

N-2 ADAMANTANYL-2-PHENOXY-ACETAMIDE DERIVATIVES AS 11-BETA HYDROXYSTEROID DEHYDROGENASE INHIBITORS

5 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).

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Glucocorticoids and 11 β -HSD1 are known to be important factors in differentiation of adipose stromal cells into mature adipocytes. In the visceral stromal cells of obese patients, 11 β -HSD1 mRNA level is increased compared with subcutaneous tissue. Further, adipose tissue over-expression of 11 β -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, 11 β -HSD1 is most likely be involved in the development of visceral obesity and the metabolic syndrome.

20 Inhibition of 11 β -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 11 β -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.

30 The impact of the effect of decreased 11 β -HSD1 activity is highlighted by the β -HSD1 knockout mouse that has increased plasma levels of endogenous active glucocorticoid, but inspite of this remains protected from insulin resistance induced by stress and obesity. Additionally, these knockout mouse present an anti-atherogenic plasmid lipid profile and benefits from decreased age-related cognitive impairment.

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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.

11 β -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 11 β -HSD1 was present. Carbenoxolone administration to patients resulted in a significant decrease in intra-ocular pressure (S. Rauz et al. (2001), Invest. Ophthalmol. 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 11 β -HSD inhibitors, with a high selectivity for 11 β -HSD1, and the use thereof in treating pathologies associated with excess cortisol formation, i.e. disorders where a decreased level of active glucocorticoid is desirable, such as metabolic syndrome, type 2 diabetes, impaired glucose tolerance (IGT), impaired fasting glucose (IFG), dyslipidemia, hypertension, obesity, diabetes, obesity related cardiovascular diseases, arteriosclerosis, atherosclerosis, myopathy, osteoporosis, neurodegenerative and psychiatric disorders, stress related disorders and glaucoma. As shown hereinbelow, the 2-adamantanylacetamides of formula (I) were found to be useful as a medicine, in particular in the manufacture of a medicament for the treatment of pathologies associated with excess cortisol formation.

Salim S.S. et al. (J.Chem.Eng. Data (1984), 29, 229-231) provides the synthesis of some new *N*-(3-methyl-2-quinoxaloyl) amino alcohols and in particular discloses 2-Quinoxalinecarboxamide, 3-methyl-*N*-tricyclo[3.3.1.1^{3,7}]dec-2-yl-. The 1,4-dioxides of said quinoxalines were shown to have antibacterial activity, where the parent quinoxalines were inactive as antibacterial agents.

Masamune H. et al. (PCT International patent application WO 01/23399) discloses *N*-2-adamantyl-2-phenoxy-acetamides as intermediates in the preparation of nucleosides as adenosine receptors, antidiabetics, enzyme inhibitors and for the treatment of ischemia. See in particular scheme IV, p41, and the examples 70, 73, B32 and B35.

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However, in none of the above-cited documents the therapeutic application of the *N*-2-adamantyl-acetamide derivatives of the present invention has been disclosed.

The use of adamantyl acetamides as 11- β hydroxysteroid dehydrogenase inhibitors was disclosed in Linders J. et al (PCT International patent application WO 2004/056745). Compared to the compounds disclosed in said publication, the compounds of the present invention differ in that they comprise an additional heteroatom, represented as – Z- in formula (I) below. The presence of this additional heteroatom, together with the particular backbone configuration (represented in bold hereinbelow), significantly improved the overall activity of the adamantyl acetamides as 11- β hydroxysteroid dehydrogenase inhibitors (Figure 1).

Figure 1 provides a comparison of the cellular 3T3-L1 activity (pIC50 values - see example C hereinbelow) of the bicyclic adamantyl acetamides disclosed in PCT International patent application WO 2004/056745 with the bicyclic ethers of the present application and the single ethers of the present application.

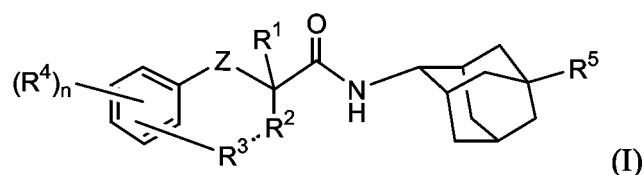
The pharmaceutical use of substituted amides for modulating the activity of 11 β -HSD1 either alone or in combination with a glucocorticoid receptor agonist or an antihypertensive agent has been disclosed in PCT International patent applications WO2004/089470, WO 2004/089415 and WO 2004/089416. In said patent publications only one compound, i.e *N*-adamantan-2-yl-2-o-tolyloxy-acetamide, within the scope of the present application has been disclosed and is accordingly disclaimed from the first and further medical use claims in the present application. Further compounds within the scope of the present application, but previously not described for use as a medicine are;

Cas Number	CA Index Name
[721907-95-5]	Acetamide, N-tricyclo[3.3.1.1 ^{3,7}]dec-2-yl-2-[3-(trifluoromethyl)-phenoxy]- (9CI)
[701966-64-5]	Acetamide, 2-[4-(1-methylpropyl)phenoxy]-N-tricyclo[3.3.1.1 ^{3,7}]dec-2-yl- (9CI)

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- [693829-07-1] Butanamide, 2-phenoxy-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)
- [693264-73-2] Acetamide, 2-(2-bromo-4-ethylphenoxy)-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)
- [690979-00-1] Acetamide, N-tricyclo[3.3.1.1^{3,7}]dec-2-yl-2-(2,3,5-trimethylphenoxy)- (9CI)
- 5 [667874-33-1] Acetamide, 2-(2,3-dimethylphenoxy)-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)
- [638150-96-6] Acetamide, 2-(2,4-dibromo-6-methylphenoxy)-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)
- 10 [638150-94-4] Acetamide, 2-(4-chloro-2-methylphenoxy)-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)
- [638150-88-6] Acetamide, 2-(3,5-dimethylphenoxy)-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)
- [638150-85-3] Acetamide, 2-(2-chlorophenoxy)-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)
- 15 [638150-82-0] Acetamide, 2-[4-(1,1-dimethylethyl)phenoxy]-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)
- [638150-79-5] Acetamide, 2-[(4-chlorophenyl)thio]-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)
- [593240-71-2] Acetamide, 2-[5-methyl-2-(1-methylethyl)phenoxy]-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)
- 20 [593240-69-8] Acetamide, 2-(4-ethylphenoxy)-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)
- [496921-25-6] Acetamide, 2-(2,5-dimethylphenoxy)-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)
- [461446-43-5] Acetamide, 2-(3,4-dimethylphenoxy)-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)
- 25 [438477-86-2] Acetamide, 2-(2,4-dimethylphenoxy)-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)
- [433948-36-8] Acetamide, 2-(4-bromo-2-methylphenoxy)-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)
- 30 [433947-37-6] Acetamide, 2-(4-bromo-3,5-dimethylphenoxy)-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)
- [432539-68-9] Acetamide, 2-[4-(1-methylethyl)phenoxy]-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)
- [430462-84-3] Acetamide, 2-(4-bromo-2-chlorophenoxy)-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)
- 35 [429631-57-2] Acetamide, 2-(4-chloro-3-methylphenoxy)-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)

- [429626-19-7] Acetamide, 2-(4-methoxyphenoxy)-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)
- [426250-14-8] Propanamide, 2-(2,4-dichlorophenoxy)-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)
- 5 [424814-81-3] Acetamide, 2-(2-bromo-4-methylphenoxy)-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)
- [424814-50-6] Acetamide, 2-(4-chloro-3,5-dimethylphenoxy)-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)
- [424814-18-6] Acetamide, 2-(4-bromo-3-methylphenoxy)-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)
- 10 [405076-76-8] Acetamide, 2-(2,4-dichlorophenoxy)-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)
- [405076-63-3] Acetamide, 2-phenoxy-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)
- [339060-39-8] Acetamide, 2-(4-bromophenoxy)-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)
- 15 [332399-46-9] Acetamide, 2-(4-methylphenoxy)-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)
- [305341-04-2] Acetamide, 2-(3-bromophenoxy)-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)
- [298701-43-6] Acetamide, 2-(4-chlorophenoxy)-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)
- [351418-76-3] Acetamide, 2-(3-methylphenoxy)-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)
- 20 Accordingly, in a first aspect this invention concerns compounds of formula (I)

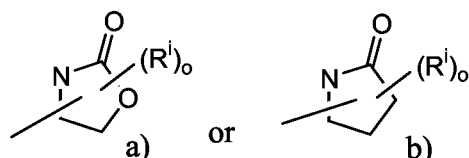


- the *N*-oxide forms, the pharmaceutically acceptable addition salts and the
- 25 stereochemically isomeric forms thereof, wherein

- n* is 1, 2, 3, or 4;
- Z* represents O, S, NR⁶, SO or SO₂;
- R¹ represent hydrogen, cyano, hydroxy, or
- 30 C₁₋₄alkyl optionally substituted with halo,
- R² represents hydrogen, C₁₋₄alkyl, or C₁₋₄alkyloxy-;
- R³ represents hydrogen, C₁₋₄alkyl, C₁₋₄alkyloxy- or R³ combined with R² form together a divalent radical selected from the group consisting of
- O-CH₂- (a), -NR⁷-CH₂- (b), -(CR⁸R⁹)_m- (c) and -CR¹⁰= (d) wherein *m* represents

- 1 or 2 and R^7 , R^8 , R^9 and R^{10} are each independently selected from hydrogen or C_{1-4} alkyl;
- R^4 represents hydrogen, halo, hydroxy, cyano, amino, $NR^{11}R^{12}$, C_{1-4} alkyloxycarbonyl, hydroxycarbonyl, C_{1-4} alkyloxy- optionally substituted with one or where possible two or three substituents selected from hydroxy and halo or
- 5 R^4 represents C_{1-4} alkyl optionally substituted with one or where possible two or three substituents selected from hydroxy and halo;
- R^5 represents hydrogen, halo, cyano, amino, phenyl, hydroxy, C_{1-4} alkyloxycarbonyl, hydroxycarbonyl-, Het^1 , $-NR^{13}R^{14}$, $-O-(C=O)-NR^{21}R^{22}$, $-O-(C=O)-C_{1-4}$ alkyl, carbonyl- $NR^{23}R^{24}$ or C_{1-4} alkyl optionally substituted with one or more substituents selected from hydroxy, halo, hydroxycarbonyl, phenyl, C_{1-4} alkyloxy or $NR^{15}R^{16}$ or R^5 represents C_{1-4} alkyloxy optionally substituted with one or more substituents selected from hydroxy, halo, hydroxycarbonyl, phenyl, C_{1-4} alkyloxy or $NR^{17}R^{18}$, or R^5 represents $-O-(C=O)-C_{1-4}$ alkyl substituted with one or more
- 10 amino, hydroxy, Het^3 or halo substituents;
- R^6 represents hydrogen or C_{1-6} alkyl;
- R^{11} and R^{12} each independently represent hydrogen, C_{1-4} alkyl, C_{1-4} alkyloxycarbonyl- or C_{1-4} alkylcarbonyl-;
- R^{13} and R^{14} each independently represent hydrogen, C_{1-4} alkyl, C_{1-6} alkyl- SO_2 -, mono- or di(C_{1-4} alkyl)amino- SO_2 -, Ar^1-SO_2 -, mono- or di(C_{1-4} alkyl)amino-carbonyl-, C_{1-4} alkyl-oxycarbonyl or C_{1-4} alkylcarbonyl- wherein said C_{1-6} alkyl- SO_2 -, C_{1-4} alkyl-oxycarbonyl or C_{1-4} alkylcarbonyl- are each independently and optionally substituted with one, two or three substituents selected from halo, C_{1-4} alkyloxycarbonyl, $NR^{19}R^{20}$ and Het^2 ;
- 20 R^{15} and R^{16} each independently represent hydrogen, C_{1-4} alkyl, C_{1-4} alkyloxycarbonyl- or C_{1-4} alkylcarbonyl-;
- R^{17} and R^{18} each independently represent hydrogen, C_{1-4} alkyl, C_{1-4} alkyloxycarbonyl- or C_{1-4} alkylcarbonyl-;
- R^{19} and R^{20} each independently represent hydrogen, C_{1-4} alkylcarbonyl, C_{1-4} alkyloxycarbonyl- or C_{1-4} alkyl optionally substituted with one or more substituents selected from halo or hydroxy;
- 30 R^{21} and R^{22} each independently represent hydrogen, Ar^2 or C_{1-4} alkyl optionally substituted with one or more substituents selected from halo or hydroxy;
- R^{23} and R^{24} each independently represent hydrogen, C_{1-4} alkylcarbonyl, Het^4 or C_{1-4} alkyl optionally substituted with one or more substituents selected from halo or hydroxy;
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Het¹ represents pyrrolinyl, pyrrolidinyl, pyrrolyl, oxazolyl, isoxazolyl or a radical of formula



wherein Rⁱ represents hydrogen or C₁₋₄alkyl and o is 1 or 2;

5 Het² represents morpholinyl, piperidinyl, piperazinyl, thiomorpholinyl or pyrrolidinyl;

Het³ represents morpholinyl, piperidinyl, piperazinyl, thiomorpholinyl or pyrrolidinyl;

10 Het⁴ represents piperidinyl, morpholinyl, piperazinyl, thiomorpholinyl or pyrrolidinyl;

Ar¹ represents phenyl optionally substituted with C₁₋₄alkyl; and

Ar² represents phenyl optionally substituted with C₁₋₄alkyl, for use as a medicine, provided however that said compound of formula (I) is other than N-adamantyl-2-yl-2-ortho-tolyloxy-acetamide.

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In a further aspect the present invention provides the use of the aforementioned compounds 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.

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It is also an object of the present invention to provide compounds of formula (I) the *N*-oxide forms, the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof, wherein R¹, R², R³, R⁴, R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, Z and n are defined as hereinbefore and wherein R⁵ represents halo, cyano, amino, phenyl, hydroxy, C₁₋₄alkyloxycarbonyl-, hydroxycarbonyl, NR¹³R¹⁴ or C₁₋₄alkyl optionally substituted with one or more substituents selected from hydroxycarbonyl, phenyl, C₁₋₄alkyloxy or NR¹⁵R¹⁶ or R⁵ represents C₁₋₄alkyloxy optionally substituted with one or more substituents selected from hydroxycarbonyl, phenyl, C₁₋₄alkyloxy or NR¹⁷R¹⁸, in particular R⁵ represents halo, cyano, amino, phenyl, hydroxy, C₁₋₄alkyloxycarbonyl-, hydroxycarbonyl, NR¹³R¹⁴ or C₁₋₄alkyl substituted with one or more substituents selected from hydroxycarbonyl, phenyl, C₁₋₄alkyloxy or NR¹⁵R¹⁶.

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As used in the foregoing definitions and hereinafter, halo is generic to fluoro, chloro, bromo and iodo; C₁₋₄alkyl 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; C₁₋₆alkyl defines straight and branched chain saturated hydrocarbon radicals having from 1 to 6 carbon atoms such as the groups defined for C₍₁₋₄₎alkyl and pentyl, hexyl, 2-methylbutyl and the like; C₁₋₄alkyloxy defines straight or branched saturated hydrocarbon radicals having from 1 to 4 carbon atoms such as methoxy, ethoxy, propyloxy, butyloxy, 1-methylethyloxy, 2-methylpropyloxy and the like.

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.

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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.

10 A particular group of compounds are those compounds of formula (I) wherein one or more of the following restrictions apply;

- (i) n is 1, 2, 3, or 4;
- (ii) Z represents O, S, NR^6 , SO or SO_2 ;
- (iii) R^1 represent hydrogen, cyano, hydroxy, or
15 C_{1-4} alkyl optionally substituted with halo,
- (iv) R^2 represents hydrogen, C_{1-4} alkyl, or C_{1-4} alkyloxy-;
- (v) R^3 represents hydrogen, C_{1-4} alkyl, C_{1-4} alkyloxy- or R^3 combined with R^2 form together a divalent radical selected from the group consisting of
20 $-\text{O}-\text{CH}_2-$ (a), $-\text{NR}^7-\text{CH}_2-$ (b), $-(\text{CR}^8\text{R}^9)_m-$ (c) and $-\text{CR}^{10}=$ (d) wherein m represents 1 or 2 and R^7 , R^8 , R^9 and R^{10} are each independently selected from hydrogen or C_{1-4} alkyl;
- (vi) R^4 represents hydrogen, halo, hydroxy, cyano, amino, $\text{NR}^{11}\text{R}^{12}$,
 C_{1-4} alkyloxy- optionally substituted with one or where possible two or three
25 substituents selected from hydroxy and halo or R^4 represents C_{1-4} alkyl
optionally substituted with one or where possible two or three substituents
selected from hydroxy and halo;
- (vii) R^5 represents hydrogen, halo, cyano, amino, phenyl, hydroxy,
 C_{1-4} alkyloxycarbonyl-, hydroxycarbonyl, $\text{NR}^{13}\text{R}^{14}$ or C_{1-4} alkyl substituted
30 with one or more substituents selected from hydroxycarbonyl, phenyl,
 C_{1-4} alkyloxy or $\text{NR}^{15}\text{R}^{16}$; in particular R^5 represents halo, cyano, amino,
phenyl, hydroxy, C_{1-4} alkyloxycarbonyl-, hydroxycarbonyl, $\text{NR}^{13}\text{R}^{14}$ or
 C_{1-4} alkyl substituted with one or more substituents selected from
hydroxycarbonyl, phenyl, C_{1-4} alkyloxy or $\text{NR}^{15}\text{R}^{16}$;
- (viii) R^6 represents hydrogen;
- (ix) R^{11} and R^{12} each independently represent hydrogen, C_{1-4} alkyl or
35 C_{1-4} alkylcarbonyl-;

- (x) R^{13} and R^{14} each independently represent hydrogen, C_{1-4} alkyl or C_{1-4} alkylcarbonyl-;
- (xi) R^{15} and R^{16} each independently represent hydrogen, C_{1-4} alkyl or C_{1-4} alkylcarbonyl-.

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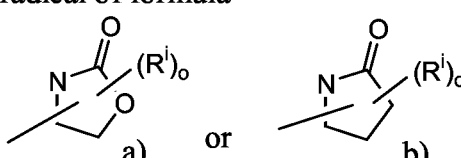
A first group of compounds consists of those compounds of formula (I) wherein one or more of the following restrictions apply :

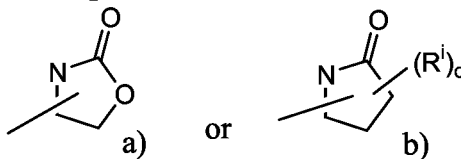
- n is 1, 2, 3, or 4;
- Z represents O, S, NR^6 , SO or SO_2 ;
- 10 R^1 represent hydrogen, cyano, hydroxy, or C_{1-4} alkyl optionally substituted with halo,
- R^2 represents hydrogen, C_{1-4} alkyl, or C_{1-4} alkyloxy-;
- R^3 represents hydrogen, C_{1-4} alkyl, C_{1-4} alkyloxy- or R^3 combined with R^2 form together a divalent radical selected from the group consisting of
- 15 $-O-CH_2-$ (a), $-NR^7-CH_2-$ (b), $-(CR^8R^9)_m-$ (c) and $-CR^{10}=$ (d) wherein m represents 1 or 2 and R^7 , R^8 , R^9 and R^{10} are each independently selected from hydrogen or C_{1-4} alkyl;
- R^4 represents hydrogen, halo, hydroxy, cyano, amino, $NR^{11}R^{12}$, C_{1-4} alkyloxy- optionally substituted with one or where possible two or three substituents
- 20 selected from hydroxy and halo or R^4 represents C_{1-4} alkyl optionally substituted with one or where possible two or three substituents selected from hydroxy and halo;
- R^5 represents hydrogen, halo, cyano, amino, phenyl, hydroxy, C_{1-4} alkyloxycarbonyl, hydroxycarbonyl, $NR^{13}R^{14}$ or C_{1-4} alkyl optionally substituted with one or more
- 25 substituents selected from hydroxycarbonyl, phenyl, C_{1-4} alkyloxy or $NR^{15}R^{16}$ or R^5 represents C_{1-4} alkyloxy optionally substituted with one or more substituents selected from hydroxycarbonyl, phenyl, C_{1-4} alkyloxy or $NR^{17}R^{18}$; in particular R^5 represents halo, cyano, amino, phenyl, hydroxy, C_{1-4} alkyloxycarbonyl-, hydroxycarbonyl, $NR^{13}R^{14}$ or C_{1-4} alkyl optionally substituted with one or more
- 30 substituents selected from hydroxycarbonyl, phenyl, C_{1-4} alkyloxy or $NR^{15}R^{16}$ or R^5 represents C_{1-4} alkyloxy optionally substituted with one or more substituents selected from hydroxycarbonyl, phenyl, C_{1-4} alkyloxy or $NR^{17}R^{18}$
- R^6 represents hydrogen or C_{1-4} alkyl;
- R^{11} and R^{12} each independently represent hydrogen, C_{1-4} alkyl or C_{1-4} alkylcarbonyl-;
- 35 R^{13} and R^{14} each independently represent hydrogen, C_{1-4} alkyl or C_{1-4} alkylcarbonyl-;
- R^{15} and R^{16} each independently represent hydrogen, C_{1-4} alkyl or C_{1-4} alkylcarbonyl-;

R^{17} and R^{18} each independently represent hydrogen, C_{1-4} alkyl or C_{1-4} alkylcarbonyl-, for use as a medicine, provided however that said compound is other than N-adamantyl-2-yl-2-ortho-tolyloxy-acetamide.

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

- (i) n is 1, 2, 3, or 4;
- (ii) Z represents O, S, NR^6 , SO or SO_2 ;
- (iii) R^1 represent hydrogen, cyano, hydroxy, or
- (iv) C_{1-4} alkyl optionally substituted with halo,
- 10 (v) R^2 represents hydrogen, C_{1-4} alkyl, or C_{1-4} alkyloxy-;
- (vi) R^3 represents hydrogen, C_{1-4} alkyl, C_{1-4} alkyloxy- or R^3 combined with R^2 form together a divalent radical selected from the group consisting of $-O-CH_2-$ (a), $-NR^7-CH_2-$ (b), $-(CR^8R^9)_m-$ (c) and $-CR^{10}=$ (d) wherein m represents 1 or 2 and R^7 , R^8 , R^9 and R^{10} are each independently selected from hydrogen or C_{1-4} alkyl;
- 15 (vii) R^4 represents hydrogen, halo, hydroxy, cyano, amino, $NR^{11}R^{12}$, C_{1-4} alkyloxycarbonyl, hydroxycarbonyl, C_{1-4} alkyloxy- optionally substituted with one or where possible two or three substituents selected from hydroxy and halo or R^4 represents C_{1-4} alkyl optionally substituted with one or where possible two or three substituents selected from hydroxy and halo;
- 20 (viii) R^5 represents halo, cyano, amino, phenyl, hydroxy, C_{1-4} alkyloxycarbonyl-, hydroxycarbonyl-, Het¹, $-NR^{13}R^{14}$, $-O-(C=O)-NR^{21}R^{22}$, $-O-(C=O)-C_{1-4}$ alkyl, carbonyl- $NR^{23}R^{24}$ or C_{1-4} alkyl optionally substituted with one or more substituents selected from hydroxycarbonyl, phenyl, C_{1-4} alkyloxy or $NR^{15}R^{16}$ or R^5 represents C_{1-4} alkyloxy optionally substituted with one or more substituents selected from hydroxycarbonyl, phenyl, C_{1-4} alkyloxy or $NR^{17}R^{18}$, or R^5 represents $-O-(C=O)-C_{1-4}$ alkyl substituted with one or more Het³ or halo substituents;
- 25 (ix) R^6 represents hydrogen or C_{1-4} alkyl;
- (x) R^{11} and R^{12} each independently represent hydrogen, C_{1-4} alkyl, C_{1-4} alkyloxy-carbonyl or C_{1-4} alkylcarbonyl-; in particular hydrogen, C_{1-4} alkyl or C_{1-4} alkylcarbonyl-;
- (xi) R^{13} and R^{14} each independently represent hydrogen, C_{1-4} alkyl,
- 30 C_{1-6} alkyl- SO_2 -, mono- or di(C_{1-4} alkyl)amino- SO_2 -, Ar^1-SO_2 -, mono- or di(C_{1-4} alkyl)amino-carbonyl-, C_{1-4} alkyl-oxycarbonyl or C_{1-4} alkylcarbonyl- wherein said C_{1-6} alkyl- SO_2 -, C_{1-4} alkyl-oxycarbonyl or
- 35

- C₁₋₄alkylcarbonyl- are each independently and optionally substituted with one, two or three substituents selected from halo, C₁₋₄alkyloxycarbonyl, NR¹⁹R²⁰ and Het²;
- (xii) R¹⁵ and R¹⁶ each independently represent hydrogen, C₁₋₄alkyl, C₁₋₄alkyloxycarbonyl or C₁₋₄alkylcarbonyl-; in particular hydrogen, C₁₋₄alkyl or C₁₋₄alkylcarbonyl-;
- (xiii) R¹⁷ and R¹⁸ each independently represent hydrogen, C₁₋₄alkyl, C₁₋₄alkyloxycarbonyl or C₁₋₄alkylcarbonyl-; in particular hydrogen, C₁₋₄alkyl or C₁₋₄alkylcarbonyl-;
- (xiv) R¹⁹ and R²⁰ each independently represent hydrogen, C₁₋₄alkylcarbonyl or C₁₋₄alkyl optionally substituted with one or more substituents selected from halo or hydroxy; in particular optionally substituted with hydroxy;
- (xv) R²¹ and R²² each independently represent hydrogen, Ar² or C₁₋₄alkyl optionally substituted with one or more substituents selected from halo or hydroxy; in particular optionally substituted with hydroxy;
- (xvi) R²³ and R²⁴ each independently represent hydrogen, C₁₋₄alkylcarbonyl, Het⁴ or C₁₋₄alkyl optionally substituted with hydroxy;
- (xvii) Het¹ represents pyrrolinyl, pyrrolidinyl, pyrrolyl, oxazolyl, isoxazolyl or a radical of formula
- 

a) or b)
- wherein Rⁱ represents hydrogen or C₁₋₄alkyl and o is 1 or 2; in particular Het¹ represents a radical of formula
- 

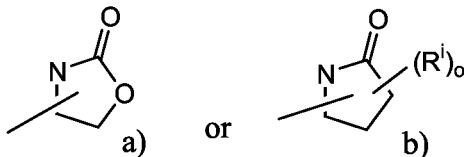
a) or b)
- wherein Rⁱ represents hydrogen or C₁₋₄alkyl and o is 1 or 2;
- (xviii) Het² represents morpholinyl, piperidinyl, piperazinyl, thiomorpholinyl or pyrrolidinyl; in particular Het² represents morpholinyl;
- (xix) Het³ represents morpholinyl, piperidinyl, piperazinyl, thiomorpholinyl or pyrrolidinyl; in particular Het³ represents morpholinyl;
- (xx) Het⁴ represents piperidinyl, morpholinyl, piperazinyl, thiomorpholinyl or pyrrolidinyl; in particular Het⁴ represents piperidinyl;
- (xxi) Ar¹ represents phenyl optionally substituted with C₁₋₄alkyl; and
- (xxii) Ar² represents phenyl optionally substituted with C₁₋₄alkyl.

