following formulae



wherein said phenyl, C_{6-12}cycloalkyl or monovalent radical may optionally be substituted with one, or where possible two or three substituents selected from the group consisting of C_{1-4}alkyl, C_{1-4}alkyloxy, halo, carbonyl, phenyl or hydroxy;

(iv) R^4 represents hydrogen or C_{1-4}alkyl;

(v) Q represents Het^1 or Ar^2, wherein said Het^1 or Ar^2 are optionally substituted with one or where possible more substituents selected from halo, C_{1-4}alkyl, C_{1-4}alkyloxy, hydroxy, nitro, Het^4, phenyl, phenyloxy, hydroxycarbonyl, NR^5R^6, C_{1-4}alkyloxy substituted with one or where possible two or three substituents each independently selected from hydroxycarbonyl, Het^2 and NR^7R^8, and C_{1-4}alkyl substituted with one or where possible two or three halo substituents;

(vi) Het^1 represents a heterocycle selected from piperinidyl, pyrimidinyl, pyrazinyl, piperazinyl, pyridazinyl, indolyl, isoindolyl, indolinyl, benzofuranyl,

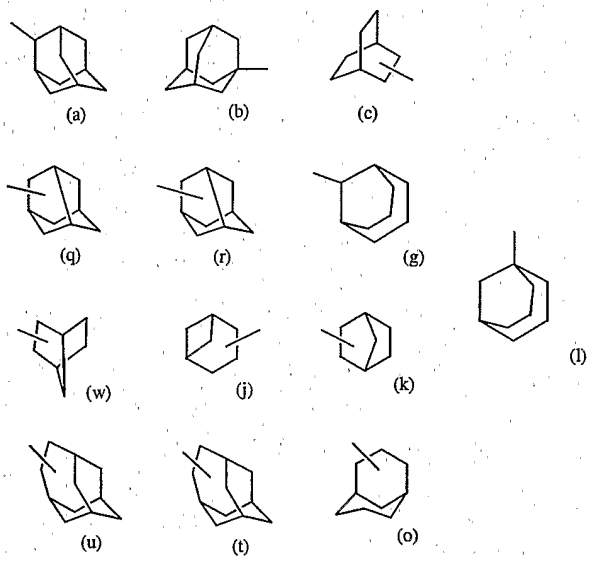
benzothiophenyl, 1,8-naphthyridinyl, 1,6-naphthyridinyl, quinazolinyl, phthalazinyl, or 1,3-benzodioxolyl.;

(vii) Ar^2 represents phenyl or naphtyl optionally substituted with C_{1-4}alkyl, C_{1-4}alkyloxy or halo; preferably substituted with methyl or methoxy.

Another interesting group of compounds consists of those compounds of formula (I) wherein one or more of the following restrictions apply :

(i) R^1 and R^2 each independently represents hydrogen C_{1-4}alkyl, NR^9R^{10}; or R^1 and R^2 taken together with the carbon atom with which they are attached form a C_{3-6}cycloalkyl; and where n is 2, either R^1 or R^2 may be absent to form an unsaturated bond;

(ii) R^3represents a C_{6-12}cycloalkyl or a monovalent radical having one of the following formulae



wherein said C_{6-12}cycloalkyl or monovalent radical may optionally be substituted with one, or where possible two, three or more substituents selected from the group consisting of C_{1-4}alkyl, C_{1-4}alkyloxy, halo, carbonyl, hydroxy, or 1,3-dioxolyl;

(iii) Q represents Het^1 or Ar^2 wherein said Het^1 or Ar^2 are optionally substituted with one or where possible two or more substituents selected from halo, C_{1-4}alkyl, C_{1-4}alkyloxy, hydroxy, C_{1-4}alkyloxycarbonyl, NR^5R^6, C_{1-4}alkyloxy substituted with one or where possible two or three substituents each independently selected from hydroxycarbonyl, Het^2 and NR^7R^8, and C_{1-4}alkyl substituted with one or where possible two or three halo substituents;

(iv) R^5 and R^6 are each independently selected from hydrogen, C_{1-4}alkyl, C_{1-4}alkylcarbonyl, C_{1-4}alkylcarbonyl substituted with one or where possible two or three halo substituents.

(v) R^9 and R^{10} are each independently selected from hydrogen or C_{1-4}alkyl;

(vi) L represents a C_{1-4}alkyl, preferably methyl;

(vii) Het^1 represents a heterocycle selected from pyridinyl, pyrimidinyl, thiophenyl or 1,3-benzodioxolyl;

(viii) Het^2 represents a monocyclic heterocycle selected from piperidinyl, pyridinyl, pyrrolidinyl or morpholinyl;

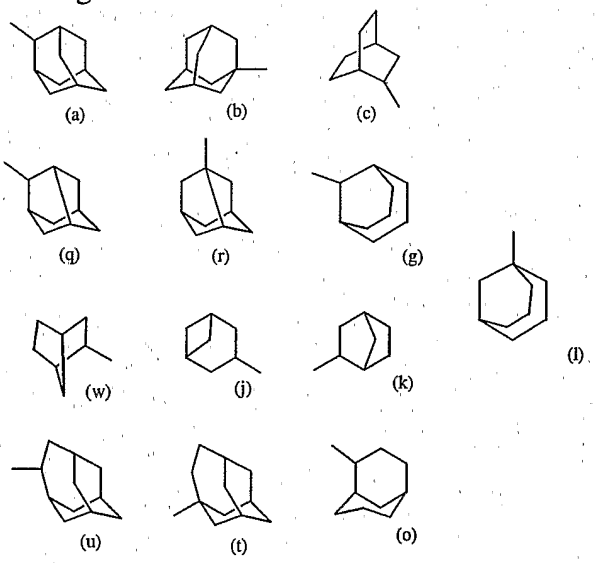
(ix) Ar^2 represents a C_{6-14}aryl preferably selected from phenyl, naphtyl or indenyl.

A particular group of compounds of formula (I) were those compounds shown to be highly HSD1 specific. For these compounds of formula (I) one or more of the following restrictions apply :

(i) n represents an integer being 1 or 2;

(ii) R^1 and R^2 each independently represents hydrogen C_{1-4}alkyl, NR^9R^{10}; or R^1 and R^2 taken together with the carbon atom with which they are attached form a C_{3-6}cycloalkyl; and where n is 2, either R^1 or R^2 may be absent to form an unsaturated bond;

(iii) R^3 represents a C_{6-12}cycloalkyl, preferably cylo-octanyl or a monovalent radical having one of the following formulae



wherein said C_{6-12}cycloalkyl or monovalent radical may optionally be substituted with one, or where possible two, three or more substituents selected from the group consisting of C_{1-4}alkyl, C_{1-4}alkyloxy, halo or hydroxy;

(iv) Q represents Het^1 or Ar^2 wherein said Het^1 or Ar^2 are optionally substituted with one or where possible two or more substituents selected from halo, C_{1-4}alkyl, C_{1-4}alkyloxy, hydroxy, NR^5R^6, C_{1-4}alkyloxy substituted with one or where possible two, three or more substituents each independently selected from

hydroxycarbonyl, Het^2 and NR^7R^8, and C_{1-4}alkyl substituted with one or where possible two or three halo substituents;

(v) R^5 and R^6 each independently represent hydrogen or C_{1-4}alkyl;

(vi) R^9 and R^{10} each independently represent hydrogen or C_{1-4}alkyloxycarbonyl;

(vii) L represents C_{1-4}alkyl;

(viii) Het^1 represents a heterocycle selected from pyridinyl, piperidinyl, thiophenyl or 1,3-benzodioxol;

(ix) Het^2 represents pyridinyl, pyrrolidinyl or morpholinyl;

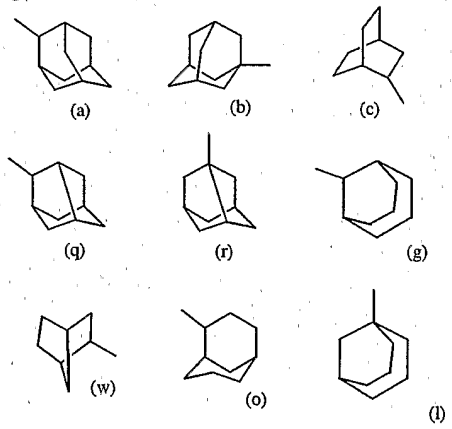
(x) Ar^2 represents phenyl, naphtyl or indenyl.

A subgroup of these highly HSD1 specific inhibitors was shown to have a superior cellular activity and consist of compounds of formulae (I) wherein one or more of the following restrictions apply

(i) n represents an integer being 1 or 2;

(ii) R^1 and R^2 each independently represents hydrogen, C_{1-4}alkyl; or R^1 and R^2 taken together with the carbon atom with which they are attached form a C_{3-6}cycloalkyl; and where n is 2, either R^1 or R^2 may be absent to form an unsaturated bond;

(iii) R^3 represents a C_{6-12}cycloalkyl, preferably cylo-octanyl or a monovalent radical having one of the following formulae



wherein said C_{6-12}cycloalkyl or monovalent radical may optionally be substituted with one, or where possible two, three or more substituents selected from the group consisting of C_{1-4}alkyl, C_{1-4}alkyloxy, halo or hydroxy;

(iv) Q represents Het^1 or Ar^2 wherein said Het^1 or Ar^2 are optionally substituted with one or where possible two or more substituents selected from halo, C_{1-4}alkyl, C_{1-4}alkyloxy, hydroxy, NR^5R^6, C_{1-4}alkyloxy substituted with one or where possible two, three or more substituents each independently selected from hydroxycarbonyl, Het^2 and NR^7R^8, and C_{1-4}alkyl substituted with one or where possible two or three halo substituents;

(v) R^5 and R^6 each independently represent hydrogen or C_{1-4}alkyl;

(vi) L represents C_{1-4}alkyl;

(vii) Het^1 represents a heterocycle selected from pyridinyl, piperidinyl, thiophenyl or 1,3-benzodioxol;

(viii) Het^2 represents pyrrolidinyl or morpholinyl;

(ix) Ar^2 represents phenyl, naphtyl or indenyl.

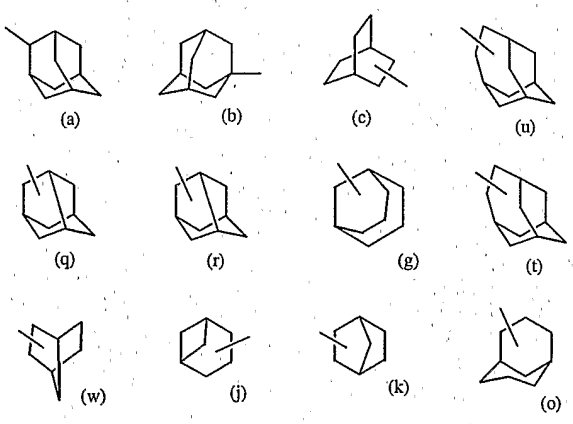
Further interesting compounds according to the invention are those compounds of formulae (I) wherein one or more of the following restrictions apply

(i) n represents an integer being 1 or 2;

(ii) R^1 and R^2 each independently represents hydrogen C_{1-4}alkyl, NR^9R^{10}, C_{1-4}alkyloxy; or

R^1 and R^2 taken together with the carbon atom with which they are attached form a C_{3-6}cycloalkyl; and where n is 2, either R^1 or R^2 may be absent to form an unsaturated bond;

(iii) R^3 represents a C_{6-12}cycloalkyl, preferably selected from cylo-octanyl and cyclohexyl or R^3 represents a monovalent radical having one of the following formulae



wherein said C_{6-12}cycloalkyl or monovalent radical may optionally be substituted with one, or where possible two, three or more substituents selected from the group consisting of C_{1-4}alkyl, C_{1-4}alkyloxy, halo or hydroxy;

(iv) Q represents C_{3-8}cycloalkyl, Het^1 or Ar^2 wherein said C_{3-8}cycloalkyl, Het^1 or Ar^2 are optionally substituted with one or where possible two or more substituents selected from halo, C_{1-4}alkyl, C_{1-4}alkyloxy, hydroxy, nitro, NR^5R^6, C_{1-4}alkyloxy substituted with one or where possible two, three or more substituents each independently selected from hydroxycarbonyl, Het^2 and NR^7R^8, and C_{1-4}alkyl substituted with one or where possible two or three halo substituents, preferably trifluoromethyl;

(v) R^5 and R^6 each independently represent hydrogen, C_{1-4}alkyl, or C_{1-4}alkyl substituted with phenyl;

(vi) L represents C_{1-4}alkyl;

(vii) Het^1 represents a heterocycle selected from pyridinyl, piperidinyl, or thiophenyl;

(viii) Het^2 represents piperidinyl, pyrrolidinyl or morpholinyl;

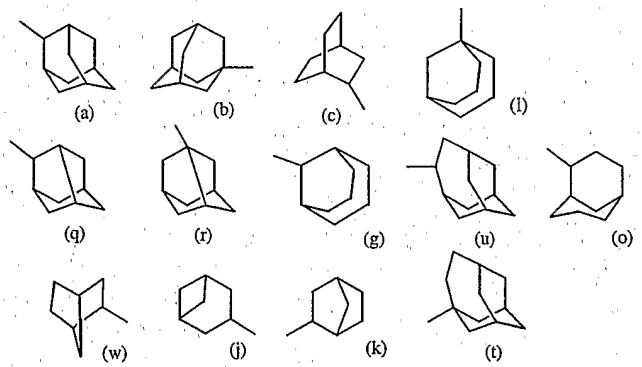
(ix) Ar^2 represents phenyl, naphtyl or indenyl.