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

- (i) n is 1, 2, 3, or 4;
- 5 (ii) Z represents O, S, NR⁶, SO or SO₂;
- (iii) R¹ represent hydrogen, cyano, hydroxy, or
- (iv) C₁₋₄alkyl optionally substituted with halo,
- (v) R² represents hydrogen, C₁₋₄alkyl, or C₁₋₄alkyloxy-;
- 10 (vi) R³ represents hydrogen, C₁₋₄alkyl, C₁₋₄alkyloxy- or R³ combined with R² form together a divalent radical selected from the group consisting of -O-CH₂- (a), -NR⁷-CH₂- (b), -(CR⁸R⁹)_m- (c) and -CR¹⁰= (d) wherein m represents 1 or 2 and R⁷, R⁸, R⁹ and R¹⁰ are each independently selected from hydrogen or C₁₋₄alkyl;
- 15 (vii) R⁴ represents hydrogen, halo, hydroxy, cyano, amino, NR¹¹R¹², C₁₋₄alkyloxy- optionally substituted with one or where possible two or three substituents selected from hydroxy and halo or R⁴ represents C₁₋₄alkyl optionally substituted with one or where possible two or three substituents selected from hydroxy and halo;
- 20 (viii) R⁵ represents halo, cyano, amino, phenyl, hydroxy, C₁₋₄alkyloxycarbonyl-, hydroxycarbonyl, NR¹³R¹⁴ or C₁₋₄alkyl optionally substituted with one or more substituents selected from hydroxycarbonyl, phenyl, C₁₋₄alkyloxy or NR¹⁵R¹⁶ or R⁵ represents C₁₋₄alkyloxy optionally substituted with one or more substituents selected from hydroxycarbonyl, phenyl, C₁₋₄alkyloxy or NR¹⁷R¹⁸;
- (ix) R⁶ represents hydrogen or C₁₋₄alkyl;
- 25 (x) R¹¹ and R¹² each independently represent hydrogen, C₁₋₄alkyl or C₁₋₄alkylcarbonyl-;
- (xi) R¹³ and R¹⁴ each independently represent hydrogen, C₁₋₄alkyl or C₁₋₄alkylcarbonyl-;
- (xii) R¹⁵ and R¹⁶ each independently represent hydrogen, C₁₋₄alkyl or
- 30 C₁₋₄alkylcarbonyl-;
- (xiii) R¹⁷ and R¹⁸ each independently represent hydrogen, C₁₋₄alkyl or C₁₋₄alkylcarbonyl-.

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

- (i) n is 1, 2, 3, or 4;
- (ii) Z represents O, S, NR⁶ or SO₂; in particular O or NR⁶;

- (iii) R^1 represents hydrogen or C_{1-4} alkyl;
- (iv) R^2 represents hydrogen or C_{1-4} alkyl;
- (v) R^3 represents hydrogen, C_{1-4} alkyl, C_{1-4} alkyloxy- or R^3 combined with R^2 form together a divalent radical selected from the group consisting of
 5 -O-CH₂- (a), -NR⁷-CH₂- (b), -(CR⁸R⁹)_m- (c) and -CR¹⁰= (d) wherein m represents 1 or 2 and R⁷, R⁸, R⁹ and R¹⁰ are each independently selected from hydrogen or C_{1-4} alkyl;
- (vi) R^4 represents hydrogen, halo, hydroxy, amino, -NR¹¹R¹², C_{1-4} alkyloxy-, C_{1-4} alkyloxycarbonyl-, hydroxycarbonyl-, or C_{1-4} alkyl optionally
 10 substituted with one or where possible two or three halo substituents;
- (vii) R^5 represents hydrogen, halo, amino, phenyl, hydroxy, hydroxycarbonyl, Het¹, NR¹³R¹⁴, -O-(C=O)- C_{1-4} alkyl, -carbonyl-NR²³R²⁴ or R^5 represents C_{1-4} alkyloxy optionally substituted with one or more substituents selected from NR¹⁷R¹⁸ or R^5 represents -O(=O)- C_{1-4} alkyl substituted with halo or
 15 Het³;
- (viii) R^{11} and R^{12} each independently represent hydrogen, C_{1-4} alkyl or C_{1-4} alkylcarbonyl;
- (ix) R^{13} and R^{14} each independently represent hydrogen, C_{1-4} alkyl, C_{1-6} alkyl-SO₂-, mono- or di(C_{1-4} alkyl)amino-SO₂-, Ar¹-SO₂, mono- or di(C_{1-4} alkyl)amino-carbonyl-, C_{1-4} alkyl-oxycarbonyl or C_{1-4} alkylcarbonyl- wherein said
 20 C_{1-6} alkyl-SO₂-, C_{1-4} alkyl-oxycarbonyl or C_{1-4} alkylcarbonyl- are each independently and optionally substituted with one, two or three substituents selected from halo, C_{1-4} alkyloxycarbonyl, NR¹⁹R²⁰ and Het²;
- (x) R^{17} and R^{18} each independently represent C_{1-4} alkyl;
- (xi) R^{19} and R^{20} each independently represent hydrogen or C_{1-4} alkyl optionally
 25 substituted with hydroxy;
- (xii) R^{21} and R^{22} each independently represent hydrogen or Ar²;
- (xiii) R^{23} and R^{24} each independently represent hydrogen or Het⁴;
- (xiv) Het¹ represents a radical of formula
- 

a) or b)
- 30 wherein Rⁱ represents hydrogen or C_{1-4} alkyl and o is 1 or 2;
- (xv) Het² represents morpholinyl;
- (xvi) Het³ represents morpholinyl;
- (xvii) Het⁴ represents piperidinyl;

(xviii) Ar^1 and Ar^2 each independently represent phenyl optionally substituted with C_{1-4} alkyl, for use as a medicine, provided however that said compound of formula (I) is other than N-adamantyl-2-yl-2-ortho-tolyloxy-acetamide.

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

- (i) n is 1, 2, 3, or 4;
- (ii) Z represents O, S or SO_2 ; in particular O;
- (iii) R^1 represents hydrogen or C_{1-4} alkyl;
- 10 (iv) R^2 represents hydrogen or C_{1-4} alkyl;
- (v) R^3 represents hydrogen, C_{1-4} alkyl, C_{1-4} alkyloxy- or R^3 combined with R^2 form together a divalent radical selected from the group consisting of $-O-CH_2-$ (a), $-NR^7-CH_2-$ (b), $-(CR^8R^9)_m-$ (c) and $-CR^{10}=$ (d) wherein m represents 1 or 2 and R^7 , R^8 , R^9 and R^{10} are each independently selected
- 15 from hydrogen or C_{1-4} alkyl;
- (vi) R^4 represents hydrogen, hydroxy, amino, $-NR^{11}R^{12}$, C_{1-4} alkyloxy- or C_{1-4} alkyl optionally substituted with one or where possible two or three halo substituents;
- (vii) R^5 represents hydrogen or hydroxy; in particular hydroxy;
- 20 (viii) R^{11} and R^{12} each independently represent hydrogen, C_{1-4} alkyl or C_{1-4} alkylcarbonyl-;

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

- 25 (i) n is 1, 2, 3, or 4;
- (ii) R^1 represents a hydrogen;
- (iii) R^3 combined with R^2 form together a divalent radical selected from the group consisting of $-O-CH_2-$ (a), $-NR^7-CH_2-$ (b), $-(CR^8R^9)_m-$ (c) and $-CR^{10}=$ (d) wherein m represents 1 or 2 and R^7 , R^8 , R^9 and R^{10} are each independently selected
- 30 from hydrogen or C_{1-4} alkyl;
- (iv) R^4 represents hydrogen, halo, hydroxy, C_{1-4} alkyloxy-, or C_{1-4} alkyl; in particular R^4 represents methyl, ethyl, methoxy, fluor, chloro or bromo;
- (v) R^5 represents halo, cyano, amino, phenyl, hydroxy, C_{1-4} alkyloxy-carbonyl-, hydroxycarbonyl, $NR^{13}R^{14}$ or C_{1-4} alkyl optionally substituted
- 35 with one or more substituents selected from hydroxycarbonyl, phenyl, C_{1-4} alkyloxy or $NR^{15}R^{16}$ or R^5 represents

- C₁₋₄alkyloxy optionally substituted with one or more substituents
 selected from hydroxycarbonyl, phenyl, C₁₋₄alkyloxy or NR¹⁷R¹⁸, in
 particular R⁵ represents halo, cyano, amino, phenyl, hydroxy,
 C₁₋₄alkyloxycarbonyl-, hydroxycarbonyl, NR¹³R¹⁴ or C₁₋₄alkyl
 5 substituted with one or more substituents selected from
 hydroxycarbonyl, phenyl, C₁₋₄alkyloxy or NR¹⁵R¹⁶; even more particular
 R⁵ represents hydrogen or hydroxy; in particular hydroxy;
- (vi) R¹³ and R¹⁴ each independently represent hydrogen, C₁₋₄alkyl or
 C₁₋₄alkylcarbonyl-;
 - 10 (vii) R¹⁵ and R¹⁶ each independently represent hydrogen, C₁₋₄alkyl or
 C₁₋₄alkylcarbonyl-;
 - (viii) R¹⁷ and R¹⁸ each independently represent hydrogen, C₁₋₄alkyl or
 C₁₋₄alkylcarbonyl-.
- 15 Another group of interesting compounds consists of those compounds of formula (I)
 wherein one or more of the following restrictions apply:
- (i) n is 1 or 2;
 - (ii) R¹ represents a C₁₋₄alkyl, in particular methyl;
 - (iii) R² represents a C₁₋₄alkyl, in particular methyl;
 - 20 (iv) R³ represents hydrogen;
 - (v) R⁴ represents hydrogen, halo, -NR¹¹R¹², C₁₋₄alkyloxy-, or C₁₋₄alkyl; in
 particular R⁴ represents methyl, ethyl, methoxy, fluor, chloro or bromo;
 - (vi) R⁵ represents hydrogen, halo, cyano, amino, phenyl, hydroxy, C₁₋₄
 alkyloxycarbonyl-, hydroxycarbonyl, NR¹³R¹⁴ or C₁₋₄alkyl optionally
 25 substituted with one or more substituents selected from
 hydroxycarbonyl, phenyl, C₁₋₄alkyloxy or NR¹⁵R¹⁶ or R⁵ represents
 C₁₋₄alkyloxy optionally substituted with one or more substituents
 selected from hydroxycarbonyl, phenyl, C₁₋₄alkyloxy or NR¹⁷R¹⁸; in
 particular R⁵ represents hydrogen, halo, cyano, amino, phenyl, hydroxy,
 30 C₁₋₄alkyloxycarbonyl-, hydroxycarbonyl, NR¹³R¹⁴ or C₁₋₄alkyl
 optionally substituted with one or more substituents selected from
 hydroxycarbonyl, phenyl, C₁₋₄alkyloxy or NR¹⁵R¹⁶ or R⁵ represents
 C₁₋₄alkyloxy optionally substituted with one or more substituents
 selected from hydroxycarbonyl, phenyl, C₁₋₄alkyloxy or NR¹⁷R¹⁸; more
 35 in particular R⁵ represents halo, cyano, amino, phenyl, hydroxy,
 C₁₋₄alkyloxycarbonyl-, hydroxycarbonyl, NR¹³R¹⁴ or C₁₋₄alkyl
 substituted with one or more substituents selected from hydroxy-

carbonyl, phenyl, C₁₋₄alkyloxy or NR¹⁵R¹⁶; even more particular R⁵ represents hydrogen or hydroxy; in particular hydroxy or amino.

(vii) R¹¹ and R¹² each independently represent hydrogen, C₁₋₄alkyl or C₁₋₄alkylcarbonyl-; in particular R¹¹ and R¹² represent methyl;

(viii) R¹³ and R¹⁴ each independently represent hydrogen, C₁₋₄alkyl, C₁₋₆alkyl-SO₂-, mono- or di(C₁₋₄alkyl)amino-SO₂-, Ar¹-SO₂-, mono- or di-(C₁₋₄alkyl)amino-carbonyl-, C₁₋₄alkyl-oxycarbonyl or C₁₋₄alkylcarbonyl- wherein said C₁₋₆alkyl-SO₂-, C₁₋₄alkyl-oxycarbonyl or C₁₋₄alkylcarbonyl- are each independently and optionally substituted with one, two or three substituents selected from halo, C₁₋₄alkyloxycarbonyl, NR¹⁹R²⁰ and Het²; in particular R¹³ represents hydrogen or C₁₋₄alkyl and R¹⁴ represents C₁₋₄alkyl, C₁₋₆alkyl-SO₂-, or mono- or di(C₁₋₄alkyl)amino-SO₂-, even more particular R¹³ represents hydrogen or methyl and R¹⁴ represents methyl, methyl-SO₂-, ethyl-SO₂- or mono- or di(methyl)amino-SO₂-

(ix) R¹⁷ and R¹⁸ each independently represent hydrogen or C₁₋₄alkyl; in particular R¹⁷ and R¹⁸ represent methyl;

(x) R¹⁹ and R²⁰ each independently represent hydrogen or C₁₋₄alkyl optionally substituted with hydroxy; in particular R¹⁹ and R²⁰ each independently represent hydrogen, methyl or hydroxyethyl;

(xi) R²¹ and R²² each independently represent hydrogen or Ar²; in particular R²¹ and R²² each independently represent hydrogen or methylphenyl;

(xii) R²³ and R²⁴ each independently represent hydrogen or Het⁴; in particular R²³ and R²⁴ each independently represent hydrogen or piperidinyl;

(xiii) Het² represents morpholinyl;

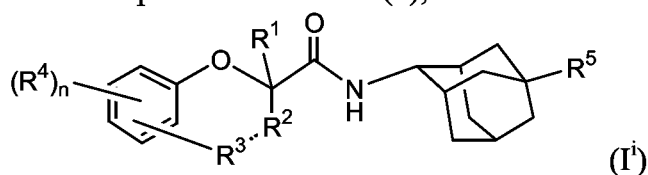
(xiv) Het³ represents morpholinyl;

(xv) Het⁴ represents piperidinyl;

(xvi) Ar¹ represents phenyl substituted with C₁₋₄alkyl; and

(xvii) Ar² represents phenyl substituted with C₁₋₄alkyl.

Also of interest are those compounds of formula (I) wherein Z represents O, hereinafter referred to as the compounds of formula (Iⁱ),



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

- n is 1, 2, 3, or 4;
- 5 R^1 represent hydrogen, cyano, hydroxy, or C_{1-4} alkyl optionally substituted with halo,
- R^2 represents hydrogen, C_{1-4} alkyl, or C_{1-4} alkyloxy-;
- R^3 represents hydrogen, C_{1-4} alkyl, C_{1-4} alkyloxy- or R^3 combined with R^2 form together a divalent radical selected from the group consisting of
- 10 $-O-CH_2-$ (a), $-NR^7-CH_2-$ (b), $-(CR^8R^9)_m-$ (c) and $-CR^{10}=$ (d) wherein m represents 1 or 2 and R^7 , R^8 , R^9 and R^{10} are each independently selected from hydrogen or C_{1-4} alkyl;
- R^4 represents hydrogen, halo, hydroxy, cyano, amino, $NR^{11}R^{12}$, C_{1-4} alkyloxycarbonyl, hydroxycarbonyl, C_{1-4} alkyloxy- optionally substituted with one or where possible two or three substituents selected from hydroxy and halo or
- 15 R^4 represents C_{1-4} alkyl optionally substituted with one or where possible two or three substituents selected from hydroxy and halo;
- R^5 represents hydrogen, halo, cyano, amino, phenyl, hydroxy, C_{1-4} alkyloxycarbonyl-, hydroxycarbonyl-, Het¹, $-NR^{13}R^{14}$, $-O-(C=O)-NR^{21}R^{22}$, $-O-(C=O)-C_{1-4}$ alkyl, carbonyl- $NR^{23}R^{24}$ or C_{1-4} alkyl optionally substituted with one or more substituents selected from hydroxycarbonyl, phenyl, C_{1-4} alkyloxy or $NR^{15}R^{16}$ or
- 20 R^5 represents C_{1-4} alkyloxy optionally substituted with one or more substituents selected from halo, hydroxy, hydroxycarbonyl, phenyl, C_{1-4} alkyloxy or $NR^{17}R^{18}$, or R^5 represents $-O-(C=O)-C_{1-4}$ alkyl substituted with one or more amino,
- 25 hydroxy, Het³ or halo substituents;
- R^6 represents hydrogen or C_{1-4} alkyl;
- R^{11} and R^{12} each independently represent hydrogen, C_{1-4} alkyl, C_{1-4} alkyloxycarbonyl- or C_{1-4} alkylcarbonyl-;
- R^{13} and R^{14} each independently represent hydrogen, C_{1-4} alkyl, C_{1-6} alkyl-SO₂-, mono- or di(C_{1-4} alkyl)amino-SO₂-, Ar¹-SO₂-, mono- or di(C_{1-4} alkyl)amino-carbonyl-,
- 30 C_{1-4} alkyl-oxycarbonyl or C_{1-4} alkylcarbonyl- wherein said C_{1-6} alkyl-SO₂-, C_{1-4} alkyl-oxycarbonyl or C_{1-4} alkylcarbonyl- are each independently and optionally substituted with one, two or three substituents selected from halo, C_{1-4} alkyloxycarbonyl, $NR^{19}R^{20}$ and Het²;
- 35 R^{15} and R^{16} each independently represent hydrogen, C_{1-4} alkyl, C_{1-4} alkyloxycarbonyl or C_{1-4} alkylcarbonyl-; in particular hydrogen, C_{1-4} alkyl or C_{1-4} alkylcarbonyl-;

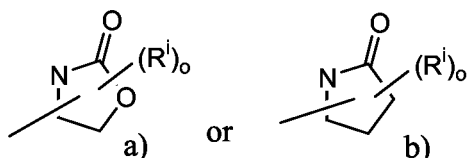
R^{17} and R^{18} each independently represent hydrogen, C_{1-4} alkyl, C_{1-4} alkyloxycarbonyl or C_{1-4} alkylcarbonyl-; in particular hydrogen, C_{1-4} alkyl or C_{1-4} alkylcarbonyl-;

R^{19} and R^{20} each independently represent hydrogen, C_{1-4} alkylcarbonyl or C_{1-4} alkyl optionally substituted with one or more substituents selected from halo or hydroxy; in particular optionally substituted with hydroxy;

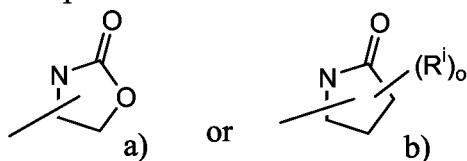
R^{21} and R^{22} each independently represent hydrogen, Ar^2 or C_{1-4} alkyl optionally substituted with one or more substituents selected from halo or hydroxy; in particular optionally substituted with hydroxy;

R^{23} and R^{24} each independently represent hydrogen, C_{1-4} alkylcarbonyl, Het^4 or C_{1-4} alkyl optionally substituted with hydroxy;

Het^1 represents pyrrolinyl, pyrrolidinyl, pyrrolyl, oxazolyl, isoxazolyl or a radical of formula



wherein R^i represents hydrogen or C_{1-4} alkyl and o is 1 or 2; in particular Het^1 represents a radical of formula



wherein R^i represents hydrogen or C_{1-4} alkyl and o is 1 or 2;

Het^2 represents morpholinyl, piperidinyl, piperazinyl, thiomorpholinyl or pyrrolidinyl; in particular Het^2 represents morpholinyl;

Het^3 represents morpholinyl, piperidinyl, piperazinyl, thiomorpholinyl or pyrrolidinyl; in particular Het^3 represents morpholinyl;

Het^4 represents piperidinyl, morpholinyl, piperazinyl, thiomorpholinyl or pyrrolidinyl; in particular Het^4 represents piperidinyl;

Ar^1 represents phenyl optionally substituted with C_{1-4} alkyl; and

Ar^2 represents phenyl optionally substituted with C_{1-4} alkyl; provided however that said compound of formula (Iⁱ) is other than

Acetamide, N-tricyclo[3.3.1.1^{3,7}]dec-2-yl-2-[3-(trifluoromethyl)phenoxy]- (9CI)

Acetamide, 2-[4-(1-methylpropyl)phenoxy]-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)

Butanamide, 2-phenoxy-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)

Acetamide, 2-(2-bromo-4-ethylphenoxy)-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)

Acetamide, N-tricyclo[3.3.1.1^{3,7}]dec-2-yl-2-(2,3,5-trimethylphenoxy)- (9CI)

Acetamide, 2-(2,3-dimethylphenoxy)-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)

- Acetamide, 2-(2,4-dibromo-6-methylphenoxy)-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)
 Acetamide, 2-(4-chloro-2-methylphenoxy)-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)
 Acetamide, 2-(3,5-dimethylphenoxy)-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)
 Acetamide, 2-(2-chlorophenoxy)-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)
 5 Acetamide, 2-[4-(1,1-dimethylethyl)phenoxy]-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)
 Acetamide, 2-[(4-chlorophenyl)thio]-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)
 Acetamide, 2-[5-methyl-2-(1-methylethyl)phenoxy]-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)
 Acetamide, 2-(4-ethylphenoxy)-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)
 Acetamide, 2-(2,5-dimethylphenoxy)-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)
 10 Acetamide, 2-(3,4-dimethylphenoxy)-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)
 Acetamide, 2-(2,4-dimethylphenoxy)-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)
 Acetamide, 2-(4-bromo-2-methylphenoxy)-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)
 Acetamide, 2-(4-bromo-3,5-dimethylphenoxy)-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)
 Acetamide, 2-[4-(1-methylethyl)phenoxy]-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)
 15 Acetamide, 2-(4-bromo-2-chlorophenoxy)-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)
 Acetamide, 2-(4-chloro-3-methylphenoxy)-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)
 Acetamide, 2-(4-methoxyphenoxy)-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)
 Propanamide, 2-(2,4-dichlorophenoxy)-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)
 Acetamide, 2-(2-bromo-4-methylphenoxy)-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)
 20 Acetamide, 2-(4-chloro-3,5-dimethylphenoxy)-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)
 Acetamide, 2-(4-bromo-3-methylphenoxy)-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)
 Acetamide, 2-(2,4-dichlorophenoxy)-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)
 Acetamide, 2-phenoxy-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)
 Acetamide, 2-(4-bromophenoxy)-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)
 25 Acetamide, 2-(4-methylphenoxy)-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)
 Acetamide, 2-(3-bromophenoxy)-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)
 Acetamide, 2-(4-chlorophenoxy)-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)
 Acetamide, 2-(3-methylphenoxy)-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)
 N-adamantan-2-yl-2-o-tolyloxy-acetamide ;
 30 or when R⁵ represents hydrogen in said compound of formula (Iⁱ), then R¹ and R²
 represent C₁₋₄alkyl.

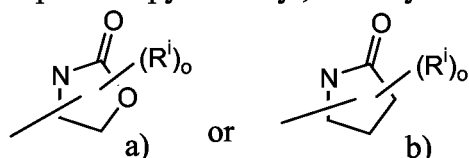
In particular those compounds of formula (Iⁱ) whereinn is 1, 2, 3, or 4;

- R¹ represent hydrogen, cyano, hydroxy, or
 35 C₁₋₄alkyl optionally substituted with halo,
 R² represents hydrogen, C₁₋₄alkyl, or C₁₋₄alkyloxy-;

- R^3 represents hydrogen, C_{1-4} alkyl, C_{1-4} alkyloxy- or R^3 combined with R^2 form together a divalent radical selected from the group consisting of $-O-CH_2-$ (a), $-NR^7-CH_2-$ (b), $-(CR^8R^9)_m-$ (c) and $-CR^{10}=$ (d) wherein m represents 1 or 2 and R^7 , R^8 , R^9 and R^{10} are each independently selected from hydrogen or C_{1-4} alkyl;
- R^4 represents hydrogen, halo, hydroxy, cyano, amino, $NR^{11}R^{12}$, C_{1-4} alkyloxy- optionally substituted with one or where possible two or three substituents selected from hydroxy and halo or R^4 represents C_{1-4} alkyl optionally substituted with one or where possible two or three substituents selected from hydroxy and halo;
- R^5 represents hydrogen, halo, cyano, amino, phenyl, hydroxy, C_{1-4} alkyloxycarbonyl, hydroxycarbonyl, $NR^{13}R^{14}$ or C_{1-4} alkyl optionally substituted with one or more substituents selected from hydroxycarbonyl, phenyl, C_{1-4} alkyloxy or $NR^{15}R^{16}$ or R^5 represents C_{1-4} alkyloxy optionally substituted with one or more substituents selected from hydroxycarbonyl, phenyl, C_{1-4} alkyloxy or $NR^{17}R^{18}$; in particular R^5 represents halo, cyano, amino, phenyl, hydroxy, C_{1-4} alkyloxycarbonyl-, hydroxycarbonyl, $NR^{13}R^{14}$ or C_{1-4} alkyl optionally substituted with one or more substituents selected from hydroxycarbonyl, phenyl, C_{1-4} alkyloxy or $NR^{15}R^{16}$ or R^5 represents C_{1-4} alkyloxy optionally substituted with one or more substituents selected from hydroxycarbonyl, phenyl, C_{1-4} alkyloxy or $NR^{17}R^{18}$
- R^6 represents hydrogen or C_{1-4} alkyl;
- R^{11} and R^{12} each independently represent hydrogen, C_{1-4} alkyl or C_{1-4} alkylcarbonyl-;
- R^{13} and R^{14} each independently represent hydrogen, C_{1-4} alkyl or C_{1-4} alkylcarbonyl-;
- R^{15} and R^{16} each independently represent hydrogen, C_{1-4} alkyl or C_{1-4} alkylcarbonyl-;
- R^{17} and R^{18} each independently represent hydrogen, C_{1-4} alkyl or C_{1-4} alkylcarbonyl-; provided however that when R^5 represents hydrogen in said compound of formula (Iⁱ) then R^1 and R^2 represent C_{1-4} alkyl.

- A particularly preferred group of compounds are those compounds of formula (I) wherein one or more of the following restrictions apply;
- (i) n is 1, 2 or 3; in particular n is 1
 - (ii) Z represents O, S, NR^6 , SO or SO_2 ; in particular Z represents O;
 - (iii) R^1 represents hydrogen or C_{1-4} alkyl; in particular R^1 represents C_{1-4} alkyl; even more particular methyl;
 - (iv) R^2 represents hydrogen or C_{1-4} alkyl; in particular R^2 represents C_{1-4} alkyl; even more particular methyl;

- (v) R^3 represents hydrogen or C_{1-4} alkyl; in particular R^3 represents C_{1-4} alkyl; even more particular methyl; or R^3 combined with R^2 form together a divalent radical selected from the group consisting of $-O-CH_2-$ (a), $-NR^7-CH_2-$ (b), $-(CR^8R^9)_m-$ (c) and $-CR^{10}=$ (d) wherein m represents 1 or 2 and R^7 , R^8 , R^9 and R^{10} are each independently selected from hydrogen or C_{1-4} alkyl;
- (vi) R^4 represents hydrogen, halo, $NR^{11}R^{12}$, hydroxycarbonyl, C_{1-4} alkyloxy- or C_{1-4} alkyl optionally substituted with one or where possible two or three halo substituents; in particular R^4 represents Cl, F, Br, dimethylamino, methylcarbonylamine, methoxy, methyl or trifluoromethyl;
- (vii) R^5 represents hydrogen, amino, hydroxy, Het¹ or $NR^{13}R^{14}$; in particular R^5 represents amino, hydroxy, methylsulfonylamine, ethylsulfonylamine, dimethylaminesulfonylamine, hydroxycarbonyl, 3-methyl-2-oxo-pyrrolidinyl or 2-oxo-oxazolidinyl;
- (viii) R^{11} represents hydrogen or C_{1-4} alkyl; in particular R^{11} represents hydrogen or methyl;
- (ix) R^{12} represents C_{1-4} alkyl or C_{1-4} alkylcarbonyl;
- (x) R^{13} represents hydrogen or C_{1-4} alkyl; in particular R^{13} represents hydrogen or methyl;
- (xi) R^{14} represents C_{1-4} alkyl, C_{1-6} alkyl-SO₂- or mono- or di(C_{1-4} alkyl)amino-SO₂-;
- (xii) Het¹ represents pyrrolidinyl, oxazolyl or a radical of formula



- In a more preferred embodiment the compounds of formula (I) are selected from the group consisting of;

2,3-dihydro-*N*-[(1*R*,3*S*)-5-hydroxytricyclo[3.3.1.^{3,7}]dec-2-yl]-1,4-benzodioxin-2-carboxamide,

N-[(1*R*,3*S*)-5-hydroxytricyclo[3.3.1.^{3,7}]dec-2-yl]-2-methyl-2-(2-methylphenoxy)-propanamide,

N-[(1*R*,3*S*)-5-hydroxytricyclo[3.3.1.^{3,7}]dec-2-yl]-2-methyl-2-(4-methylphenoxy)-propanamide,

2-(3,5-dimethylphenoxy)-*N*-[(1*R*,3*S*)-5-hydroxytricyclo[3.3.1.^{3,7}]dec-2-yl]-2-methylpropanamide,

N-[(1*R*,3*S*)-5-hydroxytricyclo[3.3.1.^{3,7}]dec-2-yl]-3-methyl-2-benzofurancarboxamide,
3,4-dihydro-*N*-[(1*R*,3*S*)-5-hydroxytricyclo[3.3.1.^{3,7}]dec-2-yl]-2*H*-1-benzopyran-
2-carboxamide,
2-(4-chloro-2-methylphenoxy)-*N*-[(1*R*,3*S*)-5-hydroxytricyclo[3.3.1.^{3,7}]dec-2-yl]-
2-methyl-propanamide,
6-fluoro-3,4-dihydro-*N*-[(1*R*,3*S*)-5-hydroxytricyclo[3.3.1.^{3,7}]dec-2-yl]-,
(2*R*)-2*H*-1-benzopyran-2-carboxamide,
N-[(1*R*,3*S*)-5-hydroxytricyclo[3.3.1.^{3,7}]dec-2-yl]-2-benzofurancarboxamide,
2,3-dihydro-*N*-[(1*R*,3*S*)-5-hydroxytricyclo[3.3.1.^{3,7}]dec-2-yl]-2-benzofuran-
carboxamide,
N-[(1*R*,3*S*)-5-hydroxytricyclo[3.3.1.^{3,7}]dec-2-yl]-7-methoxy-2-benzofuran-
carboxamide,
N-[(1*R*,3*S*)-5-hydroxytricyclo[3.3.1.^{3,7}]dec-2-yl]-2-methyl-2-[(4-methylphenyl)amino]-
propanamide,
3,4-dihydro-6-hydroxy-*N*-[(1*R*,3*S*)-5-hydroxytricyclo[3.3.1.^{3,7}]dec-2-yl]-
2,5,7,8-tetramethyl-2*H*-1-benzopyran-2-carboxamide,
2-[(4-chlorophenyl)sulfonyl]-*N*-[(1*R*,3*S*)-5-hydroxytricyclo[3.3.1.^{3,7}]dec-2-yl]-
2-methyl-propanamide,
2-[(4-chlorophenyl)thio]-*N*-[(1*R*,3*S*)-5-hydroxytricyclo[3.3.1.^{3,7}]dec-2-yl]-2-methyl-
propanamide,
2,2-difluoro-*N*-[(1*R*,3*S*)-5-hydroxytricyclo[3.3.1.^{3,7}]dec-2-yl]-2-(3-methylphenoxy)-
acetamide,
2-(3,5-dimethylphenoxy)-2-methyl-*N*-tricyclo[3.3.1.^{3,7}]dec-2-yl-propanamide,
N-[(1*R*,3*S*)-5-hydroxytricyclo[3.3.1.^{3,7}]dec-2-yl]-2-methyl-2-(3-methylphenoxy)-
propanamide,
3,4-dihydro-*N*-[(1*R*,3*S*)-5-hydroxytricyclo[3.3.1.^{3,7}]dec-2-yl]-6-methyl-
2*H*-1,4-benzoxazine-2-carboxamide,
N-[(1*R*,3*S*)-5-hydroxytricyclo[3.3.1.^{3,7}]dec-2-yl]-2-(3-methoxyphenoxy)-2-methyl-
propanamide,
2-(2-bromophenoxy)-*N*-[(1*R*,3*S*)-5-hydroxytricyclo[3.3.1.^{3,7}]dec-2-yl]-2-methyl-
propanamide,
2-(3,5-dimethoxyphenoxy)-*N*-[(1*R*,3*S*)-5-hydroxytricyclo[3.3.1.^{3,7}]dec-2-yl]-2-methyl-
propanamide,
2-[3-(dimethylamino)phenoxy]-*N*-[(1*R*,3*S*)-5-hydroxytricyclo[3.3.1.^{3,7}]dec-2-yl]-
2-methyl-propanamide,

2-[3-(acetylamino)phenoxy]-*N*-[(1*R*,3*S*)-5-hydroxytricyclo[3.3.1.^{3,7}]dec-2-yl]-2-methyl-propanamide,
N-[(1*R*,3*S*)-5-hydroxytricyclo[3.3.1.^{3,7}]dec-2-yl]-2-methyl-2-[3-(trifluoromethyl)-phenoxy]-propanamide,
2-[(4-chlorophenyl)sulfinyl]-*N*-[(1*R*,3*S*)-5-hydroxytricyclo[3.3.1.^{3,7}]dec-2-yl]-2-methyl-propanamide,
2-(4-Chloro-phenoxy)-*N*-[(1*R*,3*S*)-5-hydroxytricyclo[3.3.1.^{3,7}]dec-2-yl]-2-methyl-propionamide,
N-[(1*R*,3*S*)-5-aminotricyclo[3.3.1.^{3,7}]dec-2-yl]-2-(2-chloro-phenoxy)-2-methyl-propionamide,
N-[(1*R*,3*S*)-5-aminotricyclo[3.3.1.^{3,7}]dec-2-yl]-2-methyl-2-(2-trifluoromethyl-phenoxy)-propionamide,
N-[(1*R*,3*S*)-5-aminotricyclo[3.3.1.^{3,7}]dec-2-yl]-2-(4-chloro-2-methyl-phenoxy)-2-methyl-propionamide,
N-[(1*R*,3*S*)-5-aminotricyclo[3.3.1.^{3,7}]dec-2-yl]-2-(4-chloro-phenoxy)-2-methyl-propionamide,
N-[(1*R*,3*S*)-5-aminotricyclo[3.3.1.^{3,7}]dec-2-yl]-2-(2-chloro-5-trifluoromethyl-phenoxy)-2-methyl-propionamide,
N-[(1*R*,3*S*)-5-aminotricyclo[3.3.1.^{3,7}]dec-2-yl]-2-methyl-2-*o*-tolylloxy-propionamide,
N-[(1*R*,3*S*)-5-aminotricyclo[3.3.1.^{3,7}]dec-2-yl]-2-(2-chloro-4-methoxy-phenoxy)-2-methyl-propionamide,
N-[(1*R*,3*S*)-5-aminotricyclo[3.3.1.^{3,7}]dec-2-yl]-2-(4-fluoro-2-methoxy-phenoxy)-2-methyl-propionamide,
(3*R*,5*S*)-4-[2-(4-Chloro-2-methyl-phenoxy)-2-methyl-propionylamino]tricyclo[3.3.1.^{3,7}]decane-1-carboxylic acid,
2-(4-Chloro-2-methyl-phenoxy)-*N*-[(1*R*,3*S*)-5-(dimethylamino)sulfonylaminotricyclo[3.3.1.^{3,7}]dec-2-yl]-2-methyl-propionamide,
2-(4-Chloro-2-methyl-phenoxy)-2-methyl-*N*-[(1*R*,3*S*)-5-(3-methyl-2-oxo-pyrrolidin-1-yl)tricyclo[3.3.1.^{3,7}]dec-2-yl]-propionamide,
N-[(1*R*,3*S*)-5-methanesulfonylaminotricyclo[3.3.1.^{3,7}]dec-2-yl]-2-methyl-2-(3-trifluoromethyl-phenoxy)-propionamide,
N-[(1*R*,3*S*)-5-(dimethylamino)sulfonylaminotricyclo[3.3.1.^{3,7}]dec-2-yl]-2-methyl-2-(3-trifluoromethyl-phenoxy)-propionamide,
N-[(1*R*,3*S*)-5-Ethanesulfonylaminotricyclo[3.3.1.^{3,7}]dec-2-yl]-2-methyl-2-(3-trifluoromethyl-phenoxy)-propionamide,
2-(4-Chloro-2-methyl-phenoxy)-*N*-[(1*R*,3*S*)-5-methanesulfonylamino-tricyclo[3.3.1.^{3,7}]dec-2-yl]-2-methyl-propionamide,

2-(3-Bromo-phenoxy)-*N*-[(1*R*,3*S*)-5-methanesulfonylamino]tricyclo[3.3.1.^{3,7}]dec-2-yl]-2-methyl-propionamide,
2-(4-Chloro-phenoxy)-*N*-[(1*R*,3*S*)-5-methanesulfonylamino]tricyclo[3.3.1.^{3,7}]dec-2-yl]-2-methyl-propionamide,
2-(3-Bromo-phenoxy)-2-methyl-*N*-[(1*R*,3*S*)-5-(2-oxo-oxazolidin-3-yl)]tricyclo[3.3.1.^{3,7}]dec-2-yl]]-propionamide.

In an even more preferred embodiment the compounds of formula (I) are selected from the group consisting of;

2,3-dihydro-*N*-[(1*R*,3*S*)-5-hydroxytricyclo[3.3.1.^{3,7}]dec-2-yl]-1,4-benzodioxin-2-carboxamide,
N-[(1*R*,3*S*)-5-hydroxytricyclo[3.3.1.^{3,7}]dec-2-yl]-2-methyl-2-(2-methylphenoxy)-propanamide,
N-[(1*R*,3*S*)-5-hydroxytricyclo[3.3.1.^{3,7}]dec-2-yl]-2-methyl-2-(4-methylphenoxy)-propanamide,
2-(3,5-dimethylphenoxy)-*N*-[(1*R*,3*S*)-5-hydroxytricyclo[3.3.1.^{3,7}]dec-2-yl]-2-methyl-propanamide,
N-[(1*R*,3*S*)-5-hydroxytricyclo[3.3.1.^{3,7}]dec-2-yl]-3-methyl-2-benzofuran-carboxamide,
3,4-dihydro-*N*-[(1*R*,3*S*)-5-hydroxytricyclo[3.3.1.^{3,7}]dec-2-yl]-2*H*-1-benzopyran-2-carboxamide,
2-(4-chloro-2-methylphenoxy)-*N*-[(1*R*,3*S*)-5-hydroxytricyclo[3.3.1.^{3,7}]dec-2-yl]-2-methyl-propanamide,
2-(4-Chloro-2-methyl-phenoxy)-*N*-[(1*R*,3*S*)-5-methanesulfonylamino]tricyclo[3.3.1.^{3,7}]dec-2-yl]-2-methyl-propionamide,
2-(4-Chloro-2-methyl-phenoxy)-*N*-[(1*R*,3*S*)-5-(dimethylamino)sulfonylamino]tricyclo[3.3.1.^{3,7}]dec-2-yl]-2-methyl-propionamide,
2-(4-Chloro-phenoxy)-*N*-[(1*R*,3*S*)-5-hydroxytricyclo[3.3.1.^{3,7}]dec-2-yl]-2-methyl-propionamide,
N-[(1*R*,3*S*)-5-(dimethylamino)sulfonylamino]tricyclo[3.3.1.^{3,7}]dec-2-yl]-2-methyl-2-(3-trifluoromethyl-phenoxy)-propionamide,
N-[(1*R*,3*S*)-5-methanesulfonylamino]tricyclo[3.3.1.^{3,7}]dec-2-yl]-2-methyl-2-(3-trifluoromethyl-phenoxy)-propionamide,
N-[(1*R*,3*S*)-5-aminotricyclo[3.3.1.^{3,7}]dec-2-yl]-2-(2-chloro-phenoxy)-2-methyl-propionamide,

N-[(1*R*,3*S*)-5-aminotricyclo[3.3.1.1^{3,7}]dec-2-yl]-2-methyl-2-(2-trifluoromethyl-phenoxy)-propionamide,
N-[(1*R*,3*S*)-5-Ethanesulfonylamino-tricyclo[3.3.1.1^{3,7}]dec-2-yl]-2-methyl-2-(3-trifluoromethyl-phenoxy)-propionamide,
 (3*R*,5*S*)-4-[2-(4-Chloro-2-methyl-phenoxy)-2-methyl-propionylamino]-tricyclo[3.3.1.1^{3,7}]decane-1-carboxylic acid,
N-[(1*R*,3*S*)-5-aminotricyclo[3.3.1.1^{3,7}]dec-2-yl]-2-(4-chloro-2-methyl-phenoxy)-2-methyl-propionamide,
 2-(4-Chloro-2-methyl-phenoxy)-2-methyl-*N*-[(1*R*,3*S*)-5-(3-methyl-2-oxo-pyrrolidin-1-yl)tricyclo[3.3.1.1^{3,7}]dec-2-yl]-propionamide,
 2-(3-Bromo-phenoxy)-2-methyl-*N*-[(1*R*,3*S*)-5-(2-oxo-oxazolidin-3-yl)-tricyclo[3.3.1.1^{3,7}]dec-2-yl]-propionamide,
 2-(3-Bromo-phenoxy)-*N*-[(1*R*,3*S*)-5-methanesulfonylamino-tricyclo[3.3.1.1^{3,7}]dec-2-yl]-2-methyl-propionamide, or
 2-(4-Chloro-phenoxy)-*N*-[(1*R*,3*S*)-5-methanesulfonylamino-tricyclo[3.3.1.1^{3,7}]dec-2-yl]-2-methyl-propionamide.

In a further aspect the present invention provides any of the aforementioned group of compounds for use as a medicine. In particular in the treatment or prevention of pathologies associated with excess cortisol formation such as obesity, diabetes, obesity related cardiovascular diseases, stress and glaucoma. It is accordingly a further aspect of the present invention to provide the use of any of the aforementioned group of compounds in the manufacture of a medicament for treating pathologies associated with excess cortisol formation such as obesity, diabetes, obesity related cardiovascular diseases, stress and glaucoma.

10

PCT International patent application WO 2004/089416 provides the benefits of a combination therapy comprising the administration of a 11 β -HSD1 inhibitor and an antihypertensive agent in the treatment of e.g. insulin resistance, dyslipidemia, obesity and hypertension, in particular in the treatment of hypertension. It is accordingly an object of the present invention to provide any of the aforementioned group of compounds in a combination therapy with an antihypertensive agent, such as for example alprenolol, atenolol, timolol, pindolol, propranolol, metoprolol, bisoprololfumerate, esmolol, acebutolol, acebutolol, betaxolol, celiprolol, nebivolol, tertatolol, oxprenolol, amisolalul, carvedilol, labetalol, S-atenolol, OPC-1085,

20

quinapril, lisinopril, enalapril, captopril, benazepril, perindopril, trandolapril, fosinopril, ramipril, cilazapril, delapril, imidapril, moexipril, spirapril, temocapril, zofenopril,

S-5590, fasidotril, Hoechst-Marion Roussel : 100240 (EP00481522),
omapatrilat, gemopatriat and GW-660511, nifedipine, felodipine, nicardipine,
isradipine, nimodipine, diltiazem, amlodipine, nitrendipine, verapamil, lacidipine,
lercanidipine, aranidipine, cilnidipine, clevidipine, azelnidipine, barnidipine,
5 efonodipine, iasidipine, iemildipine, iercanidipine, manidipine, nilvadipine,
pranidipine, furnidipine, doxazosin, urapidil, prazosin, terazosin, bunazosin and
OPC-28326, bendroflumetazide, chlorothalidone, hydrochlorothiazide and clopamide,
bumetanide, furosemide, torasemide, amiloride, spironolactone, ABT-546, ambrisentan,
atrasentan, SB-234551, CI-1034, S-0139, YM-598, bosentan, J-104133, aliskiren,
10 OPC-21268, tolvaptan, SR-121463, OPC-31260, Nesiritide, irbesartan,
candesartancilexetil, losartan, valsartan, telmisartan, eprosartan, candesartan,
CL- 329167, eprosartan, iosartan, olmesartan, prazosartan, TA-606, YM-358,
fenoldopam, ketanserin, naftopidil, N-0861, FK-352, KT2-962, ecadotril, LP-805,
MYD-37, nolomirole, omacor, treprostinil, beraprost, ecraprost, PST-2238, KR-30450,
15 PMD-3117, Indapamides, CGRP-unigene, guanylate cyclase stimulators,
hydralazines, methyldopa, docarpamine, moxonidine, CoAprovel, and MondoBiotech-
811. In said aspect of the invention a pharmaceutical composition which, comprises
the combination of a 11 β -HSD1 inhibitor of the present invention and an
antihypertensive agent, is provided.

20

PCT International application WO 2004/089415 provides the benefits of a combination
therapy comprising the administration of a 11 β -HSD1 inhibitor and a glucocorticoid
receptor agonist for the reduction of undesirable side effects occurring during
glucocorticoid receptor agonist therapy and for treating some forms of cancer, diseases
25 and disorders having inflammation as a component. In particular in reducing the
adverse effects of glucocorticoid receptor agonist therapy in indications of Cushing's
disease, Cushing's syndrome, allergic-inflammatory diseases, adverse effects
of glucocorticoid receptor agonist treatment of disorders of the respiratory system,
adverse effects of glucocorticoid receptor agonist treatment of inflammatory bowel
30 disease; adverse effects of glucocorticoid receptor agonist treatment of disorders of the
immune system, connective tissue and joints; adverse effects of glucocorticoid receptor
agonist treatment of endocrinological diseases; adverse effects of glucocorticoid
receptor agonist treatment of hematological diseases; adverse effects of glucocorticoid
receptor agonist treatment of cancer, chemotherapy-induced nausea, adverse effects
35 of glucocorticoid receptor agonist treatment of diseases of muscle and at the neuro-
muscular joint; adverse effects of glucocorticoid receptor agonist treatment in the
context of surgery; transplantation; adverse effects of glucocorticoid receptor agonist

treatment of brain abscess, nausea/vomiting, infections, hypercalcemia, adrenal hyperplasia, autoimmune hepatitis, spinal cord diseases, saccular aneurysms.