A particular group of compounds of formula (I) are those where one or more of the following restrictions apply :

(i) n represents an integer being 1 or 2;

(ii) R^1 and R^2 each independently represents hydrogen C_{1-4}alkyl, NR^9R^{10}, C_{1-4}alkyloxy; or
R^1 and R^2 taken together with the carbon atom with which they are attached form a C_{3-6}cycloalkyl; and where n is 2, either R^1 or R^2 may be absent to form an unsaturated bond;

(iii) R^3 represents a C_{6-12}cycloalkyl, preferably selected from cylo-octanyl and cyclohexyl or R^3 represents a monovalent radical having one of the following formulae



wherein said C_{6-12}cycloalkyl or monovalent radical may optionally be substituted with one, or where possible two, three or more substituents selected from the group consisting of C_{1-4}alkyl, C_{1-4}alkyloxy, halo or hydroxy;

(iv) Q represents Het^1 or Ar^2 wherein said C_{3-8}cycloalkyl, Het^1 or Ar^2 are optionally substituted with one or where possible two or more substituents selected from halo, C_{1-4}alkyl, C_{1-4}alkyloxy, hydroxy, nitro, NR^5R^6, C_{1-4}alkyloxy substituted with one or where possible two, three or more substituents each independently selected from hydroxycarbonyl, Het^2 and NR^7R^8, and C_{1-4}alkyl substituted with one or where possible two or three halo substituents, preferably trifluoromethyl;

(v) R^5 and R^6 each independently represent hydrogen, C_{1-4}alkyl, or C_{1-4}alkyl substituted with phenyl;

(vi) L represents C_{1-4}alkyl;

(vii) Het^1 represents a heterocycle selected from pyridinyl, thiophenyl, or 1,3-benzodioxolyl;

(viii) Het^2 represents piperidinyl, pyrrolidinyl or morpholinyl;

(ix) Ar^2 represents phenyl, naphtyl or indenyl.

A preferred group of compounds consists of those compounds of formula (I) wherein one or more of the following restrictions apply :

(i) Q represents phenyl, said phenyl optionally substituted with one or two substituents selected from the halo, preferably chloro or fluor, or C_{1-4}alkyloxy preferably methoxy. ;

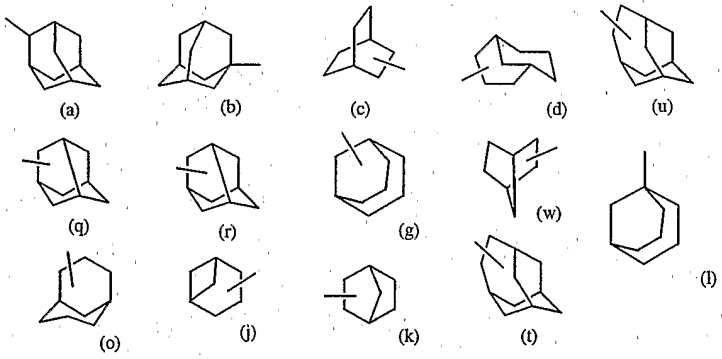
(ii) n is 1;

(iii) m is 0;

(iv) R^1 and R^2 represent C_{1-4}alkyl, preferably methyl; or R^1 and R^2 taken together with the carbon atom with which they are attached form a C_{3-6}cycloalkyl, preferably cyclopropyl;

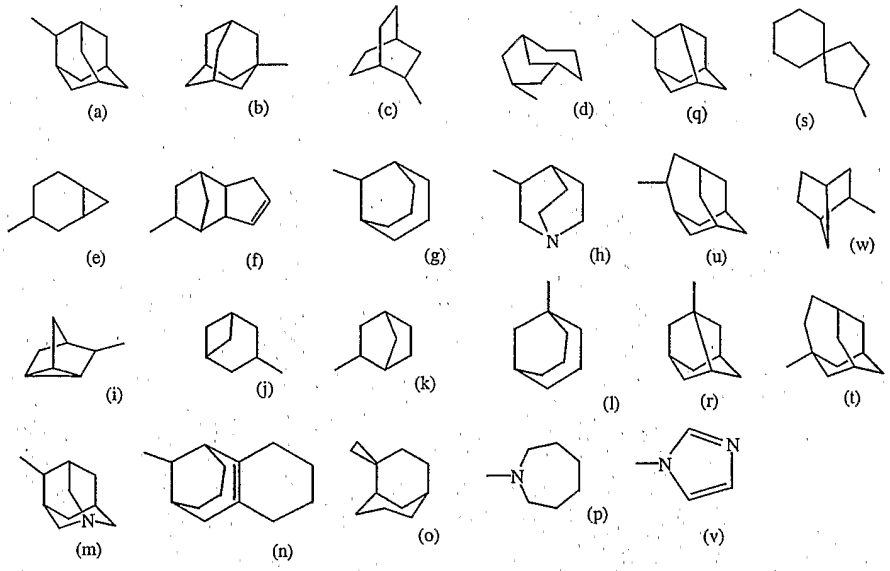
(v) R^4 represents hydrogen;

(vi) R^3 represents a monovalent radical having one of the following formulae



wherein said monovalent radical may optionally be substituted with one or where possible two or three substituents selected from halo, carbonyl, hydroxy or C_{1-4}alkyloxy, preferably methoxy.

Also of interest are those compounds of formula (I) wherein the R^3 substituent is being selected from the monovalent radicals having one of the following formulae



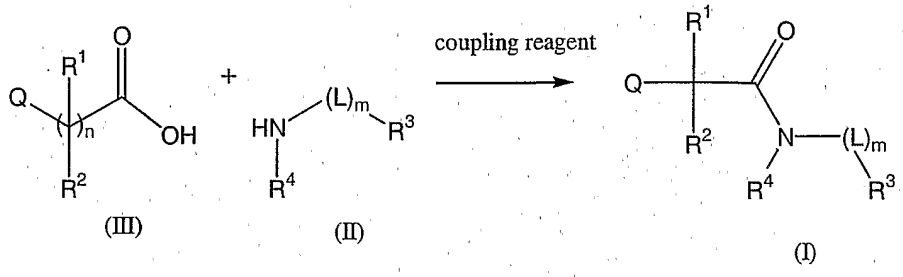
optionally substituted with one, or where possible two or three substituents selected from the group consisting of C_{1-4}alkyl, C_{1-4}alkyloxy, phenyl, halo, oxo, carbonyl, 1,3-dioxolyl or hydroxy; even more preferably those compounds wherein the R^3 substituent is 2-adamantyl optionally substituted with one, or where possible two or three substituents selected from the group consisting of C_{1-4}alkyl, C_{1-4}alkyloxy, halo, oxo, carbonyl or hydroxy.

The amide compounds of this invention can be prepared by any of several standard synthetic processes commonly used by those skilled in the art of organic chemistry and described for instance in; "Introduction to organic chemistry" Streitweiser and Heathcock – Macmillan Publishing Co., Inc. – second edition - New York – Section 24.7 (partA) p 753-756. In general, the amides can be prepared through a base-catalyzed nucleophilic addition between the appropriate carboxylic acid with the corresponding amine (scheme 1), or via a nucleophilic substitution reaction wherein the appropriate amine reacts with either the corresponding acyl halide (scheme 2), anhydride or ester, to yield the required amide.

When coupling the acids to the amines, standard chemical coupling reagents such as carbonyldiimidazole (CDI), 1.3-dicyclohexylcarbodiimide (DCC) or 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (EDCI) are used in the presence or absence of hydroxybenzotrialzole (HOBt). In general, adding of the carboxylic acids of formula (III) to the amines of formula (II) under base-catalyzed reaction conditions results in the formation of the amine salt which is in equilibrium with its weak acid and base. To force the equilibrium to the formation of the amide of formula (I), a

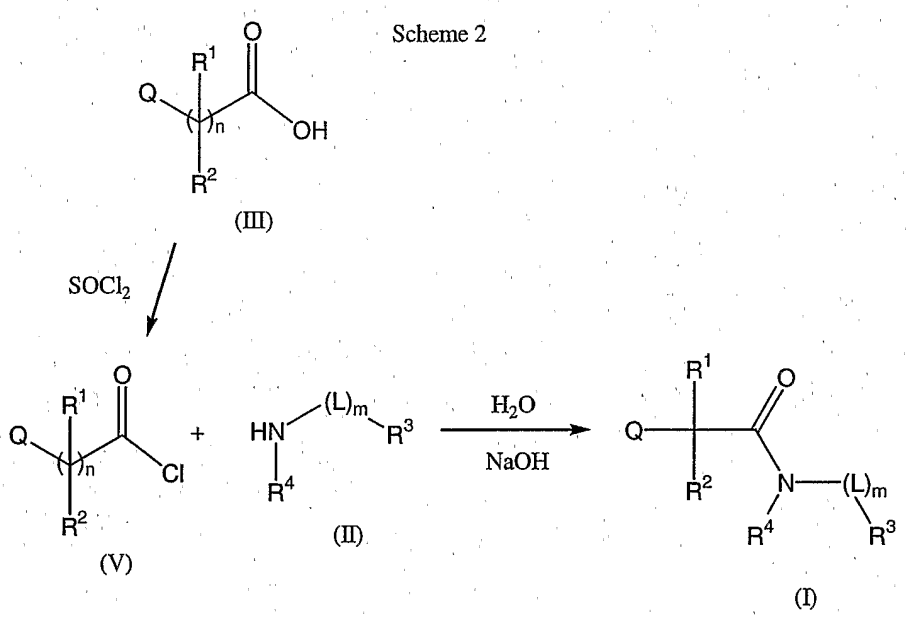
dehydrogenating agent such as carbodiimides, for example DCC and CDI are added to the reaction mixture.

Scheme 1



In an alternative embodiment the carboxylic acids or converted into the corresponding acyl halides by reaction with, for example, thionyl chloride or oxalyl chloride. Subsequently said acyl halide (V) is added to the amine of formula (II) to yield the amide of formula (I) using art known reaction procedures such as the Schotten-Baumann method.

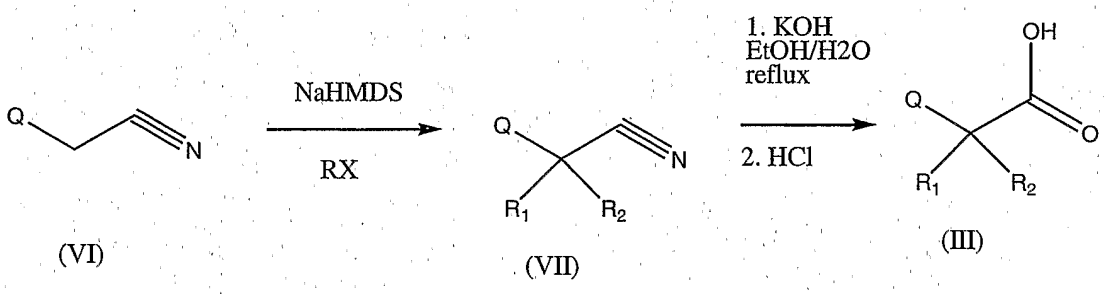
Scheme 2



The carboxylic acids of formula (III) and the amines of formula (II) are readily available, or may be prepared using methods that are well known in the art. Many compounds are commercially available, for example, from Aldrich Chemicals, or when the compounds are not commercially available, they may be readily prepared from available precursors using straightforward transformations that are well known in the art.

For example the carboxylic acids are most often prepared by hydrolysis of nitriles (scheme 3), carbonation of organometallic compounds or oxidation of primary alcohols or aldehydes, see for instance in; "Introduction to organic chemistry" Streitweiser and Heathcock – Macmillan Publishing Co., Inc. – second edition - New York – Section 19.6 p 509-511. In particular the carboxylic acids of formula (III) are prepared from the corresponding (hetero)aryl acetonitriles (VI) by conversion to the dialkyl or spiroalkyl derivative (VII) using e.g., sodium hexamethyldisilazane and methyl iodide or dibromobutane (see e.g., Trivedi et al, J. Med. Chem. **1993**, *36*, 3300), followed by hydrolysis under acidic or basic conditions to the desired carboxylic acid III. Appropriate acids and bases in the hydrolysis are for example H_2SO4 and KOH. The hydrolysis reaction can be conveniently performed using microwave heating.

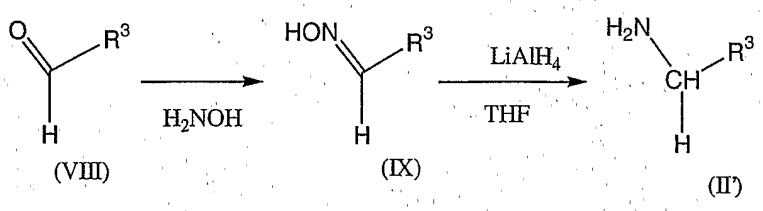
Scheme 3



(VI) (VII) (III)

The amines of formula (II) are generally prepared using art known techniques, see for instance in; "Introduction to organic chemistry" Streitweiser and Heathcock – Macmillan Publishing Co., Inc. – second edition - New York – Section 24.6 p 742-753, and comprise synthesis through indirect alkylation of the appropriate (hetero)aryl halides in particular by the Gabriel synthesis, through reduction of the corresponding nitro or nitrille compounds, through reductive amination using for example the Eschweiler-Clarke reaction and in particular through the reduction of oximes (IX) which may be prepared from aldehydes or ketones (VIII) by reaction with hydroxylamine (scheme 4). In this latter case the oximes are reduced by lithium aluminium hydride or catalytic hydrogenation using an appropriate catalysator such as Rainey Nickel, said reduction being performed in an inert anhydrous solvent such as ether or tetrahydrofuran (THF).

Scheme 4



Further examples for the synthesis of compounds of formula (I) using anyone of the above mentioned synthesis methods, are provided in the experimental part hereinafter.

Where necessary or desired, any one or more of the following further steps in any order may be performed :

(i) removing any remaining protecting group(s);

(ii) converting a compound of formula (I) or a protected form thereof into a further compound of formula (I) or a protected form thereof;

(iii) converting a compound of formula (I) or a protected form thereof into a *N*-oxide, a salt, a quaternary amine or a solvate of a compound of formula (I) or a protected form thereof;

(iv) converting a *N*-oxide, a salt, a quaternary amine or a solvate of a compound of formula (I) or a protected form thereof into a compound of formula (I) or a protected form thereof;

(v) converting a *N*-oxide, a salt, a quaternary amine or a solvate of a compound of formula (I) or a protected form thereof into another *N*-oxide, a pharmaceutically acceptable addition salt a quaternary amine or a solvate of a compound of formula (I) or a protected form thereof;

(vi) where the compound of formula (I) is obtained as a mixture of (R) and (S) enantiomers resolving the mixture to obtain the desired enantiomer.