Examples for the indications wherein a combination of a 11β -HSD1 compound of the present invention with a glucocorticoid receptor agonists may be beneficial are:

5 Cushing's disease, Cushing's syndrome, asthma, atopic dermatitis, cystic fibrosis, emphysema, bronchitis, hypersensitivity, pneumonitis, eosinophilic pneumonias, pulmonary fibrosis, Crohn's disease, Ulcerative colitis, reactive arthritis, rheumatoid arthritis, Sjogren's syndrome, systemic lupus erythematosus, lupus nephritis, Henoch-Schnlein purpura, Wegener's granulomatosis, temporal arteritis, systemic sclerosis,

10 vasculitis, sarcoidosis, dermatomyositis-polymyositis, pemphigus vulgaris, hyperthyroidism, hypoaldosteronism, hypopituitarism, hemolytic anemia, thrombocytopenia, paroxysmal nocturnal hemoglobinuria, neoplastic compression of the spinal cord, brain tumours, acutelymphoblastic leukemia, Hodgkin's disease,

15 chemotherapy-induced nausea, myasthenia gravis, hereditary myopathies, Duchenne muscular dystrophy, trauma, post-surgical stress, surgical stress, renal transplantation, liver transplantation, lung transplantation, pancreatic islet transplantation, blood stem cell transplantation, bone marrow transplantation, heart transplantation, adrenal gland transplantation, trachea transplantation, intestinal transplantation, corneal

20 transplantation, skin grafting, keratoplasty, lens implantation, brain abscess, nausea/vomiting, infections, hypercalcemia, adrenal hyperplasia, autoimmune hepatitis, spinal cord diseases, and saccular aneurysms. It is accordingly an object of the present invention to provide any of the aforementioned group of compounds in a combination therapy with a glucocorticoid receptor agonist, as well as pharmaceutical formulations

25 comprising said combination of a compound of the present invention with a glucocorticoid receptor agonist. The glucocorticoid receptor agonist is, for example, selected from the group consisting of: betametasone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, beclomethasone, butixicort, clobetasol, flunisolide, flucatisone (and analogues), momethasone, triamcinolonacetoneide,

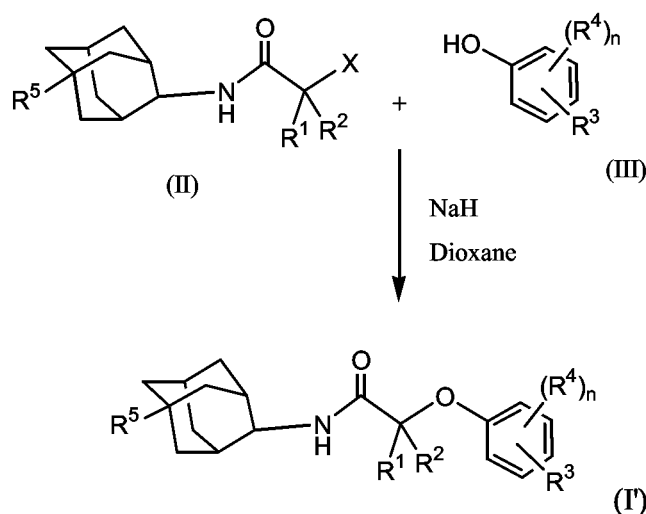
30 triamcinolonhexacetoneide GW-685698, NXC-1015, NXC-1020, NXC-1021, NS-126, P-4112, P-4114, RU-24858 and T-25 series.

The *N*-2-adamantyl-2-phenoxy-acetamide derivatives of the present invention, hereinafter referred to as the compounds of formula (I'), are generally prepared by

35 treatment of the appropriate alkylhalide (II) with the alcohol of formula (III) under art known conditions (Scheme 1). This reaction is usually performed by mixing the halide and phenol directly with solid KOH in Me_2SO or with HgO and HBF_4 in CH_2Cl_2 .

Alternatively, as described in the examples hereinafter, the reactive aroxide is obtained directly in the reaction mixture by mixing the halide and phenol in an appropriate solvent such as dioxane, in the presence of sodium hydride. The reaction temperature and the reaction time may be altered depending on the starting material or reagents but is usually performed overnight at a temperature in the range of 60°C – 120°C, typically 90°C.

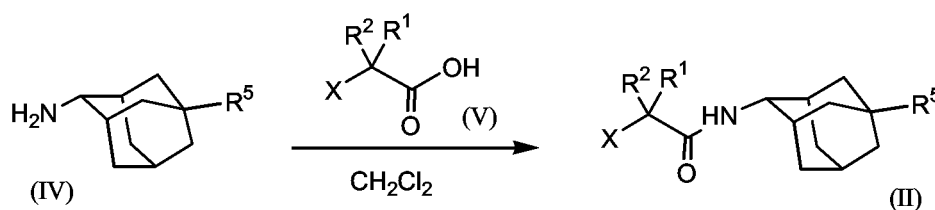
Scheme 1



wherein R¹, R², R³, R⁴, R⁵ are defined as for the compounds of formula (I) hereinbefore and wherein X represents a halo atom, in particular, chloro or bromo.

The appropriate alkylhalide of formula (II) hereinbefore, is generally prepared by condensation of 2-adamantyl-amine (IV) with the appropriate carboxylic acid (V) in the presence of a coupling reagent, such as for example *N,N'*-dicyclohexylcarbodiimide (DCC), *N,N'*-carbonyldiimidazole (CDI), POCl₃, TiCl₄, sulfur chloride fluoride (SO₂ClF) or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDCI) either in the presence or absence of hydroxybenzotriazole (HOBt) (Scheme 2). The reaction is typically performed by stirring the reaction mixture for a couple of hours (2 – 8 hours) at room temperature.

Scheme 2

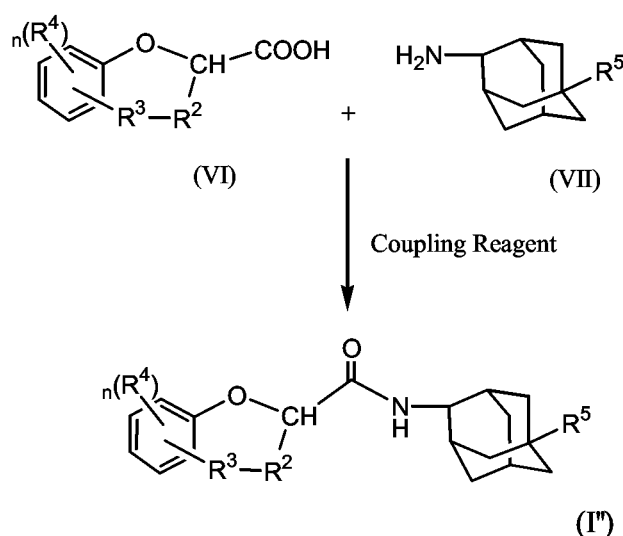


wherein R^1 , R^2 and R^5 are defined as for the compounds of formula (I) hereinbefore and X represents a halo atom, in particular chloro or bromo.

In analogy with the preparation of the *N*-2-adamantyl-2-phenoxy-acetamide derivatives of the present invention (I'), those compounds wherein Z represents S, SO, SO₂ or NR⁶ are prepared by reaction of the alkyl halide of formula (II) with the corresponding benzothiol, benzamine or benzene sulfinic acid ion using art known procedures, such as for example described in "Advanced Organic Chemistry" Jerry March – John Wiley & Sons, Inc. – third edition – New York – Section 0.38 – page 360-361; Section 0.42 – page 363 and Section 0.45 – page 364-365 respectively.

The bicyclic adamantyl-amide derivatives of formula (I'') 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 (VI) with the amino-adamantyl derivatives of formula (VII) (scheme 3) or via a nucleophilic substitution reaction wherein the appropriate amine reacts with either the corresponding acyl halide (scheme 4), anhydride or ester, to yield the required amide.

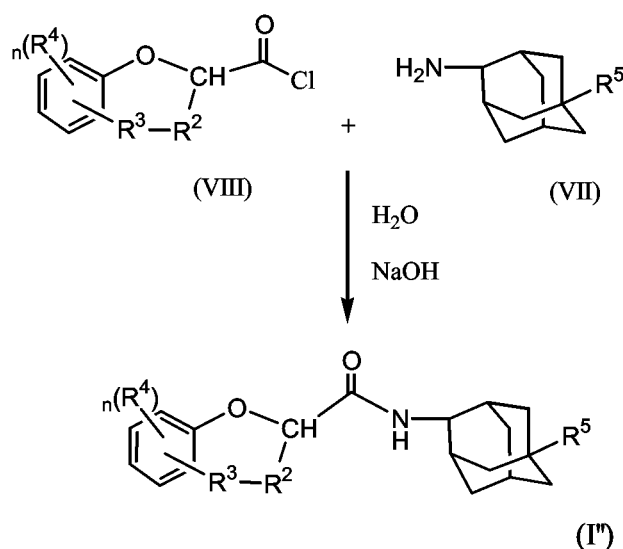
When coupling the acids to the amines (as in Scheme 2 hereinbefore), standard coupling reagents such as *N,N'*-dicyclohexylcarbodiimide (DCC), *N,N'*-carbonyldiimidazole (CDI), POCl₃, TiCl₄, sulfur chloride fluoride (SO₂ClF) or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDCI) are used in the presence or absence of hydroxybenzotriazole (HOBt). In general, adding the carboxylic acids of formula (VI) to the amino-adamantyl derivative of formula (VII) 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 3

wherein R^2 , R^3 , R^4 and R^5 are defined as for the compounds of formula (I)

In an alternative embodiment the carboxylic acids are converted into the corresponding
 5 halides by reaction with, for example, thionyl chloride or oxalyl chloride.

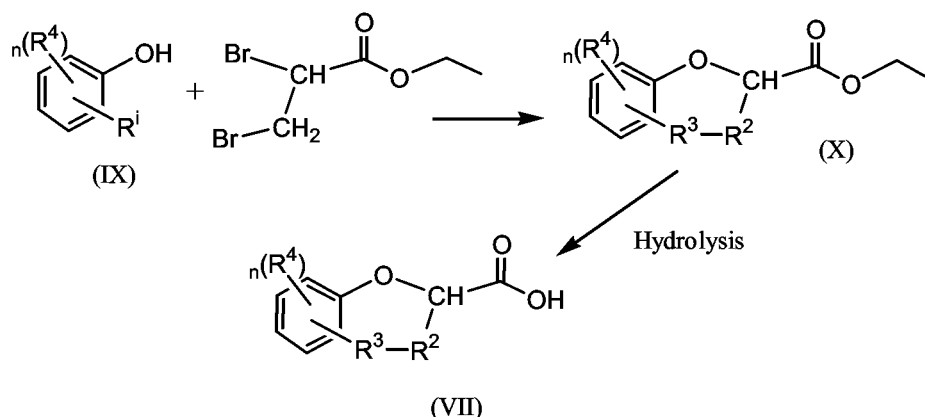
Subsequently said acyl halide (VIII) is added to the amino-adamantyl derivatives of
 formula (VII) to yield the amide of formula (I'') using art known reaction procedures
 such as the Schotten-Baumann method.

Scheme 4

10 The carboxylic acids of formula (VI) are readily available, for example commercially
 from Aldrich Chemicals, or when they are not commercially available, they may be
 readily prepared from available precursors using straightforward transformations that
 are well known to the person skilled in the art of organic chemistry.

For those compounds of formula (I) wherein Z represents O and R^3 combined with R^2 represent the bivalent radical represented by formula (a) or (b), for said compounds the bicyclic carboxylic acids of formula (VI) are prepared by coupling of aromatic 1,2-dihydroxy or 1,2-amino-hydroxy-benzo-derivatives of formula (IX) with 2,3-dibromoethyl-propionate in boiling acetone. Subsequently, an acidic or basic hydrolysis of the thus obtained esters (X) yields the bicyclic carboxylic acid intermediates of formula (VI).

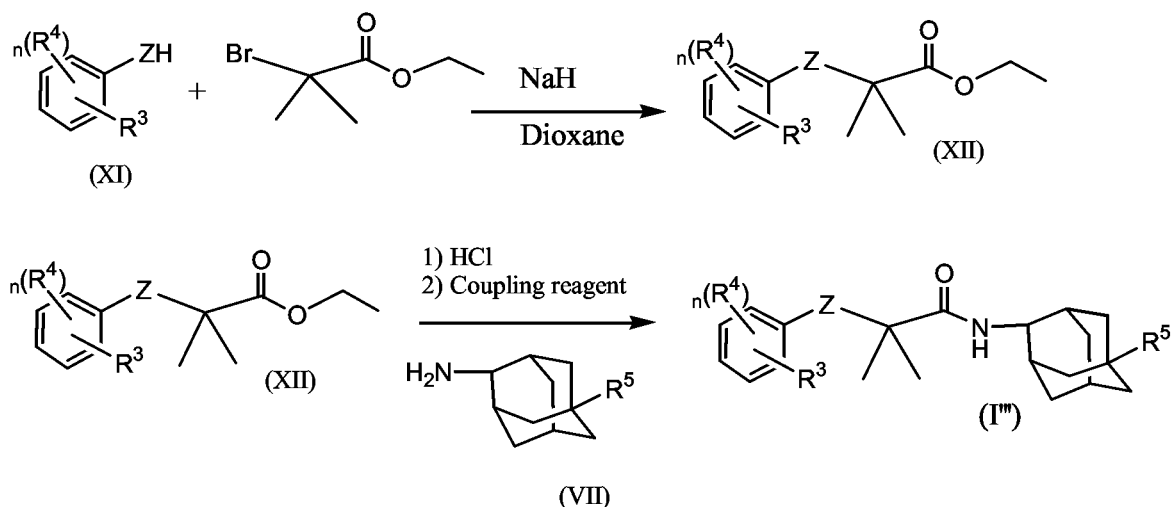
Scheme 5



wherein R^i represents hydroxy or amino and wherein R^2 , R^3 and R^4 are defined as for the compounds of formula (I).

In analogy with the above, those compounds of the present invention wherein both R^1 and R^2 represent methyl, hereinafter referred to as the compounds of formula (I'''), can be prepared according to scheme 6. In a first step 2-bromo-2-methylpropanoic acid ethyl ester [CAS No 600-00-0] is reacted with the corresponding benzothiol, benzamine or benzene sulfinic acid ion using art known procedures, such as for example described in "Advanced Organic Chemistry" Jerry March – John Wiley & Sons, Inc. – third edition – New York – Section 0.38 – page 360-361; Section 0.42 – page 363 and Section 0.45 – page 364-365 respectively. Subsequently coupling the thus obtained intermediate (XI) with the appropriate aminoadamantyl (VII) using standard coupling reagents such as *N,N'*-dicyclohexylcarbodiimide (DCC), *N,N'*-carbonyldiimidazole (CDI), POCl_3 , TiCl_4 , sulfur chloride fluoride (SO_2ClF) or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDCI) in the presence or absence of hydroxybenzotriazole (HOBt), yields the compounds of formula (I''')

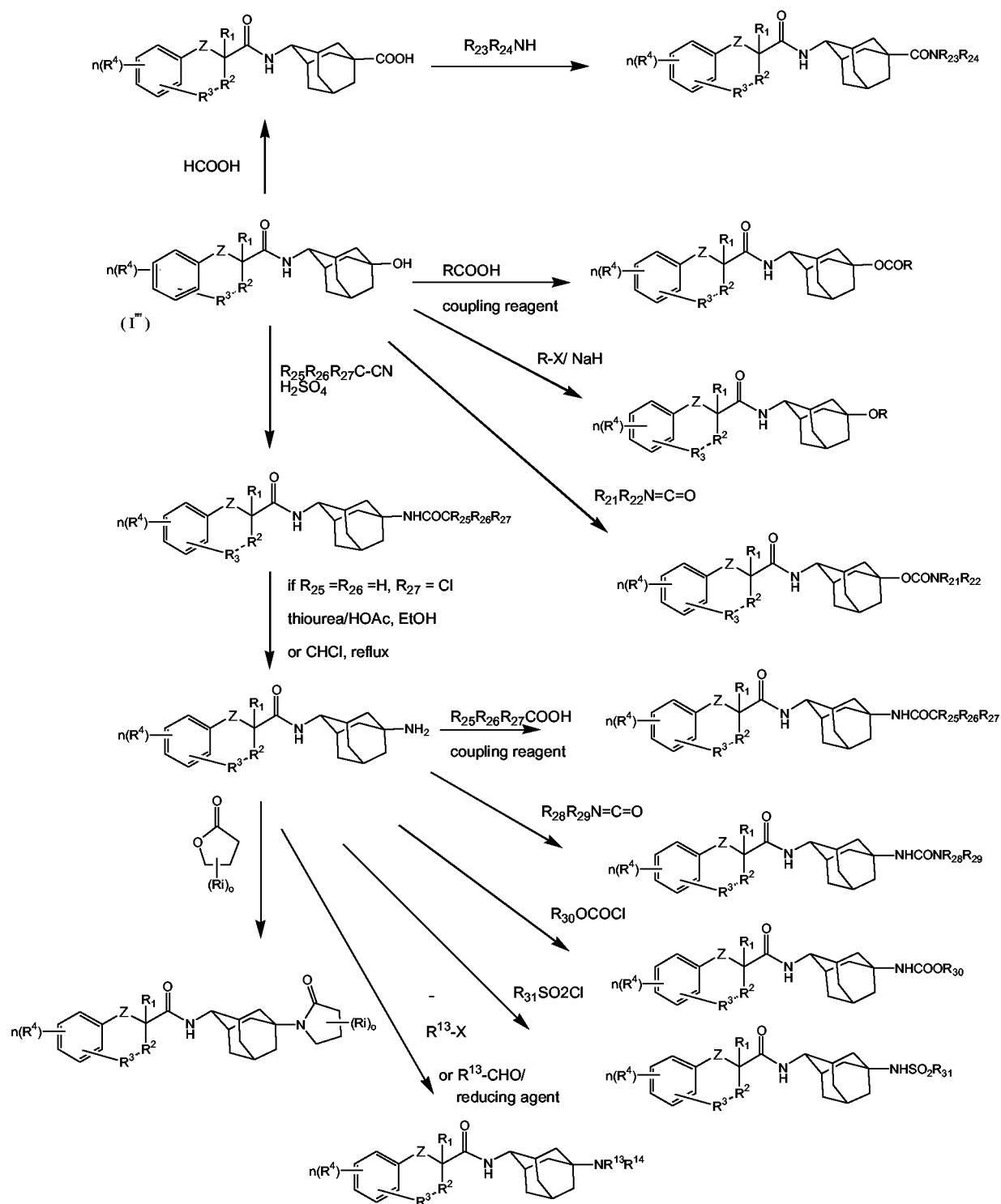
Scheme 6



wherein Z , R^3 , R^4 and R^5 are defined as for the compounds of formula (I) hereinbefore.

As provided in more detail in the experimental part hereinafter, most of the R^5 alternatives were obtained by converting the hydroxyl of general formula I''' using art known conversion reactions as schematically represented the scheme hereinafter. As used therein;

- R refers to C_{1-4} alkyl optionally substituted with one or more amino, hydroxy, Het^3 or halo substituents, wherein Het^3 is defined as for the compounds of formula (I) hereinbefore;
- R_{25} , R_{26} and R_{27} each independently represent hydrogen, halo, or C_{1-4} alkyl wherein said C_{1-4} alkyl is optionally substituted with one, two or three substituents selected from halo, C_{1-4} alkyloxycarbonyl, $NR^{19}R^{20}$ and Het^2 , wherein R^{19} , R^{20} and Het^2 are defined as for the compounds of formula (I) hereinbefore;
- R_{28} and R_{29} each independently represent hydrogen or C_{1-4} alkyl;
- R_{30} represents hydrogen or C_{1-4} alkyl wherein said C_{1-4} alkyl is optionally substituted with one, two or three substituents selected from halo, C_{1-4} alkyloxycarbonyl, $NR^{19}R^{20}$ and Het^2 , wherein R^{19} , R^{20} and Het^2 are defined as for the compounds of formula (I) hereinbefore;
- R_{31} represents C_{1-6} alkyl wherein said C_{1-6} alkyl is optionally substituted with one, two or three substituents selected from halo, C_{1-4} alkyloxycarbonyl, $NR^{19}R^{20}$ and Het^2 , wherein R^{19} , R^{20} and Het^2 are defined as for the compounds of formula (I) hereinbefore; and
- Z , R^1 , R^2 , R^3 , R^4 , R^{13} , R^{14} , n , o , and R^i are defined as for the compounds of formula (I) hereinbefore.



Further examples for the synthesis of compounds of formula (I) using anyone of the
 5 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
5 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
10 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
15 (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;

It will be appreciated by those skilled in the art that in the processes described above
20 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
25 (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.

30 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 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 $\text{CH}_3\text{-I}$ in a suitable solvent such as, for example 2-propanone, tetrahydrofuran or dimethylformamide.

- 5 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.

10 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.
15 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, peroxyalkanoic acids, e.g. peroxyacetic acid, alkylhydroperoxides, e.g. *t*-butyl hydroperoxide. Suitable solvents are, for example, water, lower alkanols, e.g. ethanol and the like, hydro-
20 carbons, 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
25 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
30 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
35 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
5 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.
10

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.

15 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, i.e. disorders where a decreased level of active glucocorticoid is desirable, such as metabolic syndrome, type 2 diabetes, impaired glucose tolerance (IGT), impaired fasting glucose (IFG),
20 dyslipidemia, hypertension, obesity, diabetes, obesity related cardiovascular diseases, arteriosclerosis, atherosclerosis, myopathy, osteoporosis, neurodegenerative and psychiatric disorders, stress related disorders and glaucoma. In particular to treat pathologies such as for example, obesity, diabetes, type 2 diabetes, obesity related cardiovascular diseases, stress and glaucoma.

25 As described in the experimental part hereinafter, the inhibitory effect of the present compounds on the 11 β -HSD1-reductase activity (conversion of cortison into cortisol) has been demonstrated *in vitro*, in an enzymatic assay using the recombinant 11 β -HSD1 enzyme, by measuring the conversion of cortison into cortisol using HPLC
30 purification and quantification methods. 11 β -HSD1-reductase inhibition was also demonstrated *in vitro*, in a cell based assay comprising contacting the cells, expressing 11 β -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
35 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) and their pharmaceutically acceptable *N*-oxides, addition salts, quaternary amines and stereochemically isomeric forms for use in therapy. In particular to treat pathologies associated with excess cortisol formation, i.e. disorders where a decreased level of active glucocorticoid is desirable, such as metabolic syndrome, type 2 diabetes, impaired glucose tolerance (IGT), impaired fasting glucose (IFG), dyslipidemia, hypertension, obesity, diabetes, obesity related cardiovascular diseases, arteriosclerosis, atherosclerosis, myopathy, osteoporosis, neurodegenerative and psychiatric disorders, stress related disorders and glaucoma. More particular to treat pathologies such as for example, obesity, diabetes, type 2 diabetes, obesity related cardiovascular diseases, stress and glaucoma. Even more particular in the treatment or prevention of pathologies associated with excess cortisol formation such as obesity, diabetes, obesity related cardiovascular diseases and glaucoma.

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 pathology associated with excess cortisol formation, 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, metabolic syndrome, type 2 diabetes, impaired glucose tolerance (IGT), impaired fasting glucose (IFG), dyslipidemia, hypertension, obesity, diabetes, obesity related cardiovascular diseases, arteriosclerosis, atherosclerosis, myopathy, osteoporosis, neurodegenerative and psychiatric disorders, stress related disorders and glaucoma, in particular obesity, diabetes, obesity related cardiovascular diseases, stress and glaucoma.

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 500 mg/kg body weight, in particular

from 0.005 mg/kg to 100 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.

- 5 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
10 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 (18th ed., Mack Publishing
15 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
20 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,
25 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
30 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
35 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) in pharmaceutical compositions, it can be advantageous to employ α -, β - or γ -cyclo-dextrins or their derivatives. Also co-solvents such as alcohols may improve the solubility and/or the stability of the compounds of formula (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.

30

Experimental part

In the procedures described hereinafter the following abbreviations were used : "DIPE" stands for diisopropylether; "EtOAc" stands for ethyl acetate; "DMF" stands for *N,N*-dimethylformamide, "TEA" for *N,N*-diethylethanamine "DMAP" for *N,N*-dimethyl-4-pyridinamine, "EDCI" stands for 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, "HOBt" stands for hydroxybenzotriazole, "NMM" stands for

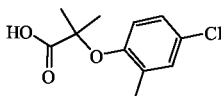
4-methylmorpholine, "DIPCDI" stands for *N,N'*-diisopropyl-carbodiimide and "DIPEA" stands for *N,N*-diisopropylethylamine.

ExtrelutTM is a product of Merck KgaA (Darmstadt, Germany) and is a short column comprising diatomaceous earth. Supelco is a prepacked silicagel liquid chromatography column.

For some chemicals the chemical formula was used, e.g. CH₂Cl₂ for dichloromethane, CH₃OH for methanol, HCl for hydrochloric acid, H₂SO₄ for sulfuric acid, and NaHCO₃ for sodium hydrogen carbonate.

10 A. Preparation of the intermediates

Example A.1

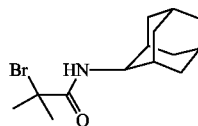


Preparation of

intermediate 1

4-chloro-2-methylphenol [1570-64-5] (0.0049 mol) was stirred in dioxane (15 ml). Sodium hydride (0.0049 mol) was added and the mixture was stirred for 30 minutes. 2-Bromo-2-methylpropanoic acid, 1,1-dimethylethyl ester [23877-12-5] (0.005 mol) was added and the reaction mixture was stirred overnight at 60°C. Water (5 ml) was added. The mixture was washed with dichloromethane. The layers were separated. The aqueous layer was acidified with HCl, then extracted with dichloromethane. The separated organic layer was washed, filtered through Extrelut, and the filtrate was evaporated. The residue was purified over silica gel (Supelco) on a glass filter (eluent : CH₂Cl₂). The product fractions were collected and the solvent was evaporated, yielding 0.145 g of intermediate 1.