Compounds of formula (I), *N*-oxides, addition salts, quaternary amines and stereochemical isomeric forms thereof can be converted into further compounds according to the invention using procedures known in the art, for example :

It will be appreciated by those skilled in the art that in the processes described above the functional groups of intermediate compounds may need to be blocked by protecting groups.

Functional groups which it is desirable to protect include hydroxy, amino and carboxylic acid. Suitable protecting groups for hydroxy include trialkylsilyl groups (e.g. tert-butyldimethylsilyl, tert-butyldiphenylsilyl or trimethylsilyl), benzyl and tetrahydropyranyl. Suitable protecting groups for amino include tert-butyloxycarbonyl or benzyloxycarbonyl. Suitable protecting groups for carboxylic acid include $C_{(1-6)}$alkyl or benzyl esters.

The protection and deprotection of functional groups may take place before or after a reaction step.

The use of protecting groups is fully described in 'Protective Groups in Organic Chemistry', edited by J W F McOmie, Plenum Press (1973), and 'Protective Groups in Organic Synthesis' 2nd edition, T W Greene & P G M Wutz, Wiley Interscience (1991).

Additionally, the N-atoms in compounds of formula (I) can be methylated by art-known methods using CH_3-I in a suitable solvent such as, for example 2-propanone, tetrahydrofuran or dimethylformamide.

The compounds of formula (I), can also be converted into each other following art-known procedures of functional group transformation of which some examples are mentioned hereinabove.

The compounds of formula (I), may also be converted to the corresponding *N*-oxide forms following art-known procedures for converting a trivalent nitrogen into its *N*-oxide form. Said *N*-oxidation reaction may generally be carried out by reacting the starting material of formula (I) with 3-phenyl-2-(phenylsulfonyl)oxaziridine or with an appropriate organic or inorganic peroxide. Appropriate inorganic peroxides comprise, for example, hydrogen peroxide, alkali metal or earth alkaline metal peroxides, e.g. sodium peroxide, potassium peroxide; appropriate organic peroxides may comprise peroxy acids such as, for example, benzenecarboperoxoic acid or halo substituted benzenecarboperoxoic acid, e.g. 3-chlorobenzenecarboperoxoic acid, peroxoalkanoic acids, e.g. peroxoacetic acid, alkylhydroperoxides, e.g. t-butyl hydroperoxide. Suitable solvents are, for example, water, lower alkanols, e.g. ethanol and the like, hydrocarbons, e.g. toluene, ketones, e.g. 2-butanone, halogenated hydrocarbons, e.g. dichloromethane, and mixtures of such solvents.

Pure stereochemically isomeric forms of the compounds of formula (I), may be obtained by the application of art-known procedures. Diastereomers may be separated

by physical methods such as selective crystallization and chromatographic techniques, e.g. counter-current distribution, liquid chromatography and the like.

Some of the compounds of formula (I), and some of the intermediates in the present invention may contain an asymmetric carbon atom. Pure stereochemically isomeric forms of said compounds and said intermediates can be obtained by the application of art-known procedures. For example, diastereoisomers can be separated by physical methods such as selective crystallization or chromatographic techniques, e.g. counter current distribution, liquid chromatography and the like methods. Enantiomers can be obtained from racemic mixtures by first converting said racemic mixtures with suitable resolving agents such as, for example, chiral acids, to mixtures of diastereomeric salts or compounds; then physically separating said mixtures of diastereomeric salts or compounds by, for example, selective crystallization or chromatographic techniques, e.g. liquid chromatography and the like methods; and finally converting said separated diastereomeric salts or compounds into the corresponding enantiomers. Pure stereochemically isomeric forms may also be obtained from the pure stereochemically isomeric forms of the appropriate intermediates and starting materials, provided that the intervening reactions occur stereospecifically.

An alternative manner of separating the enantiomeric forms of the compounds of formula (I) and intermediates involves liquid chromatography, in particular liquid chromatography using a chiral stationary phase.

Some of the intermediates and starting materials as used in the reaction procedures mentioned hereinabove are known compounds and may be commercially available or may be prepared according to art-known procedures.

The compounds of the present invention are useful because they possess pharmacological properties. They can therefore be used as medicines, in particular to treat pathologies associated with excess cortisol formation such as for example, obesity, diabetes, obesity related cardiovascular diseases, and glaucoma.

As described in the experimental part hereinafter, the inhibitory effect of the present compounds on the 11b-HSD1-reductase activity (conversion of cortison into cortisol) has been demonstrated *in vitro*, in an enzymatic assay using the recombinant 11b-HSD1 enzyme, by measuring the conversion of cortison into cortisol using HPLC purification and quantification methods. 11b-HSD1-reductase inhibition was also demonstrated *in vitro*, in a cell based assay comprising contacting the cells, expressing

11b-HSD1 with the compounds to be tested and assessing the effect of said compounds on the formation of cortisol in the cellular medium of these cells. The cells preferably used in an assay of the present invention are selected from the group consisting of mouse fibroblast 3T3-L1 cells, HepG2 cells, pig kidney cell, in particular LCC-PK1 cells and rat hepatocytes.

Accordingly, the present invention provides the compounds of formula (I), (I') and their pharmaceutically acceptable *N*-oxides, addition salts, quaternary amines and stereochemically isomeric forms for use in therapy. More particular in the treatment or prevention of cell proliferation mediated diseases. The compounds of formula (I), (I') and their pharmaceutically acceptable *N*-oxides, addition salts, quaternary amines and the stereochemically isomeric forms may hereinafter be referred to as compounds according to the invention.

In view of the utility of the compounds according to the invention, there is provided a method for the treatment of an animal, for example, a mammal including humans, suffering from a cell proliferative disorder such as atherosclerosis, restinosis and cancer, which comprises administering an effective amount of a compound according to the present invention.
Said method comprising the systemic or topical administration of an effective amount of a compound according to the invention, to warm-blooded animals, including humans.

It is thus an object of the present invention to provide a compound according to the present invention for use as a medicine. In particular to use the compound according to the present invention in the manufacture of a medicament for treating pathologies associated with excess cortisol formation such as for example, obesity, diabetes, obesity related cardiovascular diseases, and glaucoma.

In yet a further aspect, the present invention provides the use of the compounds according to the invention in the manufacture of a medicament for treating any of the aforementioned cell proliferative disorders or indications.

The amount of a compound according to the present invention, also referred to here as the active ingredient, which is required to achieve a therapeutical effect will be, of course, vary with the particular compound, the route of administration, the age and condition of the recipient, and the particular disorder or disease being treated. A

suitable daily dose would be from 0.001 mg/kg to 50 mg/kg body weight, in particular from 0.005 mg/kg to 10 mg/kg body weight. A method of treatment may also include administering the active ingredient on a regimen of between one and four intakes per day.

While it is possible for the active ingredient to be administered alone, it is preferable to present it as a pharmaceutical composition. Accordingly, the present invention further provides a pharmaceutical composition comprising a compound according to the present invention, together with a pharmaceutically acceptable carrier or diluent. The carrier or diluent must be "acceptable" in the sense of being compatible with the other ingredients of the composition and not deleterious to the recipients thereof.

The pharmaceutical compositions of this invention may be prepared by any methods well known in the art of pharmacy, for example, using methods such as those described in Gennaro et al. Remington's Pharmaceutical Sciences (18^{th} ed., Mack Publishing Company, 1990, see especially Part 8 : Pharmaceutical preparations and their Manufacture). A therapeutically effective amount of the particular compound, in base form or addition salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirably in unitary dosage form suitable, preferably, for systemic administration such as oral, percutaneous, or parenteral administration; or topical administration such as via inhalation, a nose spray, eye drops or via a cream, gel, shampoo or the like. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs and solutions: or solid carriers such as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wettable agent, optionally combined

with suitable additives of any nature in minor proportions, which additives do not cause any significant deleterious effects on the skin. Said additives may facilitate the administration to the skin and/or may be helpful for preparing the desired compositions. These compositions may be administered in various ways, e.g., as a transdermal patch, as a spot-on or as an ointment. As appropriate compositions for topical application there may be cited all compositions usually employed for topically administering drugs e.g. creams, gellies, dressings, shampoos, tinctures, pastes, ointments, salves, powders and the like. Application of said compositions may be by aerosol, e.g. with a propellant such as nitrogen, carbon dioxide, a freon, or without a propellant such as a pump spray, drops, lotions, or a semisolid such as a thickened composition which can be applied by a swab. In particular, semisolid compositions such as salves, creams, gellies, ointments and the like will conveniently be used.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used in the specification and claims herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such dosage unit forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, injectable solutions or suspensions, teaspoonfuls, tablespoonfuls and the like, and segregated multiples thereof.

In order to enhance the solubility and/or the stability of the compounds of formula (I), (I') in pharmaceutical compositions, it can be advantageous to employ α-, β- or γ-cyclodextrins or their derivatives. Also co-solvents such as alcohols may improve the solubility and/or the stability of the compounds of formula (I), (I') in pharmaceutical compositions. In the preparation of aqueous compositions, addition salts of the subject compounds are obviously more suitable due to their increased water solubility.

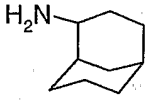
Experimental part

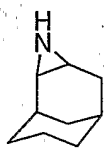
Hereinafter, the term 'RT' means room temperature, 'THF' means tetrahydrofuran, 'AcOH' means Acetic Acid, 'EtOH' means ethanol, 'DME' means dimethyl ether, 'DIPE' means diisopropyl ether, 'TFA' means trifluoroacetic acid, 'EtOAc' means ethyl acetate, 'iPrOH' means dimethylformamide, 'HOBt' means hydroxybenzotrialzole.

A. Preparation of the intermediates

Example A1

Bicyclo[3.3.1]non-2-ylamine (intermediate 4) and 3-aza-tricyclo[4.3.1.0*2,4*]decane (intermediate 5)

Preparation of  (interm. 4)

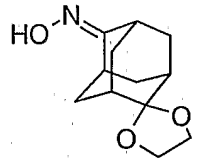
Preparation of  (interm. 5)

Bicyclo[3.3.1]nonan-2-one oxime (CAS 16473-10-2) (1.4 g) was dissolved in anhydrous THF (30 Ml) and a solution of LiAlH4 (15 Ml , 1M in diethyl ether) was added. The solution was boiled under reflux for 16h. Addition of water (0.6 Ml), 15% NaOH (0.6 Ml), and water (1.8 mL), followed by filtration, drying of the filtrate ($MgSO_4$) and evaporation gave the crude amines. The residue was dissolved in CH_2Cl_2, and extracted with 15% citric acid. The aqueous layer was basicified with 1 M KOH, and extracted with CH_2Cl_2. The organic layer was washed with brine, dried and evaporated to give the amines 1:1 mixture (0.5 g).

NMR (CDCl3) δ 1.2-2.1 (m, CH), 2.45 (t, 1H), 2.9 (m, 1H)

Example A2

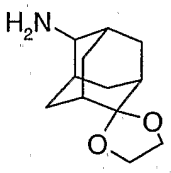
a) 6-Hydroxyimino-adamantan-2-yl ethylene ketal

Preparation of  Intermediate 16

Commercially available Spiro[1,3-dioxolane-2,2'-tricyclo[3.3.1.13,7]decan]-6'-one (CAS 50776-11-9) (2.3 g, 0.012 mol) (containing about 30% of the diketal) was dissolved in EtOH and a solution of hydroxylamine hydrochloride (1.7 g, 0.025 mol) and NaOH (1.0 g) in water (30 ml) was added. The mixture was stirred overnight. The volatiles were evaporated in vacuo, and the residue was extracted with CH_2Cl_2. The organic layer was washed with brine, dried and evaporated to give the oxime (Intermediate 16) (2.4 g).

NMR (DMSO-d6) δ 1.3-2.3 (m, CH), 2.5 (bs, 1H), 3.5 (bs, 1H), 3.95 (s, 4H, CH2CH2)

b) 6-Oxo-adamantan-2-ylamine ethylene ketal

Preparation of  Intermediate 17

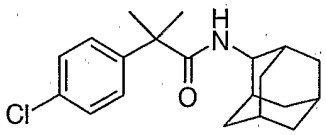
6-Hydroxyimino-adamantan-2-yl ethylene ketal (2.4 g) was dissolved &M NH_3/MeOH (100 mL), Raney nickel (1 g) was added and the mixture was hydrogenated at 14 °C. The mixture was filtered, and evaporated to give 2.0 g of the title compound (Intermediate 17).

NMR (DMSO-d6) δ 1.3-2.3 (m, CH),3.23 (bs, 2H, NH2), 3.95 (s, 4H, CH2CH2).

B. Preparation of the compounds

Example B1

N-Adamantan-2-yl-2-(4-chlorophenyl)-isobutyramide

Preparation of  compound 1

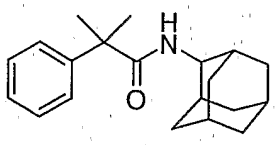
2,2-dimethyl-(4-chlorophenyl)acetic acid (CAS 6258-30-6) (2.0 g, 10 mmol) and 2-aminoadamantane hydrochloride (CAS 13074-39-0) (1.9 g, 10 mmol) were dissolved in CH_2CL_2 (50 mL), HOBt (2.7 g, 20 mol), triethylamine (2.1 g, 20 mmol), and EDCI (2.1 g, 11 mmol) were added and the mixture was stirred overnight. The reaction mixture was washed with 15% citric acid, sat. $NaHCO_3$ and brine, dried over $MgSO_4$, and evaporated in vacuo. The residue was recrystallised from isopropanol, yielding 2.0 (6 mmol, 60%) of compound 1.

NMR: (DMSO-d6) δ 1.4-1.8 (m, CH), 1.47 (s, 6H, (CH3)2), 3.79 (d, 1H, CH), 6.42 (d, 1H, NH), 7.38 (dd, Ar-H).

LC-MS: M+1 332.89, 334.89

Example B2

N-Adamantan-2-yl-2-phenyl-isobutyramide

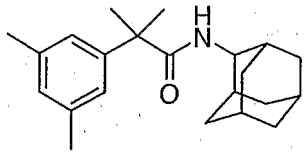
Preparation of  compound 2

Compound 1 (1.7 g, 5 mmol) was dissolved in MeOH (100 mL), 0.5 g 10% Pd-C and CaO (1 g) were added, and the mixture was hydrogenated at 50 oC, After uptake of one equivalent of hydrogen, the reaction was filtered, evaporated till dryness. The residue was dissolved in CH_2Cl_2, washed with sat. $NaHCO_3$, dried and evaporated. The residue was crystallized from diisopropyl ether, yielding 0.65 g (60%) of the title compound .

NMR: (DMSO-d6) δ 1.4-1.8 (m, CH), 1.49 (s, 6H, (CH3)2), 3.79 (d, 1H, CH), 6.21 (d, 1H, NH), 7.25-7.37 (m, 5H, Ar-H).

LC-MS: M+1 298.44

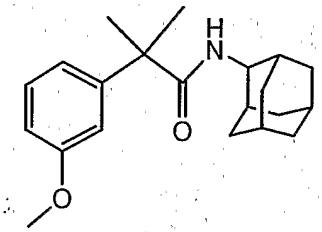
Example B3

Preparation of  compound 3

2,2-dimethylphenyl acetic acid (CAS 826-55-1) was dissolved in dry CH_2Cl_2, oxalyl chloride was added and one drop of DMF. After stirring for two hours, the solution was evaporated till dryness, redissolved in 10 mL CH_2Cl_2, and added to a solution of 2-amino adamantane (CAS 13074-39-0) and triethylamine in CH_2Cl_2. The mixture was stirred overnight, extracted with 15% citric acid, sat. $NAHCO_3$ and brine, dried over $MgSO_4$, and evaporated in vacuo. The residue was recrystallised from isopropyl ether. NMR: (CDCl3) δ 1.3-1.8 (m, CH), 1.55 (s, 6H, (CH3)2), 2.31 (s, 6H, 2 x CH3), 3.96 (d, 1H, CH), 5.50 (d, 1H, NH), 6.91 (s, 1H, Ar-H), 6.99 (s, 2H, ArH).

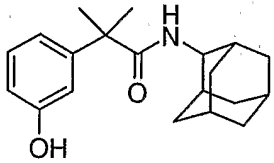
Example B4

a) 3-Methoxyphenyl-dimethyl adamantyl acetamide

Preparation of  compound 4

Intermediate 2 (2.0 g, 10 mmol) and 2-aminoadamantane hydrochloride (CAS 13074-39-0) (1.9 g, 10 mmol) were dissolved in CH_2CL_2 (50 mL), HOBt (2.7 g, 20 mol), triethylamine (2.1 g, 20 mmol), and EDCI (2.1 g, 11 mmol) were added and the mixture was stirred overnight. The reaction mixture was washed with 15% citric acid, sat. $NaHCO_3$ and brine, dried over $MgSO_4$, and evaporated in vacuo. The residue was recrystallised from isopropanol, yielding 2.0 (6 mmol, 60%) of compound 4.
NMR: (DMSO-d6) δ 1.4-1.8 (m, CH), 1.48 (s, 6H, (CH3)2), 3.75 (s, 3H, OCH3), 3.79 (d, 1H, CH), 6.23 (d, 1H, NH), 6.8-7.3 (m, 3H, Ar-H).

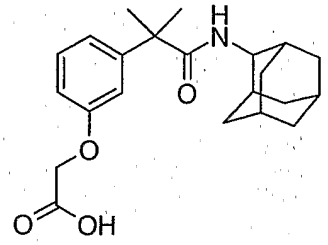
b) N-Adamantan-2-yl-2-(3-hydroxy-phenyl)-isobutyramide

Preparation of  compound 5

Compound 4 was dissolved in dry CH_2Cl_2, cooled to –78°C and boron tribromide was added. The reaction mixture was stirred at room temperature for 1 h, poured onto

aqueous ammonia and extracted with C_2Cl_2. The organic layers were washed with brine, dried and evaporated. The solid reside was crystallized from ethyl acetate.
NMR: (DMSO-d6) δ 1.4-1.8 (m, CH), 1.44 (s, 6H, (CH3)2), 3.79 (d, 1H, CH), 6.18 (d, 1H, NH), 6.65-7.16 (dd, 4H, Ar-H), 9.35 (s, 1H, OH).

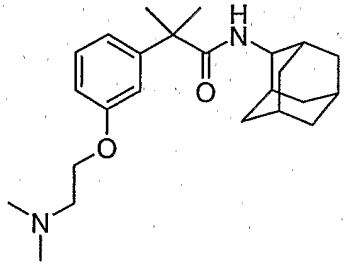
c) {3-[1-(Adamantan-2-ylcarbamoyl)-1-methyl-ethyl]-phenoxy}-acetic acid

Preparation of  compound 6

Compound 4 was dissolved in DMF and ethyl bromoacetate was added together with potassium carbonate. The mixture was stirred at 60 °C overnight, poured on ice, and extracted with CH_2Cl_2. The organic layer was washed with 1 M $NaHCO_3$, and brine, and evaporated. The residue was dissoled in EtOH, 1 M KOH was added, and the mixture was stirred for 2 h. The solution was acidified with 1M HCl, extracted with EtOAc, the organic layer was dried and evaporated. The residue was crystallized from ethyl acetate.
NMR: (DMSO-d6) δ 1.4-1.8 (m, CH), 1.47 (s, 6H, (CH3)2), 3.78 (d, 1H, CH), 4.67 (s, 2H, CH2COOH), 6.23 (d, 1H, NH), 6.77-7.3 (m, 4H, Ar-H).

Example B5

N-Adamantan-2-yl-2-[3-(2-dimethylamino-ethoxy)-phenyl]-isobutyramide

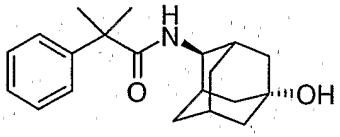
Preparation of  compound 7

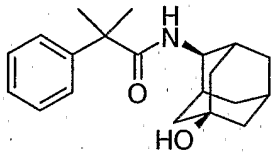
Compound 4 was dissolved in DMF, and dimethylaminoethyl chloride hydrochloride was added, followed by K_2CO_3. The mixture was stirred at 60 oC overnight, poured on ice, and extracted with CH_2Cl_2. The organic layer was washed with 1 M $NaHCO_3$, and

brine, and evaporated. The residue was dissolved in iPrOH with heating, oxalic acid was added, and the crystallie amine was filtered.
NMR: (DMSO-d6) δ 1.4-1.8 (m, CH), 1.49 (s, 6H, (CH3)2), 2.78 (s, 6H, N(CH3)2), 3.43 (t, 2H, CH2), 3.79 (d, 1H, CH), 4.27 (t, 2H, CH2), 6.29 (d, 1H, NH), 6.85-7.35 (m, 4H, Ar-H).

Example B6

N-(trans-5-Hydroxy-adamantan-2-yl)-2-phenyl-isobutyramide (Compound 8) and N-(cis-5-Hydroxy-adamantan-2-yl)-2-phenyl-isobutyramide (Compound 9)

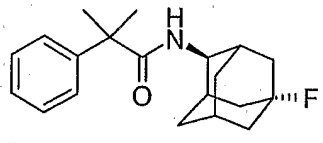
Preparation of  compound 8

Preparation of  compound 9

2,2-dimethylphenyl acetic acid (CAS 826-55-1) (2.5 g, 15 mmol) was dissolved in dry CH_2Cl_2 (50 mL), oxalyl chloride (1.5 mL, 0.017 mol) was added and one drop of DMF. After stirring for two hours, the solution was evaporated till dryness, redissolved in 50 mL of CH_2Cl_2, and added to a solution of 2-amino adamantane (CAS 13074-39-0) (2.5 g, 15 mmol) and triethylamine (3.0 g, 30 mmol) in CH_2Cl_2 (50 mL). The mixture was stirred overnight, extracted with 15% citric acid, sat. $NaHCO_3$ and brine, dried over $MgSO_4$, and evaporated in vacuo. The residue was chromatographed over silicagel (eluens 3-5% MeOH in CH_2Cl_2), yielding the title compounds. 1.8 g of trans-,
NMR: (CDCl3) δ 1.2-1.85 (m, CH), 1.59 (s, 6H, (CH3)2), 1.95-2.00 (m, 2H, CH), 3.91 (dt, 1H, CH), 5.32 (d, 1H, NH), 7.25-7.47 (m, 5H, Ar-H).
And 1.8 g of cis isomer.
NMR: (CDCl3) δ 1.2-1.7 (m, CH), 1.56 (s, 6H, (CH3)2), 2.05-2.10 (m, 2H, CH), 3.83 (dt, 1H, CH), 5.32 (d, 1H, NH), 7.25-7.50 (m, 5H, Ar-H).

Example B7

N-(5-trans-fluoro-adamantan-2-yl)-2-phenyl-isobutyramide

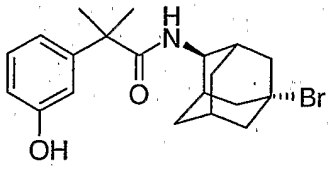
Preparation of  compound 10.

Compound 8 (80 mg) was dissolved in dichloromethane (2 mL) and cooled to –78 oC under nitrogen. DAST ((diethylamino)sulfur trifluoride, 0.1 ml) was added, and the mixture was stirred and warmed to room temperature. Sat. $NaHCO_3$ was added and the layers were separated. The organic layer was washed with brine, dried ($MgSO_4$) and evaporated. The residue was crystallized from diisopropylether to give 40 mg (50%) of the title compound.

NMR: (CDCl3) δ 1.2-1.85 (m, CH), 1.59 (s, 6H, (CH3)2), 1.95-2.10 (m, 2H, CH), 3.93 (dt, 1H, CH), 5.27 (d, 1H, NH), 7.27-7.43 (m, 5H, Ar-H).

Example B8

N-(5-Bromo-adamantan-2-yl)-2-(3-hydroxy-phenyl)-isobutyramide

Preparation of  compound 11.

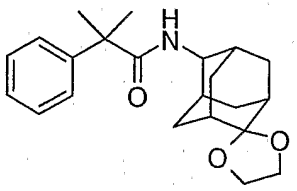
Compound 8 (100 mg, 0.3 mmol) was dissolved in CH_2Cl_2 (2 mL), cooled to –78 oc and boron tribromide (0.15 mL, 1.5 mmol) was added. The reaction mixture was warmed to room temperature, diluted with CH_2Cl_2 and poured on a mixture ice and conc. Ammonia. The layers were separated, the organic layer washed with brine, dried ($MgSO_4$) and evaporated. The residue was crystallized from ethyl acetate (40 mg, 40%).

LC-MS: M+1 393.34, 395.34

NMR: (CDCl3) δ 1.25-1.52 (m, CH), 1.57 (s, 6H, (CH3)2), 1.90-2.42 (m, CH), 3.97 (dt, 1H, CH), 5.37 (d, 1H, NH), 6.28-7.30 (m, 4H, Ar-H).

Example B9

N-(6-Oxo-adamantan-2-yl)-2-phenyl-isobutyramide ethylene ketal

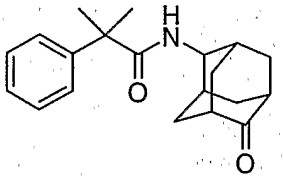
Preparation of  compound 12

2,2-dimethylphenyl acetic acid (CAS 826-55-1) (0.5 g, 2.7 mmol)was dissolved in dry CH_2Cl_2, oxalyl chloride (0.4 g) was added and one drop of DMF. After stirring for two hours, the solution was evaporated till dryness, redissolved in 10 mL CH_2Cl_2, and added to a solution of 6-oxo-adamantan-2-ylamine ethylene ketal (Intermediate 15) (0.6 g, 2.7 mmol) and triethylamine (0.5 mL) in CH_2Cl_2. The mixture was stirred overnight, extracted with 15% citric acid, sat. $NAHCO_3$ and brine, dried over $MgSO_4$, and evaporated in vacuo. The residue was purified over silacalgel (eluens 5% MeOH in CH_2Cl_2), and the title compound was recrystallised from isopropyl ether. 600 mg (50%)

NMR: (CDCl3) δ 1.52-2.05 (m, CH), 1.60 (s, 6H, (CH3)2), 3.85 (dt, 1H, CH), 3.85-3.90 (m, 4H, CH2CH2), 5.45 (d, 1H, NH), 7.23-7.42 (m, 5H, Ar-H).

Example B10

N-(6-Oxo-adamantan-2-yl)-2-phenyl-isobutyramide

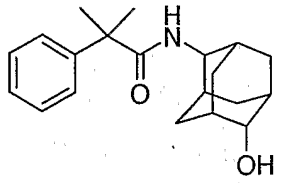
Preparation of  compound 13

The ketal from example B9 (450 mg) was dissolved in acetone (10 mL), 1 M HCl (5 mL) was added and the mixture was stirred fro 3 h at 45 °C. The reaction mixture was concentrated, and extracted with dichloromethane. The organic layers were washed with sat. $NaHCO_3$ and brine, dried and evaporated. The residue was crystallized from ethanol: 300 mg of the title compound.

NMR: (CDCl3) δ 1.52-1.75 (m, CH), 1.60 (s, 6H, (CH3)2), 1.95-2.15 (m, 2H, CH), 2.30 (d, 2H, CH), 2.50 (s, 2H, CH), 4.12 (dt, 1H, CH), 5.45 (d, 1H, NH), 7.27-7.47 (m, 5H, Ar-H).