Example A.2



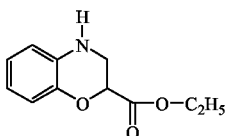
Preparation of

intermediate 2

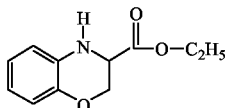
A mixture of 2-bromo-2-methyl-propanoic acid [2052-01-9] (0.01 mol), *N'*-(ethylcarbonimidoyl)-*N,N*-dimethyl-1,3-propanediamine, monohydrochloride [25952-53-8] (0.011 mol) and 1-hydroxy-1*H*-benzotriazole (0.011 mol) in dichloromethane (50 ml) was stirred for 30 minutes at room temperature, then *N,N*-diethylethanamine (0.03 mol) was added, followed by tricyclo[3.3.1.1^{3,7}]decan-2-amine, hydrochloride [10523-68-9] (0.013 mol). The reaction mixture was stirred for 5 hours at room temperature and then washed with a 15 % citric acid solution, with a 5 % NaHCO₃ solution with water and with brine. After drying, the solvent was evaporated, yielding 2.5 g of intermediate 2.

Example A.3

a) Preparation of



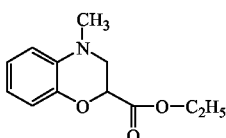
intermediate 3



intermediate 4

2,3-Dibromopropanoic acid, ethyl ester (0.05 mol) was added to a suspension of 2-aminophenol (0.046 mol) and potassium carbonate (0.135 mol) in 2-propanone (250 ml) and then the reaction mixture was stirred and refluxed over the weekend. The mixture was filtered and the filtrate was evaporated, yielding a mixture of intermediate 3 [22244-22-0 and intermediate 4 [177202-60-7].

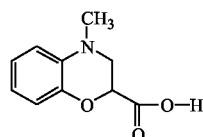
b) Preparation of



intermediate 5

Potassium carbonate (0.03 mol) and iodomethane (0.03 mol) were added to a solution of a mixture of intermediate 3 and intermediate 4 (0.01 mol) in 2-propanone. The reaction mixture was stirred and refluxed overnight. The resulting precipitate was filtered off, washed with 2-propanone and the filtrate was evaporated. The obtained residue (3.2g) was dissolved in 2-propanol (50 ml) and in DIPE (50 ml). Then the solution was washed with water and with brine and concentrated again, yielding 1.9 g of intermediate 5 [54442-28-3].

c) Preparation of

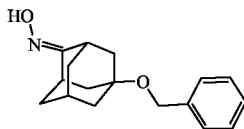


intermediate 6

A solution of intermediate 5 [54442-28-3] (0.0086 mol) in hydrochloric acid and 2-propanol was stirred and refluxed for 3 hours. Then the reaction mixture was cooled and diluted with ice-water. Potassium hydroxide was added until pH 8 and the mixture was extracted with EtOAc and with dichloromethane. The aqueous layer was acidified with HCl and extracted with dichloromethane. The extracts were combined, washed with brine and concentrated, yielding intermediate 6 [212578-38-6].

Example A.4

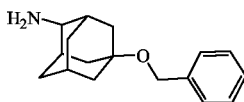
a) Preparation of



intermediate 7

- 5-(Phenylmethoxy)-tricyclo[3.3.1.1^{3,7}]decanone[167856-60-2] (1.5 g) was dissolved in ethanol (25 ml). Hydroxylamine.hydrochloride (0.9 g) was added followed by 2N KOH (10 ml). The mixture was stirred overnight. The volatiles were removed by evaporation, and the residue was extracted with dichloromethane. The organic layer was washed with brine, dried (MgSO₄) and evaporated, yielding 1.4 g of intermediate 7.

b) Preparation of

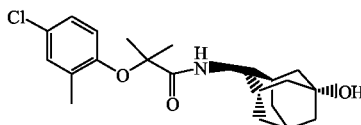


intermediate 8

- Intermediate 7 was dissolved in 7M NH₃/MeOH (40 ml), Raney Nickel (0.5 g) was added, and the mixture was hydrogenated at 14°C. The mixture was filtered, and evaporated, yielding 1.3 g of intermediate 8 as a 1 to 1 mixture of its cis and trans isomers.

15 B. Preparation of the compoundsExample B.1

Preparation of

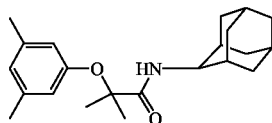


compound 1

- 1-Hydroxy-1H-benzotriazole (0.0007 mol) was added to a solution of intermediate 1 (0.0006 mol) in dichloromethane (10 ml) and DMF (5 ml) and the mixture was stirred for 10 minutes. Then *N*'-(ethylcarbonimidoyl)-*N,N*-dimethyl-1,3-propanediamine, monohydrochloride [25952-53-8] (0.0007 mol) was added and the mixture was stirred for 20 minutes. After addition of (1 α ,3 α ,4 α ,5 β ,7 α)-4-aminotricyclo[3.3.1.1^{3,7}]decan-1-ol [62058-03-1] (0.0007 mol), the reaction mixture was stirred overnight and the solvent was evaporated. The obtained residue was dissolved in dichloromethane and then washed with a 15 % citric acid solution and with a Na₂CO₃ solution. The organic layer was dried through Extrelut and the solvent was evaporated, yielding 0.170 g of compound 1.

Example B.2

Preparation of

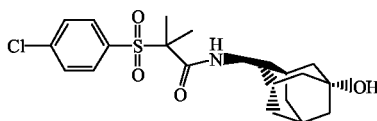


compound 2

Sodium hydride (60%)(0.0009 mol) was added to a stirred solution of 3,5-dimethylphenol (0.00098 mol) in dioxane (5 ml). The mixture was stirred for 45 minutes before intermediate 2 (0.0011 mol) was added. The reaction mixture was stirred for 4 hours at 90°C, then overnight at room temperature. Water (2 ml) was added and the mixture was extracted with dichloromethane. The organic layer was separated, dried, filtered off and the solvent was evaporated. The residue was purified by column chromatography over silica gel (Supelco) (eluent: CH₂Cl₂/CH₃OH 98/2). The product fractions were collected and the solvent was evaporated. The residue was dissolved in dichloromethane and washed 2 times with a potassium hydroxide solution. The organic layer was separated, dried, filtered off and the solvent was evaporated, yielding 0.175 g of compound 2.

Example B.3

Preparation of

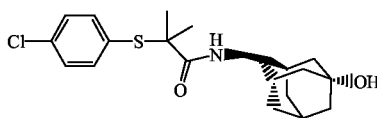


compound 3

A mixture of 2-[(p-chlorophenyl)sulfonyl]-2-methylpropionic acid [28361-38-8] (0.00028 mol) in dichloromethane (5 ml) and DMF (5 ml) was stirred and 1-hydroxy-1*H*-benzotriazole (0.00033 mol) was added. Then the mixture was stirred for 10 minutes and *N*-(ethylcarbonimidoyl)-*N,N*-dimethyl-1,3-propanediamine, monohydrochloride [25952-53-8] (0.00033 mol) was added. The resulting mixture was stirred for 10 minutes and (1 α ,3 α ,4 α ,5 β ,7 α) -4-aminotricyclo[3.3.1.1^{3,7}]decan-1-ol [62058-03-1] (0.00033 mol) was added. The reaction mixture was stirred overnight at room temperature and then the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 98/2). The product fractions were collected and the solvent was evaporated, yielding 0.094 g of compound 3.

Example B.4

a) Preparation of

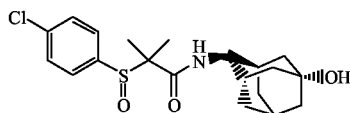


compound 4

A mixture of 2-[(4-chlorophenyl)thio]-2-methylpropanoic acid [17413-74-0] (0.0007 mol) in dichloromethane (5 ml), DMF (5 ml) and DIPEA (0.5 ml) was stirred and

1-[bis(dimethylamino)methylene]-1*H*-benzotriazolium, hexafluorophosphate(1-), 3-oxide (HBTU)(0.0075 mol) was added. After stirring for 15 minutes (1 α ,3 α ,4 α ,5 β ,7 α) -4-aminotricyclo[3.3.1.1^{3,7}]decan-1-ol [62058-03-1] (0.00075 mol) was added. The reaction mixture was stirred overnight at 40°C and the solvent was evaporated. The residue was dissolved in dichloromethane and then the solution was washed with a 15 % citric acid solution and with a sodium carbonate solution. The organic layer was separated, dried, filtered off and the solvent was evaporated. The obtained residue was purified by column chromatography over silica gel (Supelco) (eluent: dichloromethane). The product fractions were collected and the solvent was evaporated, yielding 0.164 g of compound 4.

b) Preparation of

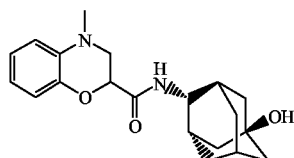


compound 5

A mixture of compound 4((0.00043 mol) in dichloromethane (15 ml) was stirred at -50°C and 3-chlorobenzenecarboxylic acid (0.0005 mol) was added. The reaction mixture was stirred overnight at room temperature and washed with a sodium carbonate solution. The organic layer was dried by filtration through Extrelut and the solvent was evaporated, yielding 0.13 g of compound 5.

Example B.5

Preparation of

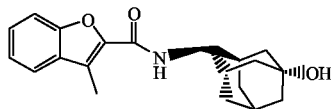


compound 6

N'-(ethylcarbonimidoyl)-*N,N*-dimethyl-1,3-propanediamine, monohydrochloride [25952-53-8] (0.0022 mol) and 1-hydroxy-1*H*-benzotriazole (0.0022 mol) were added to a solution of intermediate 6 [212578-38-6] (0.002 mol) in DMF (25 ml) and the mixture was stirred and warmed (40°C). Then a solution of 4-amino-(1 α ,3 α ,4 α ,5 β ,7 α) tricyclo[3.3.1.1^{3,7}]decan-1-ol [62058-03-1] (0.0024 mol) in hot DMF was added and the reaction mixture was stirred overnight at room temperature. The mixture was poured out into ice-water and was extracted with EtOAc. The obtained extract was washed with water and with brine and then dried and concentrated, yielding 0.040 g of compound 6.

Example B.6

Preparation of

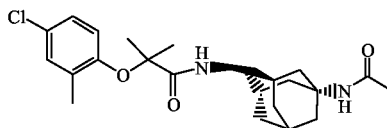


compound 7

1-Hydroxy-1*H*-benzotriazole (0.001 mol) was added to a stirred mixture of 3-methylbenzofurancarboxylic acid [24673-56-1] (0.0009 mol) in dichloromethane (5 ml) and DMF (5 ml). The mixture was stirred for 10 minutes and *N*-(ethyl-carbonimidoyl)-*N,N*-dimethyl-1,3-propanediamine, monohydrochloride [25952-53-8] (0.001 mol) was added. The resulting mixture was stirred for 1 hour before (1 α ,3 α ,4 α ,5 β ,7 α)-4-aminotricyclo[3.3.1.1^{3,7}]decan-1-ol [62058-03-1] (0.001 mol) was added. The reaction mixture was stirred at room temperature overnight and then (Polystyrylmethyl)-trimethylammonium bicarbonate (1 g; Novabiochem Cat. No.: 01-64-0419) and Methylisocyanate polystyrene (1 g; Novabiochem Cat. No.: 01-64-0169) were added. The resulting mixture was shaken for 1 hour and filtered. The filtrate was evaporated and the obtained residue was purified by flash column chromatography (eluent: CH₂Cl₂/CH₃OH 90/10). The product fractions were collected and the solvent was evaporated, yielding 0.144 g of compound 7.

Example B.7

Preparation of

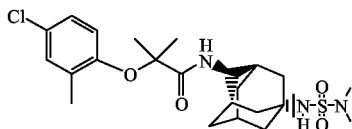


compound 29

A mixture of compound (1) (0.00026 mol) and acetonitrile (2 ml) was stirred. H₂SO₄ (0.05 ml) was added dropwise and the reaction mixture was stirred overnight. The mixture was poured out on ice. The mixture was neutralized with a Na₂CO₃ solution. The mixture was extracted with CH₂Cl₂. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (Supelco)(eluent: CH₂Cl₂/CH₃OH 98/2). The product fractions were collected and the solvent was evaporated, yielding 0.057 g of compound 29.

Example B.8

Preparation of

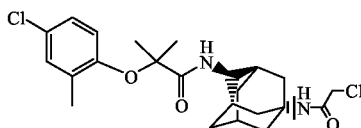


compound 30

A mixture of compound 32 () (0.1 g), CH_2Cl_2 (10 ml) and TEA (2 ml) was stirred. *N,N*-dimethylaminosulfonyl chloride (0.15 ml) was added dropwise. The reaction mixture was stirred overnight. DMAP (cat. quant.) was added and the mixture was stirred at 45°C overnight. The mixture was cooled washed with a 15% citric acid solution. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (Supelco)(eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 99/1). The product fractions were collected and the solvent was evaporated, yielding 0.046 g of compound 30.

Example B.9

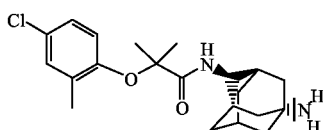
a) Preparation of



compound 31

A mixture of compound (1) () (0.005 mol) and chloroacetonitrile (5 ml) was stirred. H_2SO_4 (0.5 ml) was added and the mixture was stirred over weekend. H_2SO_4 (0.5 ml) was added and the mixture was stirred overnight. The mixture was poured out on ice. The mixture was neutralized with a Na_2CO_3 solution. The mixture was extracted with CH_2Cl_2 . The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was crystallized from DIPE. The precipitate was filtered off and dried, yielding 1.9g (84%) of compound 31.

b) Preparation of

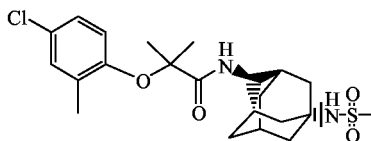


compound 32

A mixture of compound 31 () (0.0042 mol), thiourea (0.006 mol), ethanol (20 ml) and acetic acid (4 ml) was stirred and refluxed overnight. The mixture was poured out into water. The mixture was neutralized with a Na_2CO_3 solution. The mixture was extracted with CH_2Cl_2 . The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was crystallized from DIPE. The precipitate was filtered off and dried, yielding 1g (63.6%) of compound 32.

Example B.10

Preparation of

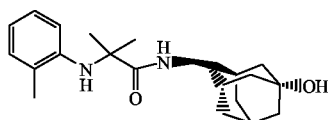


compound 33

A mixture of compound 32) (0.00026 mol), CH₂Cl₂ (10 ml) and TEA (1 ml) was stirred. Methanesulfonyl chloride (0.0006 mol) was added dropwise. The reaction mixture was stirred overnight. DMAP (cat. quant.) was added. The mixture was washed with water. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was purified by high-performance liquid chromatography. The product fractions were collected and the solvent was evaporated, yielding 0.027g of compound 33.

Example B.11

Preparation of

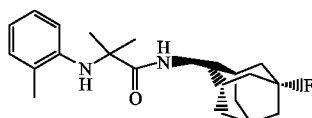


compound 34

- To a mixture of 2-methyl-*N*-o-tolyl-alanine [117755-95-0] (0.006 mol), EDCI (0.009 mol), HOBt (0.009 mol), NMM (0.024 mol) and CH₂Cl₂ (80 ml), a solution of (1 α ,3 α ,4 α ,5 β ,7 α)-4-amino-tricyclo[3.3.1.1^{3,7}]decan-1-ol [62058-03-1] (0.006 mol) in DMF (20 ml) was added after 10 minutes. The reaction mixture was stirred for 16 hours at 20°C under N₂ flow. The mixture was poured out into a column comprising diatomaceous earth. Then the column was washed with CH₃OH/CH₂Cl₂ 5/95. The filtrate was purified by flash chromatography (eluent: CH₃OH(2-3%)/CH₂Cl₂) over SiO₂, yielding 0.89 g (44%) of compound 34

Example B.12

Preparation of

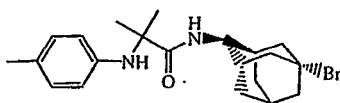


compound 35

- Compound 34 (0.009 mol) was dissolved in CH₂Cl₂ (30 ml). The mixture was cooled to -70°C under N₂ flow. (*N*-ethylethanaminato)trifluoro-sulfur [38078-09-0] (0.002 mol) was added. The reaction mixture was stirred at -70°C for 2 hours. The mixture was washed with a saturated aqueous NaHCO₃ solution (30 ml) and dried (MgSO₄). The solvent was evaporated. The residue was filtered through silica gel. The precipitate was treated with diethyl ether, yielding 0.200g of compound 35.

Example B.13

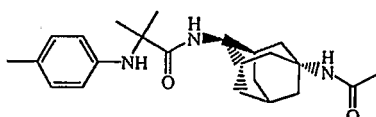
a) Preparation of



compound 36

A mixture of compound 27 (0.00146 mol) and hydrobromic acid (48%) (15 ml) was heated to 80°C overnight. The reaction mixture was evaporated to dryness under reduced pressure. The reaction was repeated, yielding compound 36 (crude).

b) Preparation of

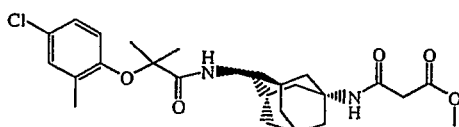


compound 37

- 5 A mixture of compound 36 (crude) and acetamide (q.s.) was heated to 130°C for 48 hours. The mixture was diluted with water, stirred for 30 minutes and then extracted with CH₂Cl₂. The organic layer was separated, dried (Na₂SO₄) and the solvent was evaporated under reduced pressure. The residue (still starting material A) was dissolved in CH₃CN. Acetamide (q.s.) was added. The reaction mixture was heated
- 10 for 4 hours at 170°C in a sealed tube in the microwave. The mixture was poured out into water. The mixture was stirred for 30 minutes and then extracted with CH₂Cl₂. The organic layer was separated, dried (Na₂SO₄) and the solvent was evaporated. The residue was purified by column chromatography (eluent: hexane/EtOAc 50/50 to 0/100). The product fractions were collected and the solvent was evaporated, yielding
- 15 0.07g of compound 37.

Example B.14

Preparation of

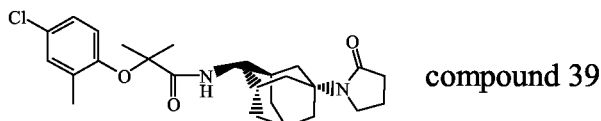


compound 38

- A mixture of compound (1) (0.00026 mol) and cyano-acetic acid, methyl ester (2 ml) was stirred. H₂SO₄ (0.05 ml) was added dropwise and the reaction mixture was stirred
- 20 overnight. The mixture was poured out on ice. The mixture was neutralized with a Na₂CO₃ solution. The mixture was extracted with CH₂Cl₂. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (Supelco)(eluent: CH₂Cl₂/CH₃OH 98/2). The product fractions were collected and the solvent was evaporated, yielding 0.066 g of
- 25 compound 38.

Example B.15

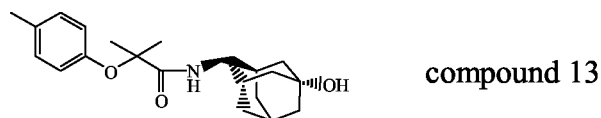
Preparation of



A mixture of compound 32) (0.00013 mol) and dihydro-2(3H)-furanone (1.5 ml) was stirred in a microwave at 240°C for 5000 sec. The mixture was cooled. The solvent was evaporated. The residue was purified by column chromatography over silica gel (Supelco)(eluent: CH₂Cl₂/CH₃OH 100/0 to 0/100). The product fractions were collected and the solvent was evaporated. The residue was purified by column chromatography over silica gel (Supelco)(eluent: CH₂Cl₂/CH₃OH 98/2). The product fractions were collected and the solvent was evaporated, yielding 0.108 g (45%) of compound 39.

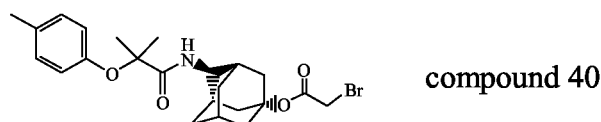
Example B.16

a) Preparation of



To a mixture of 2-methyl-2-(4-methylphenoxy)propanoic acid [23438-11-1] (0.015 mol) and DMF (100 ml), HOBt (0.0165 mol) was added at room temperature. The reaction mixture was stirred until complete dissolution. EDCI (0.0165 mol) was added and the mixture was stirred at room temperature for 30 minutes. (1 α ,3 α ,4 α ,5 β ,7 α)-4-amino-tricyclo[3.3.1.1^{3,7}]decan-1-ol [62058-03-1] (0.0165 mol) was added and the mixture was stirred at room temperature for 3 hours. The solvent was evaporated. The residue was purified by column chromatography (eluent: CH₂Cl₂/CH₃OH 100/0 to 98/2). The product fractions were collected and the solvent was evaporated, yielding 0.290g (54%) of compound 13

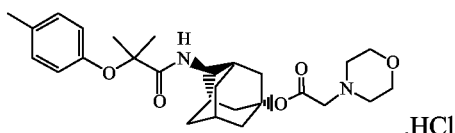
b) Preparation of



To a mixture of compound 13 (0.00466 mol) and bromoacetic acid (0.00513 mol) in CH₂Cl₂ (15 ml) at 5°C, DMAP (0.200 g) was added. A solution of DIPCDI (0.00606 mol) in CH₂Cl₂ (3 ml) was added dropwise. The reaction mixture was stirred until the temperature reached room temperature. Extra bromoacetic acid (0.00513 mol), DMAP (0.200 g) and DIPCDI (0.00606 mol) were added at 5°C. The reaction mixture was stirred for 2 hours until the temperature reached room temperature. The mixture was filtered. The precipitate was purified by high-performance liquid chromatography

(eluent: CH₂Cl₂/CH₃OH 100/0 to 98.4/1.6). The product fractions were collected and the solvent was evaporated. The residue was purified again by high-performance liquid chromatography (eluent: CH₂Cl₂/CH₃OH 100/0 to 98.4/1.6). The product fractions were collected and the solvent was evaporated, yielding 0.842 g (37%) of compound 40.

c) Preparation of

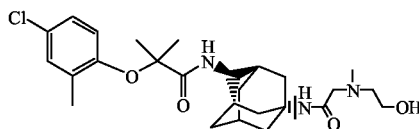


compound 41

A mixture of compound 40 (0.00174 mol), morpholine (0.00209 mol), potassium carbonate (0.00348 mol), acetonitrile (20 ml) and potassium iodide (cat. quant.) was stirred at 50°C for 2 hours. The solvent was evaporated. The residue was dissolved in CH₂Cl₂ and washed with water. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated. The residue was crystallized from 2-propanol and DIPE. The precipitate was filtered off, washed with 2-propanol and dried, yielding 0.290 g (33%) of compound 41.

Example B.17

Preparation of

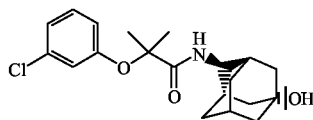


compound 42

A mixture of compound 31 (0.00022 mol), acetonitrile (10 ml) and sodium carbonate (0.06 g) was stirred. 2-(Methylamino)ethanol [109-83-1] (0.0003 mol) was added. The reaction mixture was stirred overnight. The solvent was evaporated. The residue was purified by column chromatography over silica gel (Supelco) (eluent: CH₂Cl₂/CH₃OH 98/2). The product fractions were collected and the solvent was evaporated, yielding 0.031 g of compound 42.

Example B.18

a) Preparation of

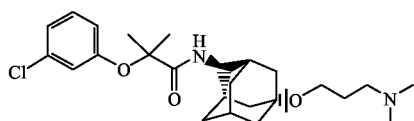


compound 43

To a mixture of 2-(3-chlorophenoxy)-2-methyl-propanoic acid [17413-73-9] (0.010 mol) and CH₂Cl₂ (70 ml), HOBt (0.012 mol) was added at room temperature. The mixture was stirred until complete dissolution of HOBt. EDCI (0.012 mol) was added and the mixture was stirred at room temperature for 30 minutes. (1 α ,3 α ,4 α ,5 β ,7 α)-4-aminotricyclo[3.3.1.1^{3,7}]decan-1-ol [62058-03-1] (0.012 mol) was added and the

- mixture was stirred at room temperature overnight. The solvent was evaporated. The residue was dissolved in CH_2Cl_2 and washed with 15% citric acid solution, 1M Na_2CO_3 and water. The organic layer was separated, dried (MgSO_4), filtered and the solvent was evaporated. The residue was purified by column chromatography (eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 100/0 to 98/2). Two product fraction groups were collected and the solvents were evaporated. The residue was crystallized from DIPE. The precipitate was filtered off and dried, yielding 1.97g of compound 43.

b) Preparation of

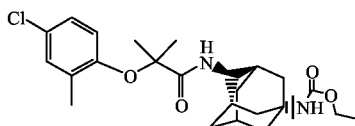


compound 44

- To a mixture of compound 43 (0.00055 mol) and 3-chloro-*N,N*-dimethyl-1-propanamine, hydrochloride [5407-04-5] (0.000826 mol) in DMF (8 ml) and toluene (2 ml), a dispersion of sodium hydride in mineral oil (60%) (0.0165 mol) was added in 4 portions over 90 minutes. The reaction mixture was stirred at 70°C for 24 hours. The solvent was evaporated. Water was added. The mixture was extracted with CH_2Cl_2 . The organic layer was separated, dried (MgSO_4), filtered and the solvent was evaporated. The residue was purified by high-performance liquid chromatography. The product fractions were collected and the solvent was evaporated, yielding 0.038g (15%) of compound 44.