Example B11

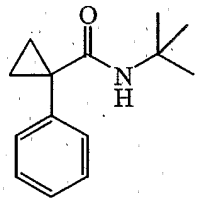
N-(6-Hydroxy-adamantan-2-yl)-2-phenyl-isobutyramide

Preparation of  compound 14

Compound 13 (50 mg) was dissolved in MeOH and $NaBH_4$ (50 mg) was added. The mixture was stirred at room temperature for 6 h. 1M HCl was added, and the mixture was extracted with dichloromethane. The organic phase was washed with brine, dried and evaporated. Chromatography over silicagel (5% MeOH in CH_2Cl_2) gave the alcohol (20 mg, 40%)

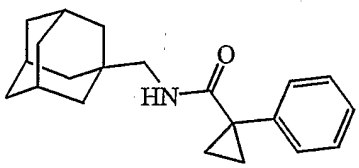
NMR: (CDCl3) δ 1.52-2.00 (m, CH), 1.60 (s, 6H, (CH3)2), 3.85 (dt, 1H, CH), 5.45 (d, 1H, NH), 7.23-7.42 (m, 5H, Ar-H).

Example B13

Preparation of  compound 17

1-Phenylcyclopropanecarboxylic acid (0.00028 mol); was added to a mixture of PS-N-cyclohexylcarbodiimide (0.0004 mol) in CH_2Cl_2 (5 ml). The mixture was stirred for 15 min. 2-methyl-2-Propanamine (0.0002 mol) was added and the reaction mixture was stirred overnight at room temperature. The resin was filtered off and the filtrate was evaporated. The residue was purified over Supelclean LC-SI (14 ml; eluent: CH_2Cl_2). The product fractions were collected and the solvent was evaporated, yielding compound 17.

Example B14

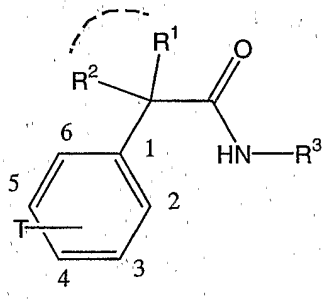
Preparation of  compound 31

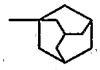
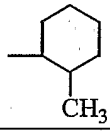
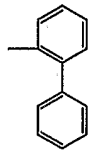
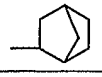
PS-carbodiimide (0.0004 mol) was suspended in CH_2Cl_2 (5 ml). Then, 1-phenyl-cyclopropanecarboxylic acid (0.00028 mol) and N,N-dimethyl-4-pyridinamine

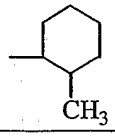
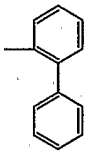
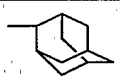
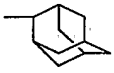
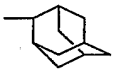
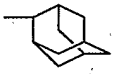
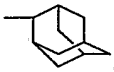
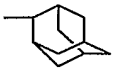
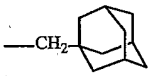
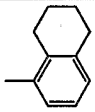
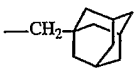
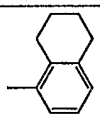
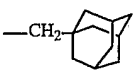
(0.00001mol) were added and the mixture was stirred for 20 min. Tricyclo[3.3.1.13,7]decane-1-methanamine (0.0002 mol; 6 variables) was added and the reaction mixture was stirred overnight at room temperature. The mixture was filtered. The filter residue was washed with CH_2Cl_2 and the filtrate's solvent was evaporated. The residue was purified by flash column chromatography on Triconex flash tubes (eluent: hexane/EtOAc 9/2). The product fractions were collected and then extracted and the extracts were evaporated. Yielding 0.037 of compound 31

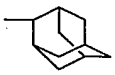
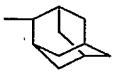
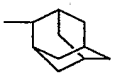
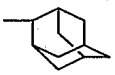
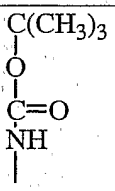
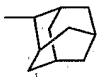
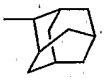
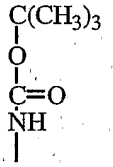
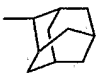
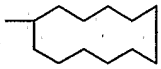
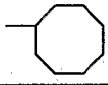
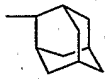
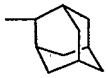
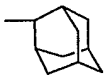
Tables 1, 2 and 3 list compounds of the present invention as prepared according to one of the above examples.

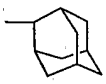
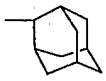
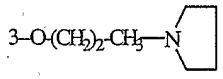
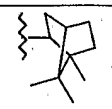
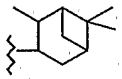
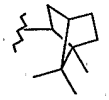
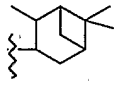
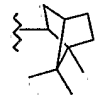
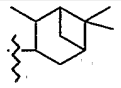
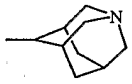
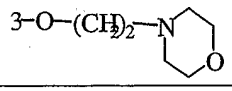
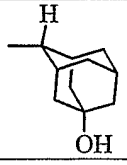
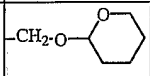
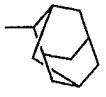
Table 1

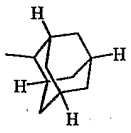
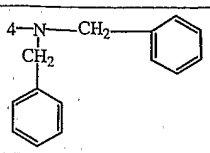
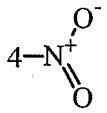
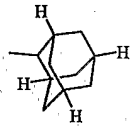
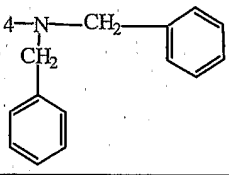
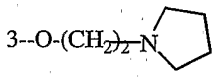
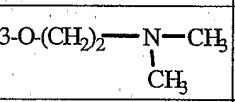
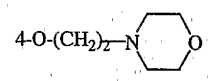
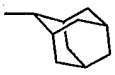
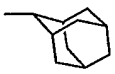


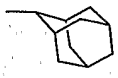
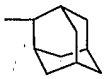
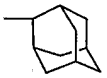
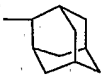
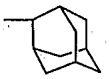
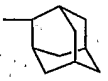
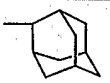
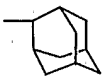
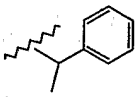
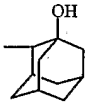
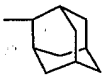
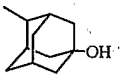
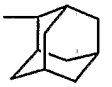
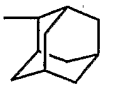
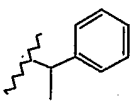
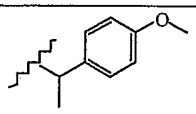
Co. No.	Ex No.	R^1	R^2	R^1 R^2	----R^3	T	Physical data
16	B3	-	-	-$(CH_2)_3$-		-	
17	B13	-	-	-$(CH_2)_2$-	-$C(CH_3)_3$	-	
18	B13	-	-	-$(CH_2)_2$-	-$C(CH_3)_2$-CH_2--$C(CH_3)_3$	-	
19	B13	-	-	-$(CH_2)_2$-		-	
20	B13	-	-	-$(CH_2)_2$-		-	
21	B13	-	-	-$(CH_2)_4$-	-$C(CH_3)_3$	-	
22	B13	-	-	-$(CH_2)_4$-		-	

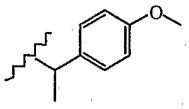
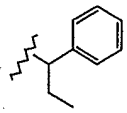
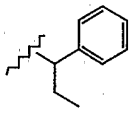
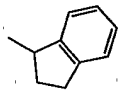
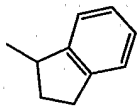
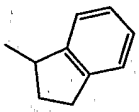
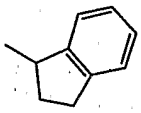
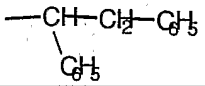
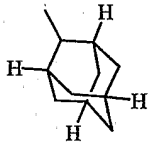
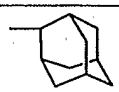
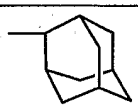
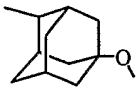
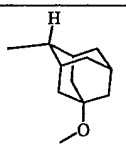
Co. No.	Ex No.	R^1	R^2	R^1 R^2	----R^3	T	Physical data
23	B13	-	-	$-(CH_2)_4-$		-	
24	B13	-	-	$-(CH_2)_4-$		-	
25	B13	-	-	$-(CH_2)_5-$		-	
26	B13	-	-	$-(CH_2)_5-$		-	
1	B1	CH_3	CH_3	-		4-Cl	
27	B1	-	-	$-(CH_2)_2-$		4-Cl	
28	B1	CH_3	-	-		-	
2	B2	CH_3	CH_3	-		-	
29	B1	C_2H_5	-	-		-	
30	B1	-	-	-		-	
31	B14	-	-	$-(CH_2)_2-$		-	
32	B1	-	-	$-(CH_2)_2-$		-	
33	B14	-	-	$-(CH_2)_2-$		-	
34	B14	-	-	$-(CH_2)_2$		-	
35	B14	-	-	$-(CH_2)_4-$		-	
36	B14	-	-	$-(CH_2)_4-$		-	
37	B14	-	-	$-(CH_2)_6-$		-	

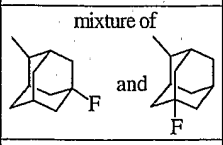
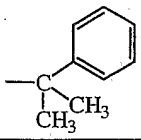
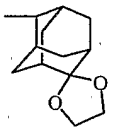
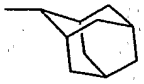
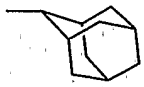
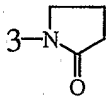
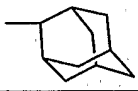
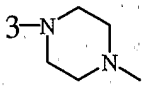
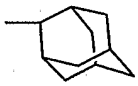
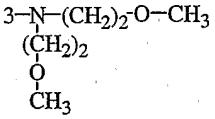
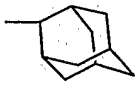
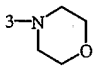
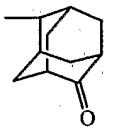
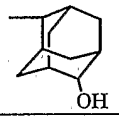
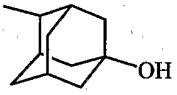
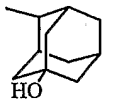
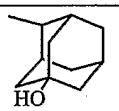
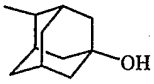
Co. No.	Ex No.	R^1	R^2	R^1 R^2	----R^3	T	Physical data
38	B1	-	-	$-(CH_2)_4-$		-	
39	B1	-	-	$-(CH_2)_3-$		4-Cl	
40	B2	-	-	$-(CH_2)_3-$		-	
41	B1	CH_3	CH_3	-		4-F	-
42	B1		-	-		-	
43	B1	CH_3O	-	-		-	
44	B1		$-C(CH3)_3-O-$ CO-NH	-		-	
45	B1	CH_3	CH_3	-		-	
46	B1	CH_3	CH_3	-		-	
4	B4	CH_3	CH_3	-		3-OCH_3	
47	B4	CH_3	CH_3	-		4-OCH_3	
48	B4	CH_3	CH_3	-		-	
49	B1	-	-	$-(CH_2)_2-$		-	
5	B4	CH_3	CH_3	-		3-OH	
50	B1	$-NH_2$	-	-		-	
51	B1	$-NH_2$	-	-		-	isomeric form of comp 50

Co. No.	Ex No.	R^1	R^2	R^1 R^2	----R^3	T	Physical data
52	B1	CH_3	CH_3	-		4 -$N(CH_3)_2$	
53	B5	CH_3	CH_3	-		3-O-$(CH_2)_2$-CH_3	
54	B5	CH_3	CH_3	-			
55	B14	-	-	-$(CH_2)_2$-		-	
56	B14	-	-	-$(CH_2)_2$-		-	
57	B14	-	-	-$(CH_2)_4$-		-	
58	B14	-	-	-$(CH_2)_4$-		-	
59	B14	-	-	-$(CH_2)_5$-		-	
60	B14	-	-	-$(CH_2)_5$-		-	
61	B1	-	-	-$(CH_2)_2$-		-	
62	B1	CH_3	CH_3	-		-	
63	B1	CH_3	CH_3	-		-	
64	B1	-	-	-$(CH_2)_2$-		-	
6	B4	CH_3	CH_3	-		3-O-$(CH_2)_2$-COOH	
65	B5	CH_3	CH_3	-			
9	B6	CH_3	CH_3	-		-	
66	B1		-	-		-	

Co. No.	Ex No.	R^1	R^2	R^1 R^2	----R^3	T	Physical data
67	B1	CH_3	CH_3	-			
68	B1	CH_3	-	-			
69	B1	-	-	-			
70	B4	CH_3	CH_3	-		4-OH	
71	B5	CH_3	CH_3	-			
7	B5	CH_3	CH_3	-			
72	B1	CH_3	CH_3	-		4-O-CH_2-COOH	
73	B5	CH_3	CH_3	-			
74	B4	CH_3	CH_3	-		3-O-CH_3	
75	B4	CH_3	CH_3	-		3-O-CH_3	
76	B1	CH_3	CH_3	-		3-NH_2	
77	B1	CH_3	CH_3	-		3-NH-CH_3	
78	B1	CH_3	CH_3	-		3-$N(CH_3)_2$	
79	B1	CH_3	CH_3	-		4-NH_2	
80	B1	CH_3	CH_3	-		4-NH-CH_3	
81	B1	CH_3	CH_3	-		4-$N(CH_3)$-(CH_2)-C_6H_5	