Example B.19

Preparation of

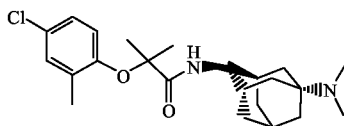


compound 45

- A mixture of compound 32) (0.00026 mol), CH_2Cl_2 (3 ml) and sodium carbonate (0.1 g) was stirred. Carbonochloridic acid, ethyl ester [541-41-3](0.001 mol) was added dropwise. The reaction mixture was stirred over weekend. The mixture was washed with water. The mixture was filtered through Extrelut and the filtrate was evaporated. The residue was purified by chromatography over silica gel (Supelco)(eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 98/2). The product fractions were collected and the solvent was evaporated, yielding 0.1g of compound 45.

Example B.20

Preparation of

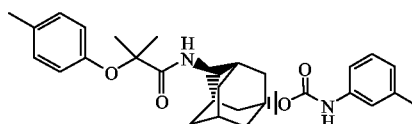


compound 46

- A mixture of compound 32) (0.1 g), paraformaldehyde (0.1 g), platinum on activated carbon (5%) (0.010 g), thiophene (0.1 ml), methanol (40 ml) and hydrogen (1 equivalent) was stirred at 50°C overnight. The mixture was filtered and the filtrate was evaporated. The residue was suspended in CH₂Cl₂ and washed with water. The mixture was filtered through Extrelut filter and the filtrate was evaporated. The residue was purified by high-performance liquid chromatography. The product fractions were collected and the solvent was evaporated, yielding 0.038 g of compound 46.

10 Example B.21

Preparation of

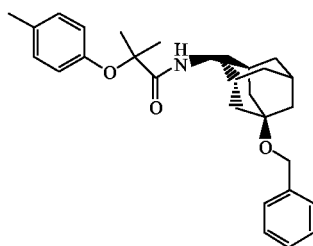


compound 47

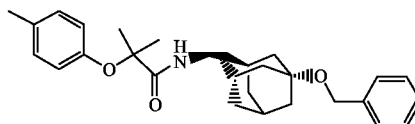
- A mixture of compound 13 () (0.00058 mol), 1-isocyanato-4-methyl-benzene [622-58-2] (0.000758 mol), chlorotrimethylsilane [75-77-4] (0.000058 mol) and 1,2-dichloroethane (5 ml) was stirred overnight at 50°C. The solvent was evaporated. The residue was purified by column chromatography (Supelco). The product fractions were collected and the solvent was evaporated, yielding 0.045g (16%) of compound 47.

Example B.22

Preparation of



compound 48



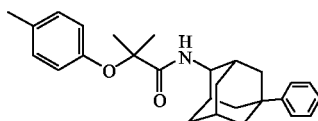
compound 52

- A mixture of 2-methyl-2-(4-methylphenoxy)propanoic acid [23438-11-1] (0.004 mol), CH₂Cl₂ (25 ml) and DMF (7 ml) was stirred. HOBt (0.004 mol) was added and the mixture was stirred until dissolution. EDCI (0.004 mol) was added and the mixture was stirred for 30 minutes. A solution of intermediate 8 (0.0027 mol) in CH₂Cl₂ (25 ml) and DMF (7 ml) was added dropwise. The reaction mixture was stirred overnight. The solvent was evaporated. The residue was dissolved in CH₂Cl₂ and washed with a

Na₂CO₃ solution. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (Biotage) (eluent: CH₂Cl₂/hexane/EtOAc 50/48/2). Two product fraction groups were collected and their solvents were evaporated. The residue was purified by high-
 5 performance liquid chromatography. The product fractions were collected and the solvent was evaporated, yielding 0.4 g of compound 48 and 0.175 g of compound 52.

Example B.23

Preparation of



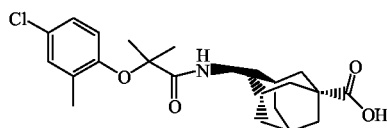
compound 49

A mixture of 2-methyl-2-(4-methylphenoxy)propanoic acid [23438-11-1] (0.004 mol),
 10 CH₂Cl₂ (25 ml) and DMF (7 ml) was stirred. HOBt (0.004 mol) was added and the mixture was stirred until dissolution. EDCI (0.004 mol) was added and the mixture was stirred for 30 minutes. A solution of 5-phenyl-tricyclo[3.3.1.1^{3,7}]decan-2-amine [733695-05-1] (0.0035 mol) in CH₂Cl₂ (25 ml) and DMF (7 ml) was added dropwise. The reaction mixture was stirred overnight. The solvent was evaporated. The residue
 15 was dissolved in CH₂Cl₂ and washed with a Na₂CO₃ solution. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/EtOAc 98/2). The product fractions were collected and the solvent was evaporated. The residue was crystallized from DIPE. The precipitate was filtered off and dried, yielding of compound 49.

20

Example B.24

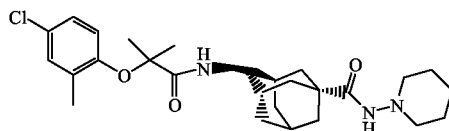
a) Preparation of



compound 50

H₂SO₄ (30 ml) was stirred on ice. A solution of compound (1) (0.00265 mol) in formic acid (30 ml) was added dropwise. The reaction mixture was stirred for 5 days. Then the mixture was stirred at 60°C for 3 days. Extra H₂SO₄ (10 ml) was added at 60°C.
 25 The mixture was poured out on ice. The mixture was extracted with CH₂Cl₂. The organic layer was separated, washed twice with water, dried, filtered and the solvent was evaporated, yielding 0.8g of compound 50.

b) Preparation of

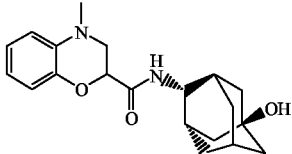
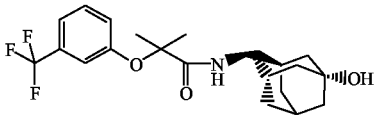
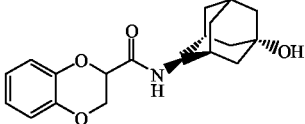
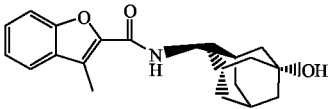
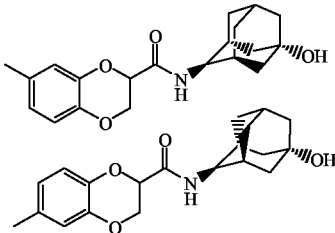
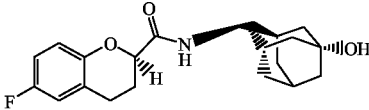
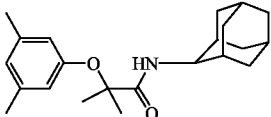
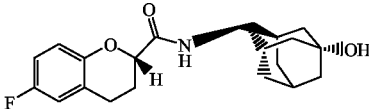
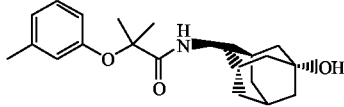
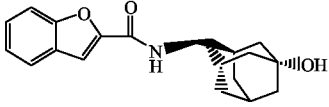


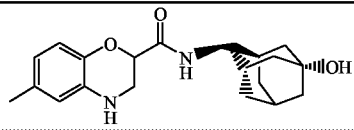
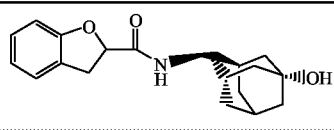
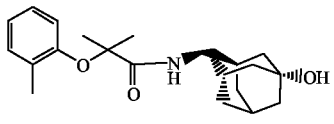
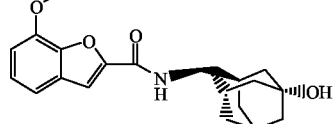
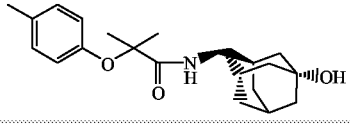
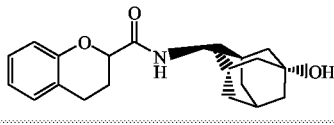
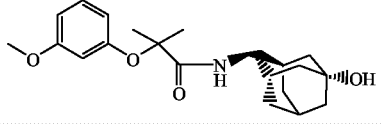
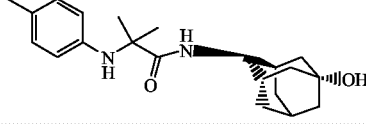
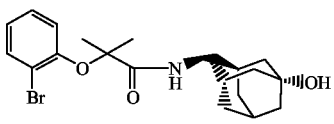
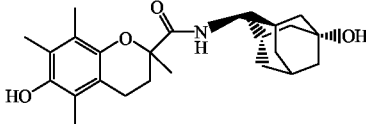
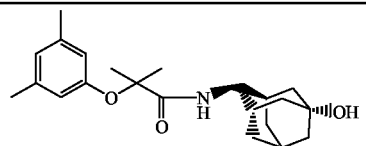
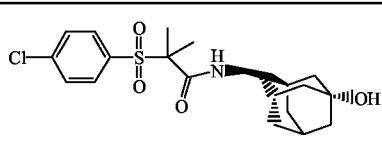
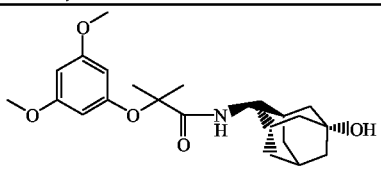
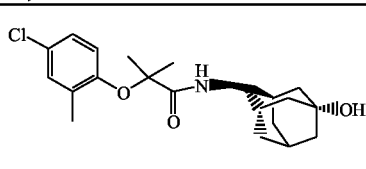
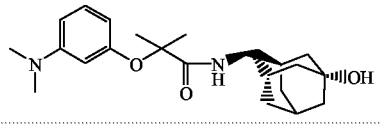
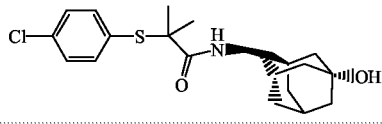
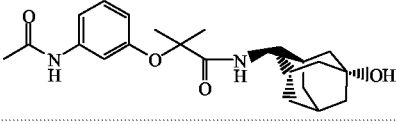
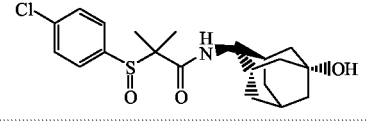
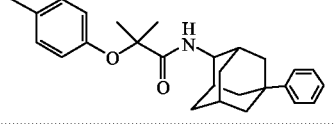
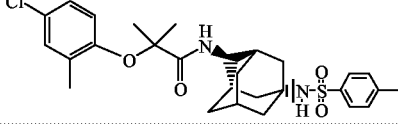
compound 51

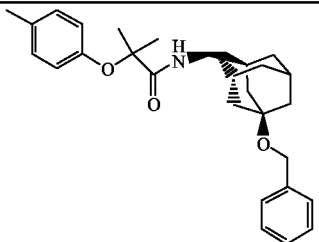
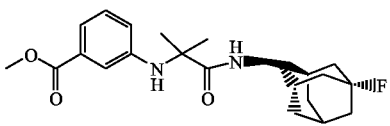
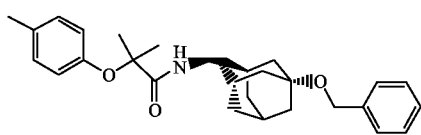
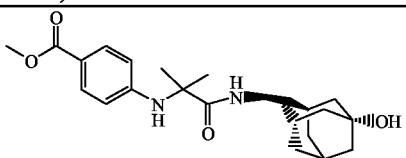
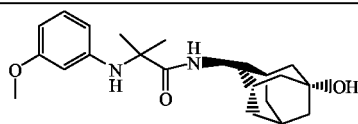
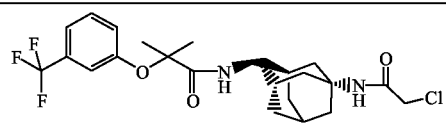
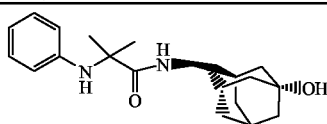
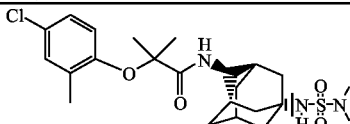
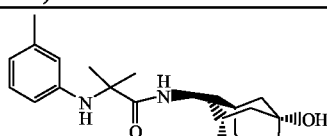
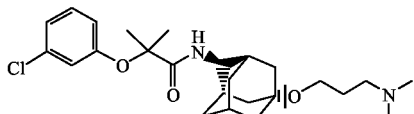
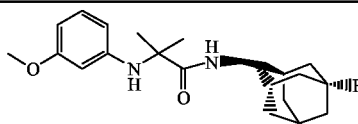
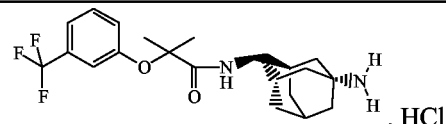
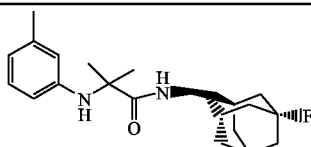
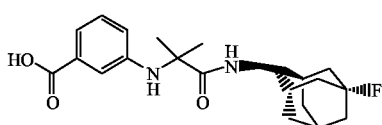
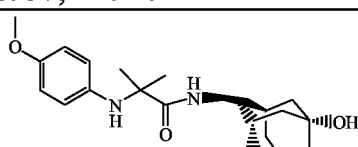
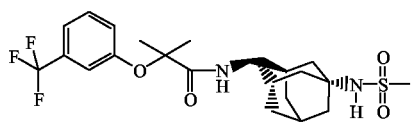
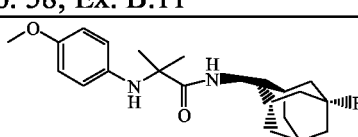
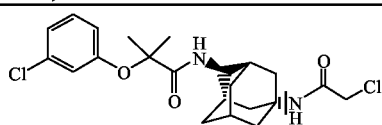
A mixture of compound 50 (0.00024 mol), CH₂Cl₂ (5 ml) and DMF (2 ml) was stirred. HOBt (0.00025 mol) was added. EDCI (0.00025 mol) was added and the mixture was stirred for 1 hour. 1-Piperidinamine (0.00025 mol) was added and the mixture was stirred overnight. The mixture was poured out into water. The mixture was extracted with CH₂Cl₂. The organic layer was separated, washed, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 98/2). The product fractions were collected and the solvent was evaporated. The residue was purified by high-performance liquid chromatography. The product fractions were collected and the solvent was evaporated, yielding 0.051g of compound 51.

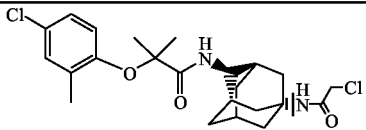
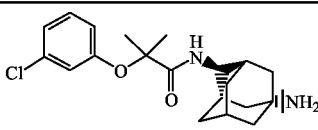
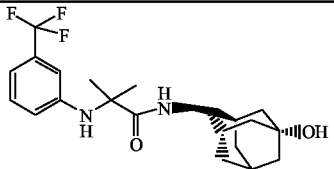
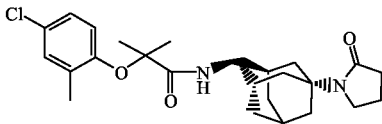
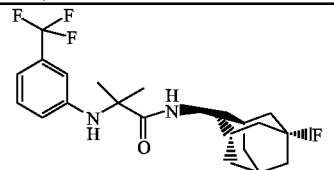
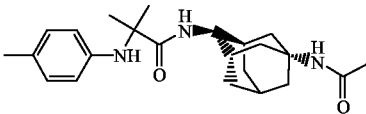
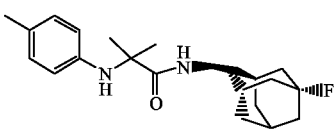
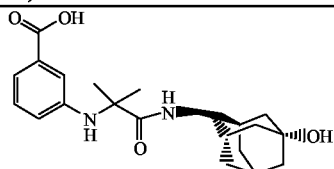
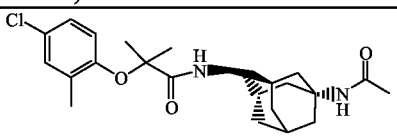
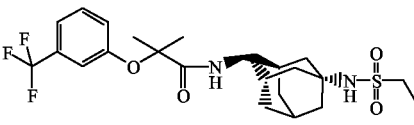
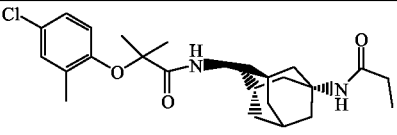
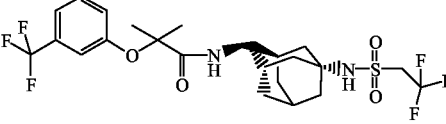
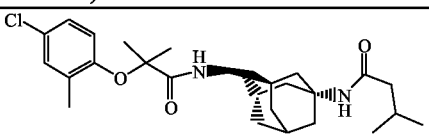
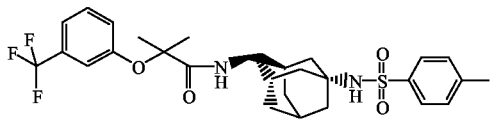
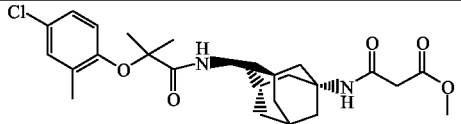
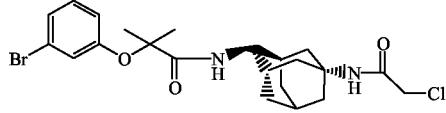
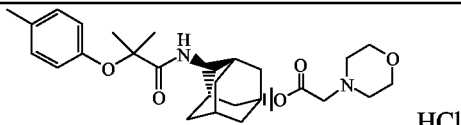
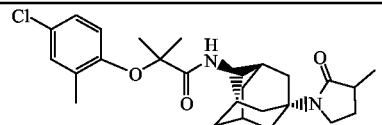
Table F-1 lists the compounds that were prepared according to one of the above Examples.

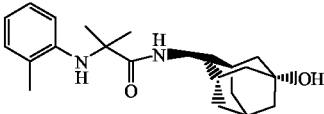
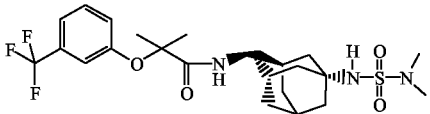
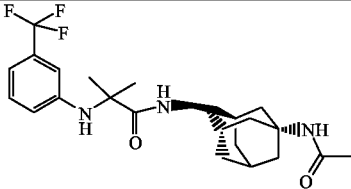
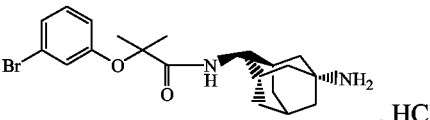
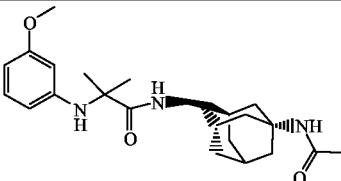
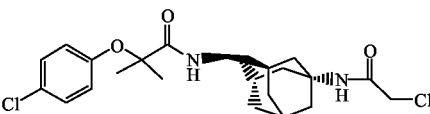
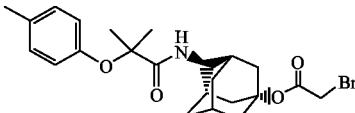
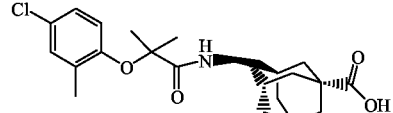
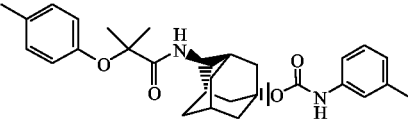
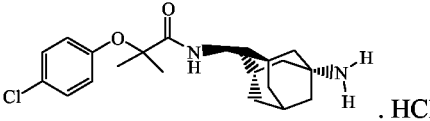
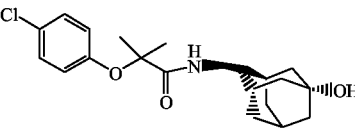
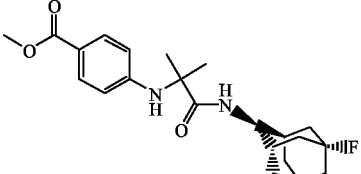
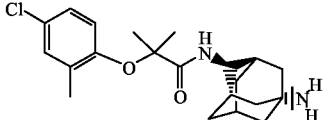
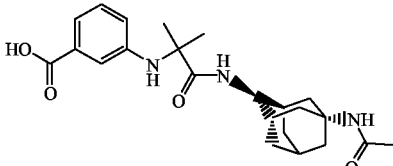
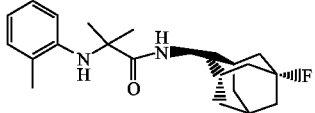
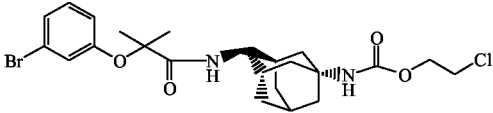
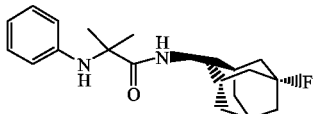
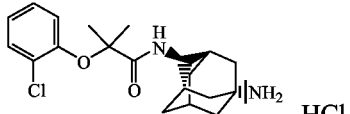
Table F-1

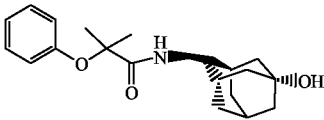
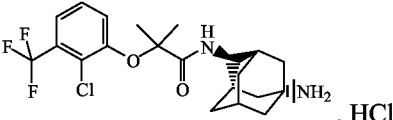
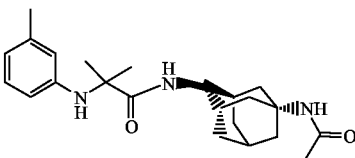
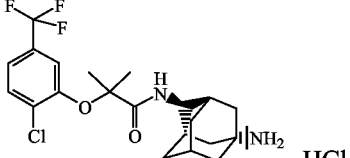
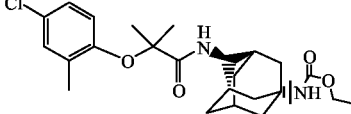
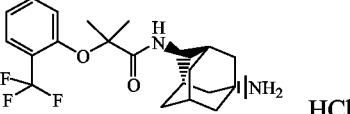
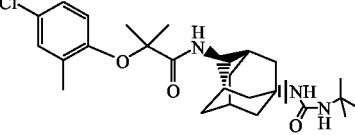
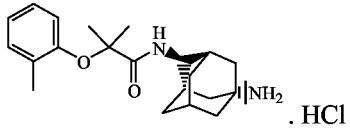
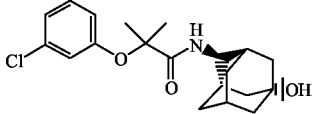
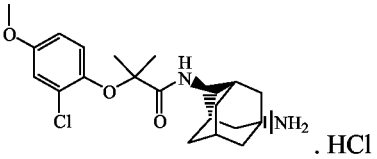
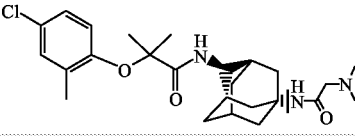
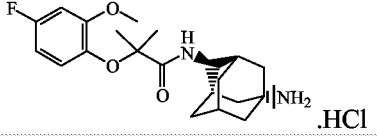
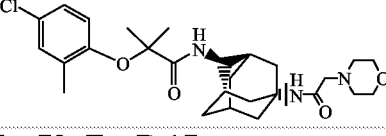
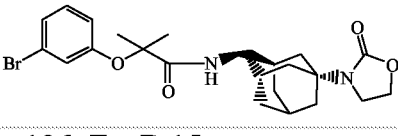
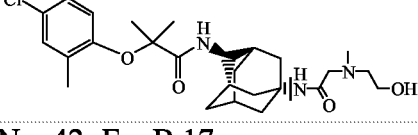
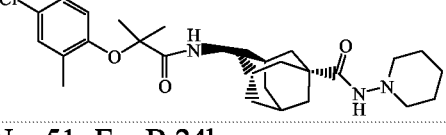
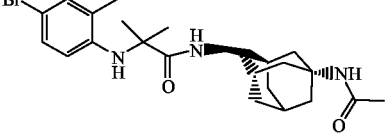
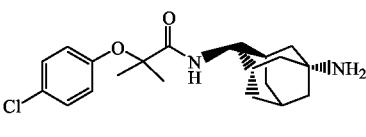
	