Co. No.	Ex No.	R^1	R^2	R^1 R^2	----R^3	T	Physical data
82	B1	$-N(CH_3)_2$	-	-		-	
83	B1	CH_3	CH_3	-		3-Cl	
84	B1	CH_3	CH_3	-		3-F	
85	B1	CH_3	CH_3	-		3-CF_3	
86	B1	CH_3	CH_3	-		3,4 $(-OCH_3)_2$	
87	B1	CH_3	CH_3	-		2,4 -F_2	
88	B1	CH_3	CH_3	-		2,5 -F_2	
89	B1	CH_3	CH_3	-		3-CH_3	
90	B1	CH_3	CH_3	-		-	
91	B1	CH_3	CH_3	-		-	
92	B5	CH_3	CH_3	-		3-O-$(CH_2)_3$-$N(CH_3)_2$	
8	B6	CH_3	CH_3	-		-	
93	B1	CH_3	CH_3	-		2,5 (-O-CH_3)	
94	B1	CH_3	CH_3	-		2-O-C_6H_5	
95	B1	CH_3	CH_3	-		3,5 F_2	
96	B3	CH_3	CH_3	-		-	isomeric form of comp 90
97	B3	CH_3	CH_3	-		-	

Co. No.	Ex No.	R^1	R^2	R^1 R^2	----R^3	T	Physical data
98	B3	CH_3	CH_3	-		-	isomeric form of comp 97
99	B3	CH_3	CH_3	-		-	
100	B3	CH_3	CH_3	-		-	isomeric form of comp 99
101	B3	CH_3	CH_3	-		-	
102	B3	CH_3	CH_3	-		-	isomeric form of comp 101
103	B3	CH_3	CH_3	-		-	isomeric form of comp 102
104	B3	CH_3	CH_3	-		-	isomeric form of comp 103
105	B3	CH_3	CH_3	-		-	
106	B1	CH_3	CH_3	-		2,4 Cl_2	
3	B1	CH_3	CH_3	-		3,5 $(CH_3)_2$	
107	B1	CH_3	CH_3	-		3-NH-CO-$(CH_2)_3$-Cl	
108	B6	CH_3	CH_3	-		-	
109	B6	CH_3	CH_3	-		-	

Co. No.	Ex No.	R^1	R^2	R^1 R^2	----R^3	T	Physical data
110	B3	CH_3	CH_3	-		-	
111	B3	CH_3	CH_3	-		-	
12	B9	CH_3	CH_3	-		-	
112	B4	CH_3	CH_3	-		3-NH-CO-CH_3	
113	B1	CH_3	CH_3	-			
114	B5	CH_3	CH_3	-			
115	B5	CH_3	CH_3	-			
116	B5	CH_3	CH_3	-			
13	B10	CH_3	CH_3	-		-	
14	B11	CH_3	CH_3	-		-	
117	B6	CH_3	CH_3	-		3-O-CH_3	
118	B6	CH_3	CH_3	-		3-O-CH_3	
119	B6	CH_3	CH_3	-		3-CH_3	pound
120	B6	CH_3	CH_3	-		3-CH_3	

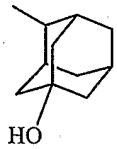
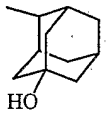
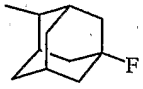
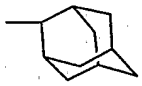
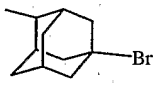
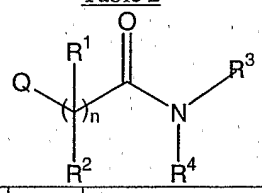
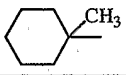
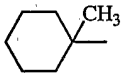
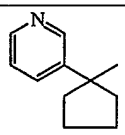
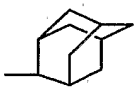
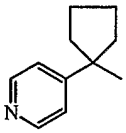
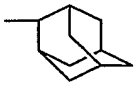
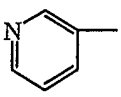
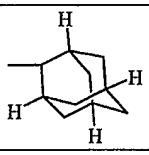
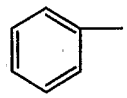
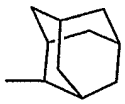
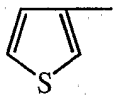
Co. No.	Ex No.	R^1	R^2	R^1 R^2	----R^3	T	Physical data
121	B6	CH_3	CH_3	-		3,5 $(-CH_3)_2$	
122	B6	CH_3	CH_3	-		3,5 $(-CH_3)_2$	isomeric form of comp121
10	B7	CH_3	CH_3	-		-	
123	B1	CH_3	CH_3	-		3-$N(CH_3)$-CO-CH_3	
11	B8	CH_3	CH_3	-		3-OH	

Table 2



Co. No.	Ex. No.	Q	n	R^1	R^2	R^3	R^4	Physical data
124	B3		0	-	-	H		
125	B3		0		-	-		
126	B1		0	-	-	H		
127	B1		0	-	-	H		
128	B6		1	CH_3	CH_3	H		

129	B1		2	-N(CH_3)$_2$	H	H		
130	B1		1	H	H	H		
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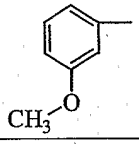
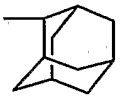
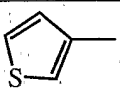
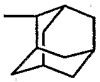
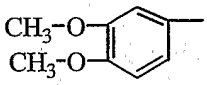
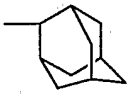
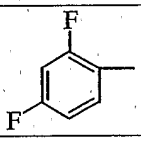
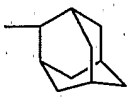
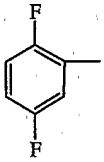
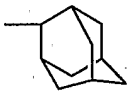
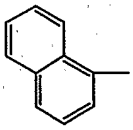
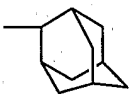
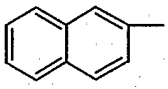
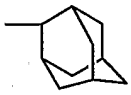
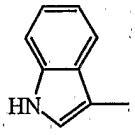
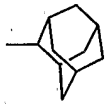
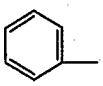
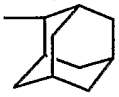
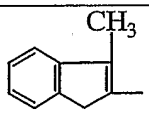
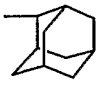
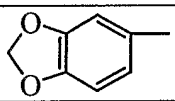
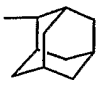
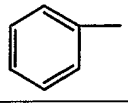
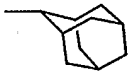
132	B3		1	CH_3	CH_3	CH_3		
133	B1		1	CH_3	CH_3	H		
134	B1		1	CH_3	CH_3	H		
135	B1		1	CH_3	CH_3	H		
136	B1		1	CH_3	CH_3	H		
137	B1		1	CH_3	CH_3	H		
138	B1		1	CH_3	CH_3	H		
139	B1		1	H	H	H		
140	B1		2	CH_3	H	H		
141	B1		0	-	-	H		
142	B1		1	CH_3	CH_3	H		
143	B1		2	CH_3	CH_3	H		

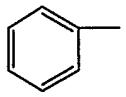
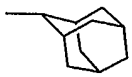
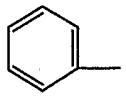
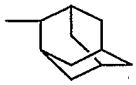
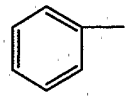
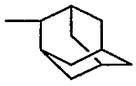
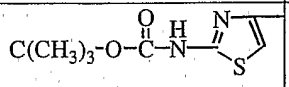
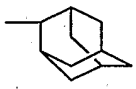
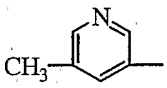
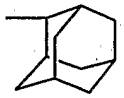
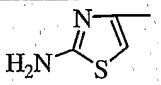
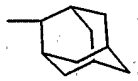
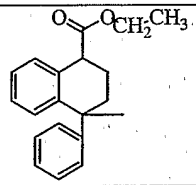
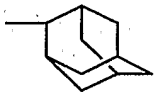
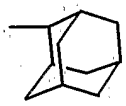
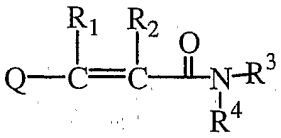
144	B1		2	CH_3	CH_3	H		
145	B1		0	-	-	H		
146	B1		1	=O	-	H		
147	B1		1	CH_3	CH_3	H		
148	B6		1	CH_3	CH_3	H		
149	B6		1	CH_3	CH_3	H		
150	B4		0	-	-	H		
172	B1	2,5 methoxy-phenyl	1	CH_3	CH_3	H		

Table 3



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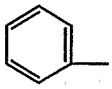
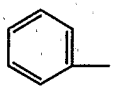
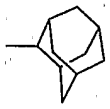
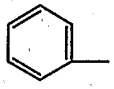
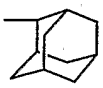
151	B1		H	CH_3	H		
152	B1		H	H	H		
153	B1		CH_3	H	H		

C. Pharmacological examples

Example C.1 : Enzymatic assays to test the effect of compounds on 11b-hydroxysteroid dehydrogenase type 1 and type 2

The effects of compounds on 11b-HSD1 dependent conversion of cortisone into cortisol (**reductase** activity) was studied in a reaction mixture containing 30 mM Tris-HCl buffer pH 7.2, 180 µM NADPH, 1mM EDTA, 2 µM cortisone, 1 µl drug and/or solvent and 11 µg recombinant protein in a final volume of 100 µl.

The effect on the 11b-HSD1-**dehydrogenase** activity (conversion of cortisol into cortisone) was measured in a reaction mixture containing 0.1M sodium phosphate buffer pH 9.0, 300 µM NADP, 25 µM cortisol, 1 µl drug and/or solvent and 3.5 µg recombinant protein in a final volume of 100 µl.

The effects on the 11b-HSD2 dependent **dehydrogenase** activity was studied in a reaction mixture containing 0.1M sodium phosphate buffer pH 7.5, 300 µM NAD, 100 nM cortisol (of which 2 nM is 3H-radio labelled), 1 µl drug and/or solvent and 2.5 µg recombinant protein in a final volume of 100 µl.

All incubations were performed for 45 min at 37C in a water bath. The reaction was stopped by adding 100 µl acetonitrile containing 20 µg corticosterone as internal standard. After centrifugation, the product formation was analysed in the supernatant by HPLC on a Hypersyl BDS-C18 column using 0.05 mM ammonium acetate / methanol (50/50) as solvent. In all of the aforementioned assays, the drugs to be tested were taken from a stock solution and tested at a final concentration ranging from - 10^{-5}M to 3.10^{-9}M. From the thus obtained dose response curves, the pIC50 value was calculated and scored as follows; Score 1 = pIC50 value < 5, Score 2 = pIC50 value in the range of 5 to 6, Score 3 = pIC50 value >6. Some of the thus obtained results are summarized in the table below. (in this table NT stands for Not Tested).

Example C2 : Cellular assays to test the effect of compounds on 11b-hydroxysteroid dehydrogenase type 1 and type 2

The effects on 11b-HSD1 activity was measured in differentiated 3T3-L1 cells and rat hepatocytes.

Mouse fibroblast 3T3-L1 cells (ATCC-CL-173) were seeded at a density of 16500 cells / ml in 12 well plates and grown for 7 days in DMEM medium (supplemented with 10 % heat inactivated foetal calf serum, 2mM glutamine and 25 mg gentamycin) at 37C in a humidified 5% CO2 atmosphere. Medium was refreshed twice a week. Fibroblasts were differentiated into adipocytes at 37C in a 5% CO2 humidified atmosphere in growth medium containing 2µg/ml insulin, 55 µg/ml IBMX and 39.2 µg/ml dexamethasone.

Primary hepatocytes from male rats were seeded on BD-Biocoat Matrigel matrix multiwell plates at a density of 250000 cells /well and incubated for 10 days at 37C in a 5% CO2 humidified atmosphere in DMEM-HAM's F12 medium containing 5% Nu-serum, 100 U/ml penicillin, 100 µg/ml streptomycin , 0.25 µg/ml amphotericin B, 50 µg/ml gentamycin sulfate, 5µg/ml insulin and 392 ng/ml dexamethasone. Medium was refreshed 3 times a week.

Following a 4 hour pre-incubation with test compound, 0.5 µCi ^{3}H-cortisone or dehydrocorticosterone, was added to the cultures. One hour later, the medium was extracted on Extrelut^{3}-columns with 15 ml diethyl ether and the extract was analysed by HPLC as described above.

The effects on 11b-HSD2 activity was studied in HepG2 and LCC-PK1-cells

HepG2-cells (ATCC HB-8065) were seeded in 12 well plates at a density of 100,000 cells/ml and grown at 37C in a humidified 5% CO2 atmosphere in MEM-Rega-3 medium supplemented with 10% heat inactivated foetal calf serum, 2 mM L-glutamine and sodium bicarbonate). Medium was refreshed twice a week.

Pig kidney cells (LCC-PK1, ATCC CRL-1392) were seeded at a density of 150,000 cells /ml in 12 well plates and grown at 37C in a humidified 5% CO2 atmosphere in Medium 199 supplemented with Earls modified salt solution, 100 U/ml penicillin, 100 µg/ml streptomycin and 10 % foetal calf serum. Medium was refreshed twice a week. Twenty four hours prior to the onset of the experiment, medium was changed by medium containing 10% charcoal stripped foetal calf serum.

Following a 4 hour pre-incubation with test compound, 0.5 µCi ^{3}H-cortisol or corticosterone, was added to the cultures. One hour later, the medium was extracted on Extrelut^{3}-columns with 15 ml diethyl ether and the extract was analysed by HPLC as described above.

As for the enzymatic assays, the compounds to be tested were taken from a stock solution and tested at a final concentration ranging from - 10^{-5}M to 3.10^{-9}M. From the thus obtained dose response curves, the pIC50 value was calculated and scored as follows; Score 1 = pIC50 value < 5, Score 2 = pIC50 value in the range of 5 to 6, Score 3 = pIC50 value >6. Some of the thus obtained results are summarized in the table below. (in this table NT stands for Not Tested).