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Co. No. 9; Ex. B.5	Co. No. 21; Ex. B.6
	
Co. No. 2; Ex. B.2	Co. No. 22; Ex. B.6
	
Co. No. 10; Ex. B.2	Co. No. 23; Ex. B.6

	
Co. No. 11; Ex. B.5	Co. No. 24; Ex. B.6
	
Co. No. 12; Ex. B.2	Co. No. 25; Ex. B.6
	
Co. No. 13; Ex. B.2 + Ex. B.16a	Co. No. 26; Ex. B.6
	
Co. No. 14; Ex. B.2	Co. No. 27; Ex. B.1
	
Co. No. 15; Ex. B.2	Co. No. 28; Ex. B.6
	
Co. No. 16; Ex. B.2	Co. No. 3; Ex. B.3
	
Co. No. 17; Ex. B.2	Co. No. 1; Ex. B.1
	
Co. No. 18; Ex. B.2	Co. No. 4; Ex. B.4a
	
Co. No. 19; Ex. B.2	Co. No. 5; Ex. B.4b
	
Co. No. 49; Ex. B.23	Co. No. 77; Ex. B.10

	
Co. No. 48; Ex. B.22	Co. No. 78; Ex. B.12
	
Co. No. 52; Ex. B.22	Co. No. 79; Ex. B.11
	
Co. No. 53; Ex. B.11	Co. No. 80; Ex. B.7
	
Co. No. 54; Ex. B.11	Co. No. 30; Ex. B.8
	
Co. No. 55; Ex. B.11	Co. No. 44; Ex. B.18
	
Co. No. 56; Ex. B.12	Co. No. 81; Ex. B.9
	
Co. No. 57; Ex. B.12	Co. No. 82; Ex. B.12
	
Co. No. 58; Ex. B.11	Co. No. 83; Ex. B.10
	
Co. No. 59; Ex. B.12	Co. No. 84; Ex. B.7

	
Co. No. 31; Ex. B.9a	Co. No. 85; Ex. B.9
	
Co. No. 60; Ex. B.11	Co. No. 39; Ex. B.15
	
Co. No. 61; Ex. B.12	Co. No. 37; Ex. B.13
	
Co. No. 62; Ex. B.12	Co. No. 86; Ex. B.11
	
Co. No. 29; Ex. B.7	Co. No. 87; Ex. B.10
	
Co. No. 63; Ex. B.7	Co. No. 88; Ex. B.10
	
Co. No. 64; Ex. B.7	Co. No. 89; Ex. B.10
	
Co. No. 38; Ex. B.14	Co. No. 90; Ex. B.7
	
Co. No. 41; Ex. B.16c	Co. No. 91; Ex. B.15

	
Co. No. 34; Ex. B.11	Co. No. 92; Ex. B.8
	
Co. No. 65; Ex. B.13	Co. No. 93; Ex. B.9
	
Co. No. 66; Ex. B.13	Co. No. 94; Ex. B.7
	
Co. No. 40; Ex. B.16b	Co. No. 50; Ex. B.24a
	
Co. No. 47; Ex. B.21	Co. No. 95; Ex. B.9
	
Co. No. 67; Ex. B.2	Co. No. 96; Ex. B.12
	
Co. No. 32; Ex. B.9b	Co. No. 97; Ex. B.13
	
Co. No. 35; Ex. B.12	Co. No. 98; Ex. B.19
	
Co. No. 68; Ex. B.12	Co. No. 99; Ex. B.10

 Co. No. 69; Ex. B.2	 Co. No. 100; Ex. B.9
 Co. No. 70; Ex. B.13	 Co. No. 101; Ex. B.9
 Co. No. 45; Ex. B.19	 Co. No. 102; Ex. B.9
 Co. No. 71; Ex. B.17	 Co. No. 103; Ex. B.9
 Co. No. 43; Ex. B.18a	 Co. No. 104; Ex. B.9
 Co. No. 72; Ex. B.17	 Co. No. 105; Ex. B.9
 Co. No. 73; Ex. B.17	 Co. No. 106; Ex. B.15
 Co. No. 42; Ex. B.17	 Co. No. 51; Ex. B.24b
 Co. No. 74; Ex. B.13	 Co. No. 107; Ex. B.9

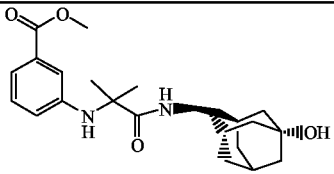
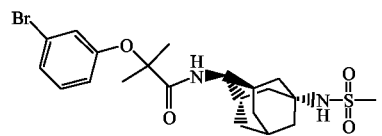
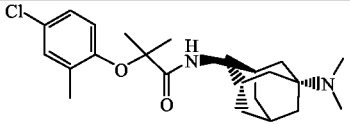
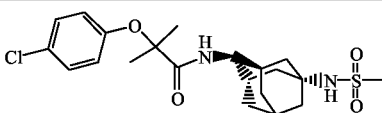
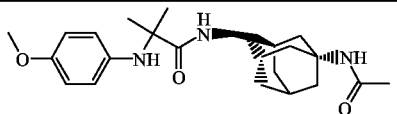
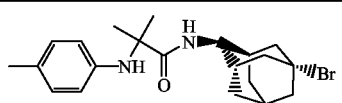
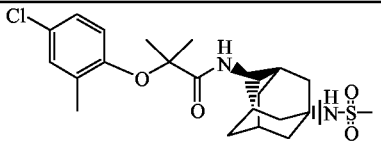
	
Co. No. 75; Ex. B.11	Co. No. 108; Ex. B.10
	
Co. No. 46; Ex. B.20	Co. No. 109; Ex. B.10
	
Co. No. 76; Ex. B.12	Co. No. 36; Ex. B.13a
	
Co. No. 33; Ex. B.10	

Table F-2 provides the ^1H NMR chemical shifts data for the compounds of the present invention using CDCl_3 as a solvent.

5 Table F-2

Co. No.	NMR data
6	$^1\text{H-NMR, CDCl}_3$; 1.37 –2.14 (m, 13H, H-adamantane); 2.88 (s, 3H, N-CH ₃); 3.36 and 3.51(2x dd, 2H, CH ₂); 4.02 (d, CH); 4.74 (dd, 1H, OCH); 6.70 and 6.90 (2x t, 4H-aromatic); 6.81 (d, 1H, NH)
8	$^1\text{H-NMR, CDCl}_3$; 1.39- 2.15 (m, 13H-adamantane); 4.03(d, 1H, CH); 4.28 and 4.48 (2x dd, CH ₂); 4.71 (dd, 1H, OCH); 6.76 (d, NH); 6.91 (m, 3H, H-aromatic); 6.98-7.01 (m, 1H-aromatic)
9	mixture
2	$^1\text{H-NMR, CDCl}_3$; 1.51 (s, 6H, 2x CH ₃); 1.54-1.95(m, 14H-adamantane); 2.26 (s, 6H, 2x CH ₃); 4.09 (d, 1H, CH); 6.56and 6.69 (2x s, 3H-aromatic); 7.11 (br d, NH)
10	$^1\text{H-NMR, CDCl}_3$; 1.52 (s, 6H, 2x CH ₃); 1.44-2.18 (m, 13H-adamantane); 2.31 (s, 3H, CH ₃); 4.06 (d, 1H, CH); 6.73 and 6.88 (2x d, 3H-aromatic); 7.01 (br d, NH); 7.14 (t, 1H-aromatic)
11	$^1\text{H-NMR, CDCl}_3$; 1.46-2.17 (m, 13H-adamantane); 2.21 (s, 3H, CH ₃); 3.49 and 3.64 (2x dd, 2H, CH ₂); 3.75 (br s, NH); 4.01 (d, CH); 4.64(dd, OCH); 6.44(s, 1H-aromatic; 6.50 (d, 1H-aromatic); 6.76-6.86 (m, NH, 1H-aromatic)
12	$^1\text{H-NMR, CDCl}_3$; 1.53 (s, 6H, 2x CH ₃); 1.45-2.16 (m, 13H-adamantane); 2.28 (s, 3H, CH ₃); 4.08 (d, 1H, CH); 6.86 and 6.95 (d and t, 2H-aromatic); 7.08 (m, NH, 1H-aromatic); 7.19 (d, 1H-aromatic)
13	$^1\text{H-NMR, CDCl}_3$; 1.48 (s, 6H, 2x CH ₃); 1.44-2.16 (m, 13H-adamantane); 2.31 (s, 3H, CH ₃); 4.05 (d, 1H, CH); 6.83 (m, 2H-aromatic); 7.08 (m, NH, 2H-aromatic)
14	$^1\text{H-NMR, CDCl}_3$; 1.48 (s, 6H, 2x CH ₃); 1.46, 1.59, 1.75, 1.89, 2.10 (5x br d, 13H-adamantane); 3.78 (s, 3H, CH ₃); 4.05 (d, 1H, CH); 6.52 (m, 2H-aromatic); 6.63 (d,

	1H-aromatic); 6.96 (d, NH) 7.18 (t, 1H-aromatic)
15	1H-NMR,CDCl ₃ ; 1.53 (s, 6H, 2x CH ₃);1.45-1.93(m, 10H-adamantane); 2.10 (br s 3H-adamantane); 4.05 (d, 1H, CH); 6.85 (m, NH, 2H-aromatic); 7.09-7.22 (m, 3H-aromatic)
16	1H-NMR,CDCl ₃ ; 1.51 (s, 6H, 2x CH ₃);1.44-2.15 (m, 13H-adamantane); 2.28 (s, 6H, 2x CH ₃); 4.06 (d, 1H, CH); 6.54 and 6.71 (2x s, 3H-aromatic); 7.01 (br d, NH)
17	1H-NMR,CDCl ₃ ; 1.53 (s, 6H, 2x CH ₃);1.42-2.15 (m, 13H-adamantane); 3.75 (s, 6H, 2x OCH ₃); 4.04 (d, 1H, CH); 6.10 (d, 2H-aromatic); 6.20 (t, 1H-aromatic); 6.93 (d, NH)
18	1H-NMR,CDCl ₃ ; 1.52 (s, 6H, 2x CH ₃);1.42-2.15 (m, 13H-adamantane); 2.93 (s, 6H, 2x NCH ₃); 4.05 (d, 1H, CH); 6.28 (m, 2H-aromatic); 6.45 (d, 1H-aromatic); 7.03 (d, NH); 7.10 (t, 1H-aromatic)
19	1H-NMR,CDCl ₃ ; 1.53 (s, 6H, 2x CH ₃);1.43-2.15 (m, 13H-adamantane); 2.17 (s, 3H, CH ₃); 4.05 (d, 1H, CH); 6.67 (d, 1H-aromatic); 6.97 (d, NH); 7.10-7.23 (m, 3H-aromatic)
20	1H-NMR,CDCl ₃ ; 1.55 (s, 6H, 2x CH ₃);1.44-2.13 (m, 13H-adamantane); 4.06 (d, 1H, CH); 6.84 (d, NH); 7.10, 7.18, 7.33, 7.41 (d, s, d, t, 4H-aromatic)
7	1H-NMR,CDCl ₃ ; 1.50 (br d, 2H-adamantane); 1.80-1.99 (m, 8H-adamantane); 2.25 (br d, 3H-adamantane); 2.62 (s, 3H, CH ₃); 4.25 (d, CH); 6.86 (d, NH); 7.28-7.64 (m, 4H-aromatic)
21	1H-NMR,CDCl ₃ ; 1.45-2.18 (m, 14H, 13H-adamantane, H ^A -CH ₂); 2.39 (m, 1H, H ^B -CH ₂); 2.80 (m, 2H, CH ₂); 4.04 (d, CH); 4.56(dd, OCH); 6.77-6.80 (m, NH, 3H-aromatic)
22	1H-NMR,CDCl ₃ ; 1.45-2.18 (m, 14H, 13H-adamantane, H ^A -CH ₂); 2.39 (m, 1H, H ^B -CH ₂); 2.80 (m, 2H, CH ₂); 4.04 (d, CH); 4.56(dd, OCH); 6.76-6.89 (m, NH, 3H-aromatic)
23	1H-NMR,CDCl ₃ ; 1.56-2.30 (m, 13H-adamantane); 4.26(d, CH); 6.84 (d, NH); 7.30 and 7.42 (2x t, 2H-aromatic); 7.53 and 7.69 (2x d, 2H- aromatic); 7.48 (s, 1H-furan)
24	1H-NMR,CDCl ₃ ; 1.40-2.21 (m, 13H-adamantane); 3.40 and 3.60 (2x dd, 2H, CH ₂); 4.03 (d, CH); 5.14 (dd, OCH); 6.91 and 7.18 (2x m, 4H-aromatic)
25	1H-NMR,CDCl ₃ ; 1.60-2.31 (m, 13H-adamantane); 4.03 (s, 3H, CH ₃); 4.23(d, CH); 6.86 (d, NH); 6.92 (dd, 1H-aromatic); 7.19-7.27 (m, 2H-aromatic); 7.47 (s, 1H-furan)
26	1H-NMR,CDCl ₃ ; 1.44-2.19 (m, 14H, 13H-adamantane, H ^A -CH ₂); 2.40 (m, 1H, H ^B -CH ₂); 2.81 (m, 2H, CH ₂); 4.05 (d, CH); 4.56(dd, OCH); 6.85-6.94 (m, NH, 2H-aromatic); 7.05-7.17 (m, 2H-aromatic)
27	1H-NMR,CDCl ₃ ; 1.48 (s, 6H, 2x CH ₃); 1.39, 1.56, 1.72, 1.89, 2.04 (5x br d, 13H-adamantane); 2.24 (s, 3H, CH ₃); 3.63 (s, 1H, NH); 4.03 (d, 1H, CH); 6.50 (d, 2H-aromatic); 6.96 (d, 2H-aromatic); 7.48 (d, 1H, NH)
28	1H-NMR,CDCl ₃ ; 1.58, 2.08, 2.18, 2.21 (4x s, 4x CH ₃); 1.05, 1.24, 1.48, (3x brd, 4H-adamantane); 1.62-1.98 (m, 9H-adamantane); 2.33-2.68 (m, 4H 2x CH ₂); 3.91 (d, 1H, CH); 6.64 (d, 1H, NH)
3	1H-NMR,CDCl ₃ ; 1.55 (2x s, 6H, 2x CH ₃);1.59 and 2.20 (2x d, 6H-adamantane); 1.77-1.91 (m, 7H-adamantane); 4.02 (d, 1H, CH); 7.29 (d, 1H, NH); 7.54 and 7.77 (2x d, 4H-aromatic)
1	1H-NMR,CDCl ₃ ; 1.44, 1.59, 1.76, 1.81 (4x d, 10H-adamantane); 1.51 (s, 6H, 2x CH ₃); 2.02 (br d, 3H-adamantane); 2.24 (s, 3H, CH ₃); 4.06 (d, 1H, CH); 6.98 (d, 1H, NH); 6.78, 7.05, 7.17 (3xd, 3H-aromatic);
4	1H-NMR,CDCl ₃ ; 1.52 (s, 6H, 2x CH ₃);1.42-2.19 (m, 13H-adamantane); 4.00 (d, 1H, CH); 7.22 (d, 1H, NH); 7.24-7.33 (m, 4H-aromatic)
5	1H-NMR,CDCl ₃ ; 1.31 and 1.59 (2x s, 6H, 2x CH ₃);1.42-2.21 (m, 13H-adamantane); 3.98 (d, 1H, CH); 7.34 (d, 1H, NH); 7.45-7.55 (m, 4H-aromatic)

Further compound identificationLCMS-method:

- 5 The HPLC gradient was supplied by a Waters Alliance HT 2790 system with a column heater set at 40°C. Flow from the column was split to a Waters 996 photodiode array (PDA) detector and a Waters-Micromass ZQ mass spectrometer with an electrospray ionization source operated in positive and negative ionization mode.
- 10 Reversed phase HPLC was carried out on a Xterra MS C18 column (3.5 mm, 4.6 x 100 mm) with a flow rate of 1.6 ml/min. Three mobile phases (mobile phase A 95% 25mM ammoniumacetate + 5% acetonitrile; mobile phase B: acetonitrile; mobile phase C: methanol) were employed to run a gradient condition from 100 % A to 50% B and 50% C in 6.5 minutes, to 100 % B in 1 minute, 100% B for 1 minute and reequilibrate with
- 15 100 % A for 1.5 minutes. An injection volume of 10 uL was used.

Table : retention time (RT in minutes) and molecular weight as the MH⁺

20

Compound No.	Rt	MH⁺
6	4.77	343.2
8	5.15	328.1
9	5.58	342
2	7.52	342.3
10	6.12	344
11	5.31	343
12	6.17	344
13	6.19	344
14	5.72	360
15	6.28	425
16	6.45	358
17	5.72	390
18	5.72	279
19	4.71	404
20	6.21	415
7	5.98	651
21	5.54	404
22	5.55	404
23	5.39	623
24	5.09	353

Compound No.	Rt	MH ⁺
25	5.29	359
26	5.55	328.1
27	5.52	343
28	5.65	400
3	5.54	279
1	6.54	376.2
4	6.42	380
5	5.04	396
49	7.52	404
48	7.28	434
52	7.38	434
53	4.98	359
54	5.08	329
55	5.44	343
56	6.02	361
57	6.37	345
58	4.95	359
59	5.98	361
31	6.78	470
60	5.68	397
61	6.49	399
62	6.41	345
29	6.59	170
63	6.51	433
64	7.01	288
38	6.32	477
41	6.72	471
34	5.61	343
65	5.78	455
66	5.15	400
47	7.21	477
67	6.22	125
32	5.62	377
35	6.48	345
68	6.14	331
69	5.78	330
70	5.55	384
45	6.99	466
71	6.99	476
43	6.17	346
72	6.78	462
73	6.79	504
42	6.52	492
74	6.18	464
75	5.02	387
46	5.68	405
76	5.09	400

Compound No.	Rt	MH⁺
33	6.55	453.2
77	7.11	548
78	6.02	389
79	4.78	387
80	6.48	490
30	6.82	501
44	5.91	449
81	5.32	397
82	4.21	375
83	6.24	492
39	6.88	462
37	5.61	384
86	3.12	373
87	6.38	506
88	6.54	541.1
89	6.85	568
90	6.17	482
91	7.05	476
92	6.52	521
93	5.32	409
94	6.48	456
50	6.12	306
95	5.22	363
96	5.84	389
97	3.35	431
98	6.29	512
99	5.11	363
100	5.61	431
102	4.98	397
103	5.14	343
104	5.02	222
105	4.95	377
106	6.44	496
51	6.85	488
108	6.34	502
109	6.25	441

C. Pharmacological examples

Example C1 : Cellular assays to test the effect of compounds on 11 β -hydroxysteroid dehydrogenase type 1 and type 2

5

The effects on 11 β -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 37°C in a humidified 5% CO₂ atmosphere. Medium was refreshed twice a week.

- 5 Fibroblasts were differentiated into adipocytes at 37°C 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 normal Falcon 12 well plates at a density of 250000 cells /well and incubated for 16 hours at 37°C 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. Following a 4 hour pre-incubation with test compound, 0.5 µCi ³H-cortisone or dehydrocorticosterone, was added to the 3T3-L1 cultures. One hour later, the medium was extracted on Extrelut³- columns with 15 ml diethyl ether and the extract was analysed by HPLC as described above. The effects of JNJ-compounds on rat hepatocyte HSD1 activity was measured after an incubation period of 90 minutes with 0.5µCi³H-dehydrocorticosterone. Corticosterone formation was analysed by HPLC.
- 10
- 15

- 20 The effects on 11β-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 37°C 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.

- 25 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 37°C 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.
- 30

Following a 4 hour pre-incubation with test compound, 0.5 µCi ³H-cortisol or corticosterone, was added to the cultures. One hour later, the medium was extracted on Extrelut³-columns with 15 ml diethyl ether and the extract was analysed by HPLC as described above.

35

As for the enzymatic assays, the compounds to be tested were taken from a stock solution and tested at a final concentration ranging from - 10⁻⁵M to 10⁻¹⁰M. 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).

5

	HSD2 cellular HepG2	HSD1 cellular 3T3-L1
Compound Number	Score	Score
5	NT	3
6	1	3
8	2	3
9	3	3
2	1	3
10	2	3
11	2	3
12	3	3
13	3	3
14	3	3
15	3	3
16	3	3
17	2	3
18	3	3
19	3	3
20	3	3
7	1	3
21	3	3
22	2	3
23	1	3
24	2	3
25	2	3
26	3	3
27	1	3
28	3	3
3	3	3
1	3	3
4	2	3
99	NT	3
102	NT	3
104	NT	3
101	NT	3
105	NT	3
103	NT	3
32	1	3
100	NT	3

-68-

	HSD2 cellular HepG2	HSD1 cellular 3T3-L1
Compound Number	Score	Score
95	1	3
93	1	3
85	1	3
81	1	3
34	2	3
54	1	3
55	1	3
53	1	3
60	1	3
58	1	3
79	NT	3
75	1	3
86	NT	2
37	1	3
74	2	3
70	2	3
65	1	3
76	1	3
66	2	3
97	NT	1
35	2	3
68	1	3
57	1	3
62	1	3
56	1	3
59	1	3
78	NT	3
61	1	3
96	NT	2
82	NT	2
38	2	3
39	3	3
91	3	3
41	2	3
50	2	3
42	2	3
73	2	3
72	2	3
71	NT	2
44	2	3
45	2	3
98	NT	3
67	2	3

	HSD2 cellular HepG2	HSD1 cellular 3T3-L1
Compound Number	Score	Score
69	2	3
43	3	3
46	1	3
47	2	3
48	3	3
52	2	3
49	1	2
29	3	3
63	3	3
31	2	3
64	2	3
94	2	3
80	2	3
90	2	3
30	2	3
92	2	3
33	2	3
83	2	3
87	2	3
77	1	3
88	2	3
89	1	3

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.

- 5 "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

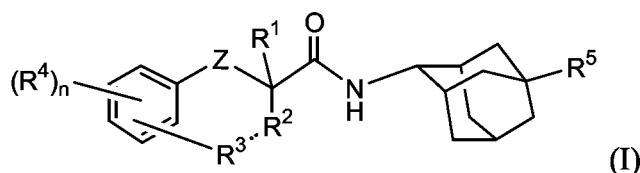
- 10 A mixture of A.I. (100 g), lactose (570 g) and starch (200 g) was mixed well and thereafter humidified with a solution of sodium dodecyl sulfate (5 g) and polyvinylpyrrolidone (10 g) in about 200 ml of water. The wet powder mixture was sieved, dried and sieved again. Then there was added microcrystalline 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.