Example Number	Compound Number	[C1] HSD1-prot Reduct	[C1] HSD2 cellular HepG2	[C2] HSD1 cellular 3T3-L1	[C2] HSD2 cellular HepG2
		Score	Score	Score	Score
B3	16	NT	1	2	1
B13	19	NT	1	2	1
B13	22	NT	1	2	1
B1	1	NT	1	3	1

Example Number	Compound Number	[C1] HSD1-prot Reduct	[C1] HSD2 cellular HepG2	[C2] HSD1 cellular 3T3-L1	[C2] HSD2 cellular HepG2
		Score	Score	Score	Score
B1	28	NT	NT	3	1
B1	29	NT	NT	3	1
B1	30	NT	NT	3	1
B14	31	NT	1	3	1
B14	35	NT	1	2	1
B1	41	3	1	3	1
B1	43	3	1	2	1
B1	46	1	1	3	1
B4	47	3	1	3	1
B4	48	1	1	3	1
B1	126	3	1	3	1
B1	127	1	1	3	1
B4	5	3	1	3	1
B1	50	1	1	2	1
B1	51	1	1	2	1
B1	52	1	1	3	1
B5	53	1	1	3	1
B5	54	2	1	3	1
B14	55	NT	1	3	1
B14	56	NT	1	2	1
B14	57	NT	1	2	1
B1	64	NT	1	2	1
B4	6	2	1	3	1
B6	128	3	1	3	1
B1	129	2	1	2	1
B1	68	2	1	2	1
B5	71	3	NT	3	1
B5	7	1	NT	3	1
B1	72	2	1	3	1
B5	73	1	1	3	1
B4	74	3	1	3	1

Example Number	Compound Number	[C1] HSD1-prot Reduct	[C1] HSD2 cellular HepG2	[C2] HSD1 cellular 3T3-L1	[C2] HSD2 cellular HepG2
		Score	Score	Score	Score
B1	133	1	1	3	1
B1	77	1	2	3	1
B1	78	3	2	3	1
B1	81	3	NT	2	1
B1	84	1	1	3	1
B1	85	1	1	3	1
B1	86	1	1	3	1
B1	87	1	1	3	1
B1	88	1	1	3	1
B1	89	3	1	3	1
B1	137	3	1	3	1
B1	138	1	1	3	1
B1	91	1	1	3	1
B1	151	2	1	3	1
B1	153	2	1	3	1
B1	140	3	1	3	1
B1	141	3	1	3	1
B1	92	3	1	3	1
B1	93	3	NT	3	1
B1	173	1	NT	3	1
B1	95	1	NT	3	1
B1	144	3	NT	3	1
B1	106	1	NT	3	1
B1	3	3	NT	3	1
B6	109	3	NT	3	1

D. Composition examples

The following formulations exemplify typical pharmaceutical compositions suitable for systemic or topical administration to animal and human subjects in accordance with the present invention.

"Active ingredient" (A.I.) as used throughout these examples relates to a compound of formula (I) or a pharmaceutically acceptable addition salt thereof.

Example D.1 : film-coated tablets

Preparation of tablet core

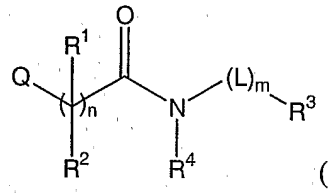
A mixture of A.I. (100 g), lactose (570 g) and starch (200 g) was mixed well and thereafter humidified with a solution of sodium dodecyl sulfate (5 g) and polyvinyl-pyrrolidone (10 g) in about 200 ml of water. The wet powder mixture was sieved, dried and sieved again. Then there was added microcrystalline cellulose (100 g) and hydrogenated vegetable oil (15 g). The whole was mixed well and compressed into tablets, giving 10.000 tablets, each comprising 10 mg of the active ingredient.

Coating

To a solution of methyl cellulose (10 g) in denaturated ethanol (75 ml) there was added a solution of ethyl cellulose (5 g) in CH_2Cl_2 (150 ml). Then there were added CH_2Cl_2 (75 ml) and 1,2,3-propanetriol (2.5 ml). Polyethylene glycol (10 g) was molten and dissolved in dichloromethane (75 ml). The latter solution was added to the former and then there were added magnesium octadecanoate (2.5 g), polyvinyl-pyrrolidone (5 g) and concentrated color suspension (30 ml) and the whole was homogenated. The tablet cores were coated with the thus obtained mixture in a coating apparatus.

Claims

1. A compound having the formula



(I)

the *N*-oxide forms, the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof, wherein

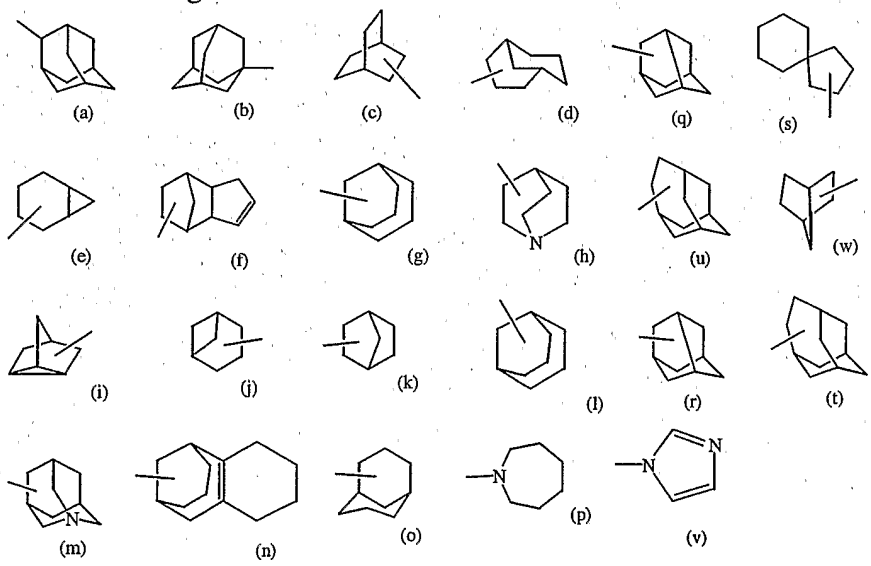
n represents an integer being 0, 1 or 2;

m represents an integer being 0 or 1;

R^1 and R^2 each independently represents hydrogen, C_{1-4}alkyl, NR^9R^{10}, C_{1-4}alkyloxy, Het^3-O-C_{1-4}alkyl; or

R^1 and R^2 taken together with the carbon atom with which they are attached form a carbonyl, or a C_{3-6}cycloalkyl; and where n is 2, either R^1 or R^2 may be absent to form an unsaturated bond;

R^3 represents hydrogen, Ar^1, C_{1-8}alkyl, C_{6-12}cycloalkyl or a monovalent radical having one of the following formulae



wherein said Ar^1, C_{6-12}cycloalkyl or monovalent radical may optionally be substituted with one, or where possible two or three substituents selected from the

group consisting of C_{1-4}alkyl, C_{1-4}alkyloxy, phenyl, halo, oxo, carbonyl, 1,3-dioxolyl or hydroxy;

R^4 represents hydrogen or C_{1-4}alkyl;

Q represents C_{3-8}cycloalkyl, Het^1 or Ar^2, wherein said C_{3-8}cycloalkyl, Het^1 or Ar^2 are optionally substituted with one or where possible more substituents selected from halo, C_{1-4}alkyl, C_{1-4}alkyloxy, hydroxy, nitro, Het^4, phenyl, phenyloxy, C_{1-4}alkyloxycarbonyl, hydroxycarbonyl, NR^5R^6, C_{1-4}alkyloxy substituted with one or where possible two or three substituents each independently selected from hydroxycarbonyl, Het^2 and NR^7R^8, and C_{1-4}alkyl substituted with one or where possible two or three halo substituents;

R^5 and R^6 are each independently selected from hydrogen, C_{1-4}alkyl, C_{1-4}alkyloxyC_{1-4}alkyl, C_{1-4}alkyloxycarbonyl, C_{1-4}alkylcarbonyl, C_{1-4}alkylcarbonyl substituted with one or where possible two or three substituents each independently selected from halo, C_{1-4}alkyl, and C_{1-4}alkyloxy or R^5 and R^6 each independently represent C_{1-4}alkyl substituted with phenyl;

R^7 and R^8 are each independently selected from hydrogen or C_{1-4}alkyl;

R^9 and R^{10} are each independently selected from hydrogen, C_{1-4}alkyl or C_{1-4}alkyloxycarbonyl;

L represents C_{1-4}alkyl optionally substituted with one or where possible more substituents selected from C_{1-4}alkyl or phenyl;

Het^1 represents a heterocycle selected from pyridinyl, piperinidyl, pyrimidinyl, pyrazinyl, piperazinyl, pyridazinyl, indolyl, isoindolyl, indolinyl, furanyl, benzofuranyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, benzothiophenyl, thiophenyl, 1,8-naphthyridinyl, 1,6-naphthyridinyl, quinolinyl, isoquinolinyl, quinoxalinyl, quinazolinyl, phthalazinyl, or 1,3-benzodioxolyl.;

Het^2 represents a monocyclic heterocycle selected from piperidinyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, piperazinyl, 2H-pyrrolyl, pyrrolyl, 2-pyrrolinyl, 3-pyrrolinyl, pyrrolidinyl, or morpholinyl;

Het^3 represents a monocyclic heterocycle selected from 2H-pyranyl, 4H-pyranyl, furanyl, tetrahydro-2H-pyranyl, pyridinyl, piperidinyl, or furanyl;

Het^4 represents a monocyclic heterocycle selected from pyridazinyl, pyrimidinyl, pyrrolidinyl, pyrazinyl, piperazinyl or morpholinyl, said Het^4 optionally being substituted with one or where possible two or more substituents each idependently selected from hydroxy, carbonyl, C_{1-4}alkyl or C_{1-4}alkyloxy;

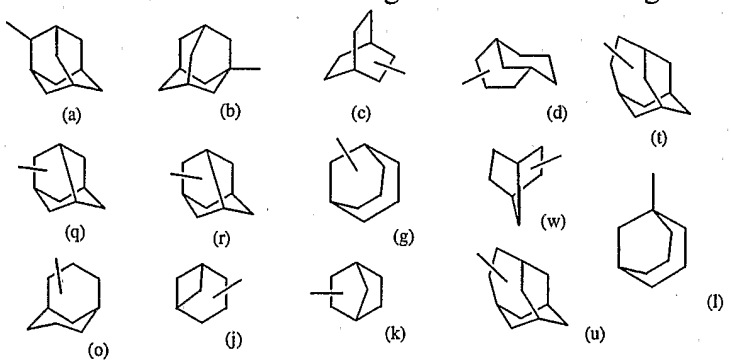
Ar^1 represents carbocyclic radicals containing one or more rings selected from the group consisting of phenyl, biphenyl, indenyl, 2,3-dihydroindenyl, fluorenyl, 5,6,7,8-tetrahydronaphtyl or naphtyl

Ar^2 represents carbocyclic radicals containing one or more rings selected from the group consisting of phenyl, biphenyl, indenyl, 2,3-dihydroindenyl, fluorenyl, 5,6,7,8-tetrahydronaphtyl or naphtyl.

2. A compound according to claim 1 wherein;
n represents an integer being 1 or 2 provided that when n represents 2, Q represents Het^1 or Ar^2, wherein said Het^1 or Ar^2 are optionally substituted with one or where possible more substituents selected from halo, C_{1-4}alkyl, C_{1-4}alkyloxy, hydroxy, nitro, Het^4, phenyl, phenyloxy, hydroxycarbonyl, NR^5R^6, C_{1-4}alkyloxy substituted with one or where possible two or three substituents each independently selected from hydroxycarbonyl, Het^2 and NR^7R^8, and
C_{1-4}alkyl substituted with one or where possible two or three halo substituents

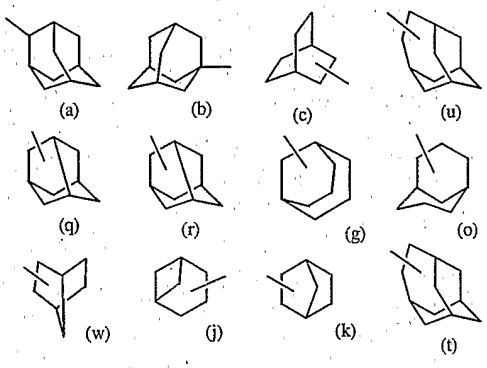
3. A compound according to anyone of claims 1 or 2 wherein;
Het^1 represents a heterocycle selected from piperinidyl, pyrimidinyl, pyrazinyl, piperazinyl, pyridazinyl, indolyl, isoindolyl, indolinyl, benzofuranyl, benzothiophenyl, 1,8-naphthyridinyl, 1,6-naphthyridinyl, quinazolinyl, phthalazinyl, or 1,3-benzodioxolyl

4. A compound according to claim 1 wherein;
Q represents phenyl, said phenyl optionally substituted with one or two substituents selected from the halo, preferably chloro or fluor, or C_{1-4}alkyloxy preferably methoxy;
n is 1;
m is 0;
R^1 and R^2 represent C_{1-4}alkyl, preferably methyl;
R^1 and R^2 taken together with the carbon atom with which they are attached form a C_{3-6}cycloalkyl, preferably cyclopropyl;
R^4 represents hydrogen;
R^3 represents a monovalent radical having one of the following formulae



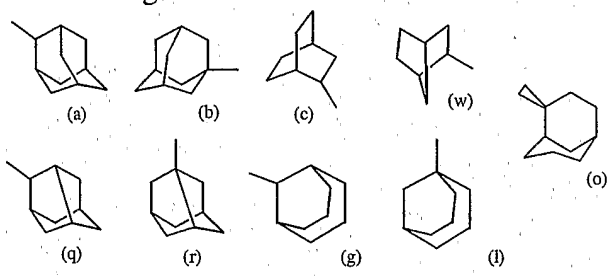
wherein said monovalent radical may optionally be substituted with one or where possible two or three substituents selected from halo, carbonyl, hydroxy or C_{1-4}alkyloxy, preferably methoxy.

5. A compound according to claim 1 wherein;
n represents an integer being 1 or 2;
R^1 and R^2 each independently represents hydrogen C_{1-4}alkyl, NR^9R^{10}; or
R^1 and R^2 taken together with the carbon atom with which they are attached form a C_{3-6}cycloalkyl; and where n is 2, either R^1 or R^2 may be absent to form an unsaturated double bond;
R^3 represents a C_{6-12}cycloalkyl or a monovalent radical having one of the following formulae



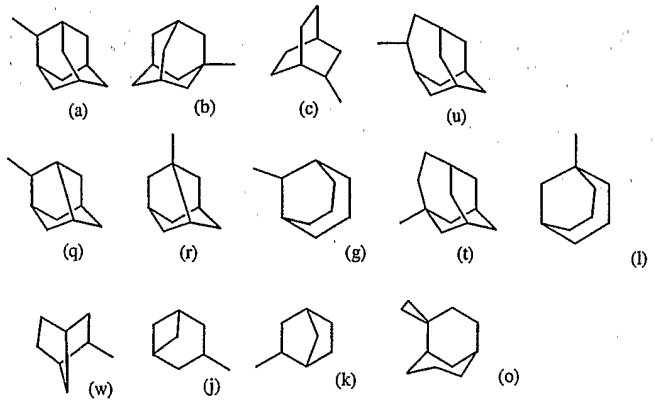
wherein said C_{6-12}cycloalkyl or monovalent radical may optionally be substituted with one, or where possible two, three or more substituents selected from the group consisting of C_{1-4}alkyl, C_{1-4}alkyloxy, halo or hydroxy;
Q represents Het^1 or Ar^2 wherein said Het^1 or Ar^2 are optionally substituted with one or where possible two or more substituents selected from halo, C_{1-4}alkyl, C_{1-4}alkyloxy, hydroxy, NR^5R^6, C_{1-4}alkyloxy substituted with one or where possible two, three or more substituents each independently selected from hydroxycarbonyl, Het^2 and NR^7R^8, and C_{1-4}alkyl substituted with one or where possible two or three halo substituents;
R^5 and R^6 each independently represent hydrogen or C_{1-4}alkyl;
R^9 and R^{10} each independently represent hydrogen or C_{1-4}alkyloxycarbonyl;
L represents C_{1-4}alkyl;
Het^1 represents a heterocycle selected from pyridinyl, piperidinyl, thiophenyl or 1,3-benzodioxol;
Het^2 represents pyridinyl, pyrrolidinyl or morpholinyl;
Ar^2 represents phenyl, naphtyl or indenyl.

6. A compound according to claim 5 wherein;
R^1 and R^2 each independently represents hydrogen C_{1-4}alkyl; or
R^1 and R^2 taken together with the carbon atom with which they are attached form a C_{3-6}cycloalkyl; and where n is 2, either R^1 or R^2 may be absent to form an unsaturated double bond;
R^3 represents a C_{6-12}cycloalkyl, preferably cylo-octanyl or a monovalent radical having one of the following formulae



wherein said C_{6-12}cycloalkyl or monovalent radical may optionally be substituted with one, or where possible two, three or more substituents selected from the group consisting of C_{1-4}alkyl, C_{1-4}alkyloxy, halo or hydroxy.

7. A compound according to claim 1 wherein
n represents an integer being 1 or 2;
R^1 and R^2 each independently represents hydrogen C_{1-4}alkyl, NR^9R^{10}, C_{1-4}alkyloxy; or
R^1 and R^2 taken together with the carbon atom with which they are attached form a C_{3-6}cycloalkyl; and where n is 2, either R^1 or R^2 may be absent to form an unsaturated double bond;
R^3 represents a C_{6-12}cycloalkyl, preferably selected from cylo-octanyl and cyclohexyl or R^3 represents a monovalent radical having one of the following formulae



wherein said C_{6-12}cycloalkyl or monovalent radical may optionally be substituted with one, or where possible two, three or more substituents selected from the group consisting of C_{1-4}alkyl, C_{1-4}alkyloxy, halo or hydroxy;
Q represents C_{3-8}cycloalkyl, Het^1 or Ar^2 wherein said Het^1 or Ar^2 are optionally substituted with one or where possible two or more substituents selected from halo, C_{1-4}alkyl, C_{1-4}alkyloxy, hydroxy, nitro, NR^5R^6, C_{1-4}alkyloxy substituted with one or where possible two, three or more substituents each independently selected from hydroxycarbonyl, Het^2 and NR^7R^8, and C_{1-4}alkyl substituted with one or where possible two or three halo substituents, preferably trifluoromethyl;
R^5 and R^6 each independently represent hydrogen, C_{1-4}alkyl, or C_{1-4}alkyl substituted with phenyl;
L represents C_{1-4}alkyl;
Het^1 represents a heterocycle selected from pyridinyl, piperidinyl, or thiophenyl;
Het^2 represents piperidinyl, pyrrolidinyl or morpholinyl;
Ar^2 represents phenyl, naphtyl or indenyl.

8. A compound as claimed in claim 1 wherein the compound is
(1α,2β,3β,5β,7β)-N-(5-hydroxytricyclo[3.3.1.13,7]dec-2-yl)-α,α-dimethyl-benzeneacetamide;
(1α,2β,3β,5β,7β)-N-(5-hydroxytricyclo[3.3.1.13,7]dec-2-yl)-α,α-dimethyl-3-methyl-benzeneacetamide;
(1α,2β,3β,5β,7β)-N-(5-hydroxytricyclo[3.3.1.13,7]dec-2-yl)-α,α-dimethyl-3-methoxy-benzeneacetamide;
(1α,2β,3β,5β,7β)-N-(5-hydroxytricyclo[3.3.1.13,7]dec-2-yl)-α,α-dimethyl-3-hydroxy-benzeneacetamide;
(1α,2β,3β,5β,7β)-N-(5-hydroxytricyclo[3.3.1.13,7]dec-2-yl)-α,α-dimethyl-3,5-dimethyl-benzeneacetamide);
(1α,2β,3β,5β,7β)-N-(5-hydroxytricyclo[3.3.1.13,7]dec-2-yl)-3-(phenylmethoxy)benzeneacetamide;
(1α,2β,3β,5β,7β)-N-(5-hydroxytricyclo[3.3.1.13,7]dec-2-yl)-α,α-dimethyl-3-(carboxymethoxy)-benzeneacetamide;
(1α,2β,3β,5β,7β)-N-(5-hydroxytricyclo[3.3.1.13,7]dec-2-yl)-α,α-dimethyl-3-[2-(4-morpholinyl)ethoxy]-benzeneacetamide;
(1α,2β,3β,5β,7β)-N-(5-fluorotricyclo[3.3.1.13,7]dec-2-yl)-α,α-dimethyl-benzeneacetamide;
(1α,2β,3β,5β,7β)-N-(5-methoxytricyclo[3.3.1.13,7]dec-2-yl)-α,α-dimethyl-benzeneacetamide;

(1α,2α,3β,5β,7β)-N-(5-methoxytricyclo[3.3.1.13,7]dec-2-yl)-α,α-dimethyl-benzeneacetamide;
N-(tricyclo[3.3.1.13,7]dec-2-yl)-α,α-dimethyl-benzeneacetamide;
N-(tricyclo[3.3.1.13,7]dec-2-yl)-α,α-dimethyl-3-(carboxymethoxy)-benzeneacetamide;
N-(tricyclo[3.3.1.13,7]dec-2-yl)-α,α-dimethyl-3-[2-(4-morpholinyl)ethoxy]-benzeneacetamide;
N-(tricyclo[3.3.1.13,7]dec-2-yl)-α,α-dimethyl-3,5-dimethoxy-benzeneacetamide;
N-(tricyclo[3.3.1.13,7]dec-2-yl)-α,α-dimethyl-3-methyl-benzeneacetamide;
N-(tricyclo[3.3.1.13,7]dec-2-yl)-α,α-dimethyl-3-methoxy-benzeneacetamide;
N-(tricyclo[3.3.1.13,7]dec-2-yl)-α,α-dimethyl-3-hydroxy-benzeneacetamide;
N-(tricyclo[3.3.1.13,7]dec-2-yl)-α,α-dimethyl-3,5-dimethyl-benzeneacetamide;
N-(tricyclo[3.3.1.13,7]dec-2-yl)-α,α-dimethyl-4-fluoro-benzeneacetamide;
N-(tricyclo[3.3.1.13,7]dec-2-yl)-1-phenyl-cyclopropanecarboxamide;
N-(tricyclo[3.3.1.13,7]dec-2-yl)-α,α-dimethyl-2,6-difluoro-benzeneacetamide;
or
N-(tricyclo[3.3.1.13,7]dec-2-yl)-α,α-dimethyl-2-thiopheneacetamide; a *N*-oxide, a pharmaceutically acceptable addition salt or a stereochemically isomeric form thereof.

9. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and, as active ingredient, an effective 11β-HSD1 inhibitory amount of a compound as described in any one of claims 1 to 8.

10. A process of preparing a pharmaceutical composition as defined in claim 8, characterized in that, a pharmaceutically acceptable carrier is intimately mixed with an effective 11β-HSD1 inhibitory amount of a compound as described in any one of claims 1 to 8.

11. A compound as claimed in any one of claims 1 to 8 for use as a medicine.

12. Use of a compound as claimed in any one of claims 1 to 8 in the manufacture of a medicament for treating pathologies associated with excess cortisol formation such as for example, obesity, diabetes, obesity related cardiovascular diseases, dementia, cognition, osteoporosis and glaucoma.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/14832

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C233/11 C07C235/36 C07C233/14 C07C233/23 C07C233/58
C07C271/22 C07C237/20 C07C233/41 C07C233/22 C07C237/22
C07C233/32 C07D317/72 C07D295/088 C07D207/12 C07D213/56

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 C07C

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)
EPO-Internal, CHEM ABS Data, BEILSTEIN Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 3 919 313 A (VILLANI FRANK J) 11 November 1975 (1975-11-11) claims; examples ---	1,2,5,7, 9-11
X	LATYPOV S K ET AL: "Determination of the absolute stereochemistry of alcohols and amines by NMR of the group directly linked to the chiral derivatizing reagent" TETRAHEDRON, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 57, no. 11, 10 March 2001 (2001-03-10), pages 2231-2236, XP004230761 ISSN: 0040-4020 page 2233, example 9 --- -/--	1,2,7

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 July 2003	04/08/2003

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	Seufert, G

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/14832

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/165 A61K31/335 A61K31/40 A61K31/44 A61P3/04 A61P3/10

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)

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; TAKAHASHI, TORIZO: "Syntheses of analgesics. XX. Camphane derivatives. 2" retrieved from STN Database accession no. 53:72551 XP002248033 abstract & YAKUGAKU ZASSHI , vol. 79, 1959, pages 162-6, --- -/--	1-3,9-11

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 July 2003	

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	Seufert, G

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Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CROSSFIRE BEILSTEIN 'Online! Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; Database accession no. BRN 209124 XP002248034 abstract & FORSTER, ATTWELL: J. CHEM. SOC., vol. 85, 1904, page 1190 ---	1-3
X	DATABASE CROSSFIRE BEILSTEIN 'Online! Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; Database accession no. Reaction ID 1481005 XP002248035 abstract & SCHROTH W. ET AL.: J. PRAKT. CHEM. , vol. 325, no. 5, 1983, pages 787-802, ---	1-3,5-7
X	DATABASE CROSSFIRE BEILSTEIN 'Online! Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; Database accession no. Reaction ID 127579 XP002248036 abstract & KOETZ; MERKEL: J. PRAKT. CHEM. <2> 113, 1926, page 74 ---	1-3
X	DATABASE CROSSFIRE BEILSTEIN 'Online! Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; Database accession no. BRN 8562669 XP002248037 abstract & STARNES S. ET AL.: J. AMER. CHEM. SOC., vol. 123, no. 20, 2001, pages 4659-69, ---	1,2,5-7
X	DATABASE CROSSFIRE BEILSTEIN 'Online! Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; Database accession no. Reaction ID 378559 XP002248038 abstract & SUGASAWA; OHARA: YAKUGAKU ZASSHI 72, 1952, page 7461 --- -/--	1,2,5-7

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Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CROSSFIRE BEILSTEIN 'Online! Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; Database accession no. BRN 2125777 XP002248039 abstract & OLAH G. A. ET AL.: SYNTHESIS, 1979, pages 274-76, ---	1,2,5-7
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X	DATABASE CROSSFIRE BEILSTEIN 'Online! Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; Database accession no. BRN 2697500 XP002248043 abstract & CAGLIOTI L. ET AL.: J. ORG. CHEM., vol. 33, no. 7, 1968, pages 2979-81, ---	1,2,5-7

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
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Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CROSSFIRE BEILSTEIN 'Online! Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; Database accession no. Reaction ID 1040871 XP002248049 abstract & BONNEKESSEL, J; RUECHARDT, C. : CHEM. BER., 106, 1973, pages 2890-2903, ---	1 —
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Continuation of Box I.2

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty. Attention is drawn to the fact that even such well-known and commercially available compounds like benzamide or nicotinamide fall within the scope of the claims. So many documents were retrieved that it is impossible to determine which parts of the claim(s) may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, a meaningful search over the whole breadth of the claims is impossible.
Additionally, the claims relate to an extremely large number of possible compounds, while support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found for only a small proportion of the compounds claimed.

Consequently, the search has been restricted to compounds of formula (I) whereby neither R1 nor R2 may be hydrogen, L is a linker of 0-8 CH2, R3 is a condensed carbocyclic ring system of the formulae (a) to (l), (n), (o), (q) to (u) and (w) as well as to compounds of claim 8, which do not fall within this definition. The other variables are as defined in claim 1. All relevant compounds, if any, falling within this groups have been cited.
Search and search report may therefore be considered complete for claims 4 and 8 as well as claims 9-12 as far as they relate to compounds according to claims 4 and 8. For claims 1-3 and 5-7 as well as the claims 9-12 insofar as they relate to compounds of claims 1-3 and 5-7 the search report merely cites an arbitrary selection of the vast amount of novelty destroying documents.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

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Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internat[illegible] Application No
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