- 15 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
5 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



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

- 10 n is 1, 2, 3, or 4;
 Z represents O, S, NR^6 , SO or SO_2 ;
 R^1 represent hydrogen, cyano, hydroxy, or
 C_{1-4} alkyl optionally substituted with halo,
 R^2 represents hydrogen, C_{1-4} alkyl, or C_{1-4} alkyloxy-;
 15 R^3 represents hydrogen, C_{1-4} alkyl, C_{1-4} alkyloxy- or R^3 combined with R^2 form
 together a divalent radical selected from the group consisting of
 $-\text{O}-\text{CH}_2-$ (a), $-\text{NR}^7-\text{CH}_2-$ (b), $-(\text{CR}^8\text{R}^9)_m-$ (c) and $-\text{CR}^{10}=$ (d) wherein m represents
 1 or 2 and R^7 , R^8 , R^9 and R^{10} are each independently selected from hydrogen or
 C_{1-4} alkyl;
 20 R^4 represents hydrogen, halo, hydroxy, cyano, amino, $\text{NR}^{11}\text{R}^{12}$,
 C_{1-4} alkyloxycarbonyl, hydroxycarbonyl, C_{1-4} alkyloxy- optionally substituted with
 one or where possible two or three substituents selected from hydroxy and halo or
 R^4 represents C_{1-4} alkyl optionally substituted with one or where possible two or
 three substituents selected from hydroxy and halo;
 25 R^5 represents hydrogen, halo, cyano, amino, phenyl, hydroxy, C_{1-4} alkyloxycarbonyl-
 , hydroxycarbonyl-, Het¹, $-\text{NR}^{13}\text{R}^{14}$, $-\text{O}-(\text{C}=\text{O})-\text{NR}^{21}\text{R}^{22}$, $-\text{O}-(\text{C}=\text{O})-\text{C}_{1-4}$ alkyl,
 carbonyl- $\text{NR}^{23}\text{R}^{24}$ or C_{1-4} alkyl optionally substituted with one or more
 substituents selected from hydroxy, halo, hydroxycarbonyl, phenyl, C_{1-4} alkyloxy
 or $\text{NR}^{15}\text{R}^{16}$ or R^5 represents C_{1-4} alkyloxy optionally substituted with one or more
 30 substituents selected from hydroxy, halo, hydroxycarbonyl, phenyl, C_{1-4} alkyloxy
 or $\text{NR}^{17}\text{R}^{18}$, or R^5 represents $-\text{O}-(\text{C}=\text{O})-\text{C}_{1-4}$ alkyl substituted with one or more
 amino, hydroxy, Het³ or halo substituents;
 R^6 represents hydrogen or C_{1-6} alkyl;

R¹¹ and R¹² each independently represent hydrogen, C₁₋₄alkyl, C₁₋₄alkyloxycarbonyl- or C₁₋₄alkylcarbonyl-;

R¹³ and R¹⁴ each independently represent hydrogen, C₁₋₄alkyl, C₁₋₆alkyl-SO₂-, mono- or di(C₁₋₄alkyl)amino-SO₂-, Ar¹-SO₂-, mono- or di(C₁₋₄alkyl)amino-carbonyl-,
 5 C₁₋₄alkyl-oxycarbonyl or C₁₋₄alkylcarbonyl- wherein said C₁₋₆alkyl-SO₂-, C₁₋₄alkyl-oxycarbonyl or C₁₋₄alkylcarbonyl- are each independently and optionally substituted with one, two or three substituents selected from halo, C₁₋₄alkyloxycarbonyl, NR¹⁹R²⁰ and Het²;

R¹⁵ and R¹⁶ each independently represent hydrogen, C₁₋₄alkyl, C₁₋₄alkyloxycarbonyl- or C₁₋₄alkylcarbonyl-;

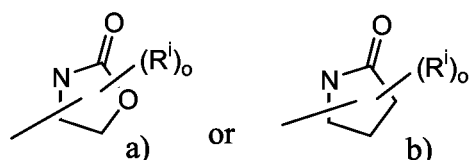
R¹⁷ and R¹⁸ each independently represent hydrogen, C₁₋₄alkyl, C₁₋₄alkyloxycarbonyl- or C₁₋₄alkylcarbonyl-;

R¹⁹ and R²⁰ each independently represent hydrogen, C₁₋₄alkylcarbonyl, C₁₋₄alkyloxycarbonyl- or C₁₋₄alkyl optionally substituted with one or more
 15 substituents selected from halo or hydroxy;

R²¹ and R²² each independently represent hydrogen, Ar² or C₁₋₄alkyl optionally substituted with one or more substituents selected from halo or hydroxy;

R²³ and R²⁴ each independently represent hydrogen, C₁₋₄alkylcarbonyl, Het⁴ or C₁₋₄alkyl optionally substituted with one or more substituents selected from halo
 20 or hydroxy;

Het¹ represents pyrrolinyl, pyrrolidinyl, pyrrolyl, oxazolyl, isoxazolyl or a radical of formula



wherein Rⁱ represents hydrogen or C₁₋₄alkyl and o is 1 or 2;

Het² represents morpholinyl, piperidinyl, piperazinyl, thiomorpholinyl or pyrrolidinyl;

Het³ represents morpholinyl, piperidinyl, piperazinyl, thiomorpholinyl or pyrrolidinyl;

Het⁴ represents piperidinyl, morpholinyl, piperazinyl, thiomorpholinyl or
 30 pyrrolidinyl;

Ar¹ represents phenyl optionally substituted with C₁₋₄alkyl; and

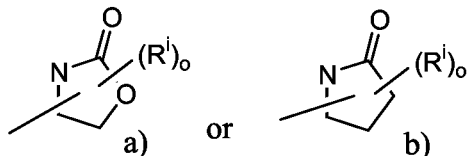
Ar² represents phenyl optionally substituted with C₁₋₄alkyl, for use as a medicine, provided however that said compound of formula (I) is other than N-adamantyl-2-yl-2-ortho-tolyloxy-acetamide.

2. A compound according to claim 1, wherein
 n is 1, 2, 3, or 4;
 Z represents O, S, NR⁶, SO or SO₂;
- 5 R¹ represent hydrogen, cyano, hydroxy, or
 C₁₋₄alkyl optionally substituted with halo,
 R² represents hydrogen, C₁₋₄alkyl, or C₁₋₄alkyloxy-;
 R³ represents hydrogen, C₁₋₄alkyl, C₁₋₄alkyloxy- or R³ combined with R² form
 together a divalent radical selected from the group consisting of
 10 -O-CH₂- (a), -NR⁷-CH₂- (b), -(CR⁸R⁹)_m- (c) and -CR¹⁰= (d) wherein m represents
 1 or 2 and R⁷, R⁸, R⁹ and R¹⁰ are each independently selected from hydrogen or
 C₁₋₄alkyl;
 R⁴ represents hydrogen, halo, hydroxy, cyano, amino, NR¹¹R¹², C₁₋₄alkyloxy-
 optionally substituted with one or where possible two or three substituents
 15 selected from hydroxy and halo or R⁴ represents C₁₋₄alkyl optionally substituted
 with one or where possible two or three substituents selected from hydroxy and
 halo;
 R⁵ represents hydrogen, halo, cyano, amino, phenyl, hydroxy, C₁₋₄alkyloxycarbonyl,
 hydroxycarbonyl, NR¹³R¹⁴ or C₁₋₄alkyl optionally substituted with one or more
 20 substituents selected from hydroxycarbonyl, phenyl, C₁₋₄alkyloxy or NR¹⁵R¹⁶ or
 R⁵ represents C₁₋₄alkyloxy optionally substituted with one or more substituents
 selected from hydroxycarbonyl, phenyl, C₁₋₄alkyloxy or NR¹⁷R¹⁸;
 R⁶ represents hydrogen or C₁₋₄alkyl;
 R¹¹ and R¹² each independently represent hydrogen, C₁₋₄alkyl or C₁₋₄alkylcarbonyl-;
 25 R¹³ and R¹⁴ each independently represent hydrogen, C₁₋₄alkyl or C₁₋₄alkylcarbonyl-;
 R¹⁵ and R¹⁶ each independently represent hydrogen, C₁₋₄alkyl or C₁₋₄alkylcarbonyl-;
 and
 R¹⁷ and R¹⁸ each independently represent hydrogen, C₁₋₄alkyl or C₁₋₄alkylcarbonyl-,
 for use as a medicine, provided however that said compound is other than
 30 N-adamantyl-2-yl-2-ortho-tolyloxy-acetamide.
3. A compound of formula (I), the *N*-oxide forms, the pharmaceutically acceptable
 addition salts and the stereochemically isomeric forms thereof, wherein
 n is 1, 2, 3, or 4;
 35 Z represents O, S, NR⁶, SO or SO₂;
 R¹ represent hydrogen, cyano, hydroxy, or
 C₁₋₄alkyl optionally substituted with halo,

- R^2 represents hydrogen, C_{1-4} alkyl, or C_{1-4} alkyloxy-;
- R^3 represents hydrogen, C_{1-4} alkyl, C_{1-4} alkyloxy- or R^3 combined with R^2 form together a divalent radical selected from the group consisting of
 $-O-CH_2-$ (a), $-NR^7-CH_2-$ (b), $-(CR^8R^9)_m-$ (c) and $-CR^{10}=$ (d) wherein m
 5 represents 1 or 2 and R^7 , R^8 , R^9 and R^{10} are each independently selected from hydrogen or C_{1-4} alkyl;
- R^4 represents hydrogen, halo, hydroxy, cyano, amino, $NR^{11}R^{12}$,
 C_{1-4} alkyloxycarbonyl, hydroxycarbonyl, C_{1-4} alkyloxy- optionally substituted with
 one or where possible two or three substituents selected from hydroxy and halo or
 10 R^4 represents C_{1-4} alkyl optionally substituted with one or where possible two or three substituents selected from hydroxy and halo;
- R^5 represents halo, cyano, amino, phenyl, hydroxy, C_{1-4} alkyloxycarbonyl-,
 hydroxycarbonyl-, Het¹, $-NR^{13}R^{14}$, $-O-(C=O)-NR^{21}R^{22}$, $-O-(C=O)-C_{1-4}$ alkyl,
 carbonyl- $NR^{23}R^{24}$ or C_{1-4} alkyl optionally substituted with one or more
 15 substituents selected from hydroxycarbonyl, phenyl, C_{1-4} alkyloxy or $NR^{15}R^{16}$ or
 R^5 represents C_{1-4} alkyloxy optionally substituted with one or more substituents
 selected from hydroxycarbonyl, phenyl, C_{1-4} alkyloxy or $NR^{17}R^{18}$, or R^5
 represents $-O-(C=O)-C_{1-4}$ alkyl substituted with one or more Het³ or halo
 substituents;
- 20 R^6 represents hydrogen or C_{1-4} alkyl;
- R^{11} and R^{12} each independently represent hydrogen, C_{1-4} alkyl or C_{1-4} alkylcarbonyl-;
- R^{13} and R^{14} each independently represent hydrogen, C_{1-4} alkyl, C_{1-6} alkyl-SO₂-, mono-
 or di(C_{1-4} alkyl)amino-SO₂-, Ar¹-SO₂-, mono- or di(C_{1-4} alkyl)amino-carbonyl-,
 C_{1-4} alkyl-oxycarbonyl or C_{1-4} alkylcarbonyl- wherein said C_{1-6} alkyl-SO₂-, C_{1-4} alkyl-
 25 oxycarbonyl or C_{1-4} alkylcarbonyl- are each independently and optionally
 substituted with one, two or three substituents selected from halo,
 C_{1-4} alkyloxycarbonyl, $NR^{19}R^{20}$ and Het²;
- R^{15} and R^{16} each independently represent hydrogen, C_{1-4} alkyl, C_{1-4} alkyloxycarbonyl
 or C_{1-4} alkylcarbonyl-;
- 30 R^{17} and R^{18} each independently represent hydrogen, C_{1-4} alkyl, C_{1-4} alkyloxycarbonyl
 or C_{1-4} alkylcarbonyl-;
- R^{19} and R^{20} each independently represent hydrogen, C_{1-4} alkylcarbonyl or C_{1-4} alkyl
 optionally substituted with one or more substituents selected from halo or
 hydroxy;
- 35 R^{21} and R^{22} each independently represent hydrogen, Ar² or C_{1-4} alkyl optionally
 substituted with one or more substituents selected from halo or hydroxy;
- R^{23} and R^{24} each independently represent hydrogen, C_{1-4} alkylcarbonyl, Het⁴ or

C₁₋₄alkyl optionally substituted with hydroxy;

Het¹ represents pyrrolinyl, pyrrolidinyl, pyrrolyl, oxazolyl, isoxazolyl or a radical of formula



5 wherein Rⁱ represents hydrogen or C₁₋₄alkyl and o is 1 or 2;

Het² represents morpholinyl, piperidinyl, piperazinyl, thiomorpholinyl or pyrrolidinyl;

Het³ represents morpholinyl, piperidinyl, piperazinyl, thiomorpholinyl or pyrrolidinyl;

10 Het⁴ represents piperidinyl, morpholinyl, piperazinyl, thiomorpholinyl or pyrrolidinyl;

Ar¹ represents phenyl optionally substituted with C₁₋₄alkyl; and

Ar² represents phenyl optionally substituted with C₁₋₄alkyl.

15 4. A compound according to claim 3 wherein

n is 1, 2, 3, or 4;

Z represents O, S, NR⁶, SO or SO₂;

R¹ represent hydrogen, cyano, hydroxy, or

C₁₋₄alkyl optionally substituted with halo,

20 R² represents hydrogen, C₁₋₄alkyl, or C₁₋₄alkyloxy-;

R³ represents hydrogen, C₁₋₄alkyl, C₁₋₄alkyloxy- or R³ combined with R² form together a divalent radical selected from the group consisting of

-O-CH₂- (a), -NR⁷-CH₂- (b), -(CR⁸R⁹)_m- (c) and -CR¹⁰= (d) wherein m

represents 1 or 2 and R⁷, R⁸, R⁹ and R¹⁰ are each independently selected from

25 hydrogen or C₁₋₄alkyl;

R⁴ represents hydrogen, halo, hydroxy, cyano, amino, NR¹¹R¹², C₁₋₄alkyloxy-

optionally substituted with one or where possible two or three substituents

selected from hydroxy and halo or R⁴ represents C₁₋₄alkyl optionally substituted

with one or where possible two or three substituents selected from hydroxy and

30 halo;

R⁵ represents halo, cyano, amino, phenyl, hydroxy, C₁₋₄alkyloxycarbonyl-,

hydroxycarbonyl, NR¹³R¹⁴ or C₁₋₄alkyl optionally substituted with one or more

substituents selected from hydroxycarbonyl, phenyl, C₁₋₄alkyloxy or NR¹⁵R¹⁶ or

R^5 represents C_{1-4} alkyloxy optionally substituted with one or more substituents selected from hydroxycarbonyl, phenyl, C_{1-4} alkyloxy or $NR^{17}R^{18}$;

R^6 represents hydrogen or C_{1-4} alkyl;

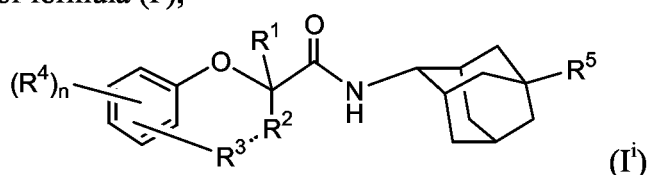
R^{11} and R^{12} each independently represent hydrogen, C_{1-4} alkyl or C_{1-4} alkylcarbonyl-;

5 R^{13} and R^{14} each independently represent hydrogen, C_{1-4} alkyl or C_{1-4} alkylcarbonyl-;

R^{15} and R^{16} each independently represent hydrogen, C_{1-4} alkyl or C_{1-4} alkylcarbonyl-;
and

R^{17} and R^{18} each independently represent hydrogen, C_{1-4} alkyl or C_{1-4} alkylcarbonyl-.

10 5. A compound of formula (Iⁱ),



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

15

n is 1, 2, 3, or 4;

R^1 represent hydrogen, cyano, hydroxy, or

C_{1-4} alkyl optionally substituted with halo,

R^2 represents hydrogen, C_{1-4} alkyl, or C_{1-4} alkyloxy-;

20 R^3 represents hydrogen, C_{1-4} alkyl, C_{1-4} alkyloxy- or R^3 combined with R^2 form together a divalent radical selected from the group consisting of
-O-CH₂- (a), -NR⁷-CH₂- (b), -(CR⁸R⁹)_m- (c) and -CR¹⁰= (d) wherein m represents 1 or 2 and R^7 , R^8 , R^9 and R^{10} are each independently selected from hydrogen or C_{1-4} alkyl;

25 R^4 represents hydrogen, halo, hydroxy, cyano, amino, $NR^{11}R^{12}$,

C_{1-4} alkyloxycarbonyl, hydroxycarbonyl, C_{1-4} alkyloxy- optionally substituted with one or where possible two or three substituents selected from hydroxy and halo or R^4 represents C_{1-4} alkyl optionally substituted with one or where possible two or three substituents selected from hydroxy and halo;

30 R^5 represents hydrogen, halo, cyano, amino, phenyl, hydroxy, C_{1-4} alkyloxycarbonyl, hydroxycarbonyl-, Het¹, -NR¹³R¹⁴, -O-(C=O)-NR²¹R²², -O-(C=O)- C_{1-4} alkyl, carbonyl-NR²³R²⁴ or C_{1-4} alkyl optionally substituted with one or more substituents selected from hydroxycarbonyl, phenyl, C_{1-4} alkyloxy or $NR^{15}R^{16}$ or R^5 represents C_{1-4} alkyloxy optionally substituted with one or more substituents

selected from halo, hydroxy, hydroxycarbonyl, phenyl, C₁₋₄alkyloxy or NR¹⁷R¹⁸,
or R⁵ represents -O-(C=O)-C₁₋₄alkyl substituted with one or more amino,
hydroxy, Het³ or halo substituents;

R⁶ represents hydrogen or C₁₋₄alkyl;

5 R¹¹ and R¹² each independently represent hydrogen, C₁₋₄alkyl, C₁₋₄alkyloxycarbonyl-
or C₁₋₄alkylcarbonyl-;

R¹³ and R¹⁴ each independently represent hydrogen, C₁₋₄alkyl, C₁₋₆alkyl-SO₂-, mono-
or di(C₁₋₄alkyl)amino-SO₂-, Ar¹-SO₂-, mono- or di(C₁₋₄alkyl)amino-carbonyl-,
C₁₋₄alkyl-oxycarbonyl or C₁₋₄alkylcarbonyl- wherein said C₁₋₆alkyl-SO₂-,
10 C₁₋₄alkyl-oxycarbonyl or C₁₋₄alkylcarbonyl- are each independently and
optionally substituted with one, two or three substituents selected from halo,
C₁₋₄alkyloxycarbonyl, NR¹⁹R²⁰ and Het²;

R¹⁵ and R¹⁶ each independently represent hydrogen, C₁₋₄alkyl, C₁₋₄alkyloxycarbonyl-
or C₁₋₄alkylcarbonyl-;

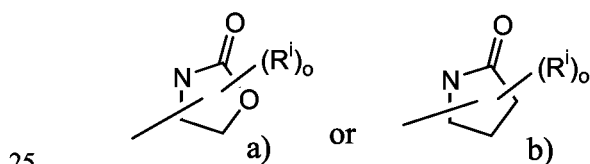
15 R¹⁷ and R¹⁸ each independently represent hydrogen, C₁₋₄alkyl, C₁₋₄alkyloxycarbonyl-
or C₁₋₄alkylcarbonyl-;

R¹⁹ and R²⁰ each independently represent hydrogen, C₁₋₄alkyloxycarbonyl-,
C₁₋₄alkylcarbonyl or C₁₋₄alkyl optionally substituted with halo or hydroxy;

R²¹ and R²² each independently represent hydrogen, Ar² or C₁₋₄alkyl optionally
20 substituted with halo or hydroxy;

R²³ and R²⁴ each independently represent hydrogen, C₁₋₄alkylcarbonyl, Het⁴ or
C₁₋₄alkyl optionally substituted with halo or hydroxy;

Het¹ represents pyrrolinyl, pyrrolidinyl, pyrrolyl, oxazolyl, isoxazolyl or a radical of
formula



wherein Rⁱ represents hydrogen or C₁₋₄alkyl and o is 1 or 2;

Het² represents morpholinyl, piperidinyl, piperazinyl, thiomorpholinyl or
pyrrolidinyl;

30 Het³ represents morpholinyl, piperidinyl, piperazinyl, thiomorpholinyl or
pyrrolidinyl;

Het⁴ represents piperidinyl, morpholinyl, piperazinyl, thiomorpholinyl or
pyrrolidinyl;

Ar¹ represents phenyl optionally substituted with C₁₋₄alkyl; and

Ar² represents phenyl optionally substituted with C₁₋₄alkyl; provided however that

- said compound of formula (I¹) is other than
- Acetamide, N-tricyclo[3.3.1.1^{3,7}]dec-2-yl-2-[3-(trifluoromethyl)phenoxy]- (9CI)
- Acetamide, 2-[4-(1-methylpropyl)phenoxy]-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)
- Butanamide, 2-phenoxy-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)
- 5 Acetamide, 2-(2-bromo-4-ethylphenoxy)-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)
- Acetamide, N-tricyclo[3.3.1.1^{3,7}]dec-2-yl-2-(2,3,5-trimethylphenoxy)- (9CI)
- Acetamide, 2-(2,3-dimethylphenoxy)-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)
- Acetamide, 2-(2,4-dibromo-6-methylphenoxy)-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)
- Acetamide, 2-(4-chloro-2-methylphenoxy)-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)
- 10 Acetamide, 2-(3,5-dimethylphenoxy)-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)
- Acetamide, 2-(2-chlorophenoxy)-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)
- Acetamide, 2-[4-(1,1-dimethylethyl)phenoxy]-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)
- Acetamide, 2-[(4-chlorophenyl)thio]-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)
- Acetamide, 2-[5-methyl-2-(1-methylethyl)phenoxy]-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)
- 15 Acetamide, 2-(4-ethylphenoxy)-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)
- Acetamide, 2-(2,5-dimethylphenoxy)-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)
- Acetamide, 2-(3,4-dimethylphenoxy)-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)
- Acetamide, 2-(2,4-dimethylphenoxy)-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)
- Acetamide, 2-(4-bromo-2-methylphenoxy)-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)
- 20 Acetamide, 2-(4-bromo-3,5-dimethylphenoxy)-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)
- Acetamide, 2-[4-(1-methylethyl)phenoxy]-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)
- Acetamide, 2-(4-bromo-2-chlorophenoxy)-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)
- Acetamide, 2-(4-chloro-3-methylphenoxy)-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)
- Acetamide, 2-(4-methoxyphenoxy)-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)
- 25 Propanamide, 2-(2,4-dichlorophenoxy)-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)
- Acetamide, 2-(2-bromo-4-methylphenoxy)-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)
- Acetamide, 2-(4-chloro-3,5-dimethylphenoxy)-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)
- Acetamide, 2-(4-bromo-3-methylphenoxy)-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)
- Acetamide, 2-(2,4-dichlorophenoxy)-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)
- 30 Acetamide, 2-phenoxy-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)
- Acetamide, 2-(4-bromophenoxy)-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)
- Acetamide, 2-(4-methylphenoxy)-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)
- Acetamide, 2-(3-bromophenoxy)-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)
- Acetamide, 2-(4-chlorophenoxy)-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI)
- 35 Acetamide, 2-(3-methylphenoxy)-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl- (9CI) or
- N-adamantan-2-yl-2-o-tolyloxy-acetamide.

6. A compound according to claim 5, wherein
 n is 1, 2, 3, or 4;
 R^1 represent hydrogen, cyano, hydroxy, or
 C_{1-4} alkyl optionally substituted with halo,
 5 R^2 represents hydrogen, C_{1-4} alkyl, or C_{1-4} alkyloxy-;
 R^3 represents hydrogen, C_{1-4} alkyl, C_{1-4} alkyloxy- or R^3 combined with R^2 form
 together a divalent radical selected from the group consisting of
 $-O-CH_2-$ (a), $-NR^7-CH_2-$ (b), $-(CR^8R^9)_m-$ (c) and $-CR^{10}=$ (d) wherein m represents
 1 or 2 and R^7 , R^8 , R^9 and R^{10} are each independently selected from hydrogen or
 10 C_{1-4} alkyl;
 R^4 represents hydrogen, halo, hydroxy, cyano, amino, $NR^{11}R^{12}$, C_{1-4} alkyloxy-
 optionally substituted with one or where possible two or three substituents
 selected from hydroxy and halo or R^4 represents C_{1-4} alkyl optionally substituted
 with one or where possible two or three substituents selected from hydroxy and
 15 halo;
 R^5 represents hydrogen, halo, cyano, amino, phenyl, hydroxy, C_{1-4} alkyloxycarbonyl,
 hydroxycarbonyl, $NR^{13}R^{14}$ or C_{1-4} alkyl optionally substituted with one or more
 substituents selected from hydroxycarbonyl, phenyl, C_{1-4} alkyloxy or $NR^{15}R^{16}$ or
 R^5 represents C_{1-4} alkyloxy optionally substituted with one or more substituents
 20 selected from hydroxycarbonyl, phenyl, C_{1-4} alkyloxy or $NR^{17}R^{18}$; in particular R^5
 represents halo, cyano, amino, phenyl, hydroxy, C_{1-4} alkyloxycarbonyl-,
 hydroxycarbonyl, $NR^{13}R^{14}$ or C_{1-4} alkyl optionally substituted with one or more
 substituents selected from hydroxycarbonyl, phenyl, C_{1-4} alkyloxy or $NR^{15}R^{16}$ or
 R^5 represents C_{1-4} alkyloxy optionally substituted with one or more substituents
 25 selected from hydroxycarbonyl, phenyl, C_{1-4} alkyloxy or $NR^{17}R^{18}$
 R^6 represents hydrogen or C_{1-4} alkyl;
 R^{11} and R^{12} each independently represent hydrogen, C_{1-4} alkyl or C_{1-4} alkylcarbonyl-;
 R^{13} and R^{14} each independently represent hydrogen, C_{1-4} alkyl or C_{1-4} alkylcarbonyl-;
 R^{15} and R^{16} each independently represent hydrogen, C_{1-4} alkyl or C_{1-4} alkylcarbonyl-;
 30 and
 R^{17} and R^{18} each independently represent hydrogen, C_{1-4} alkyl or C_{1-4} alkylcarbonyl-,
 provided however that when R^5 represents hydrogen in said compound of
 formula (Iⁱ), then R^1 and R^2 represent C_{1-4} alkyl.
- 35 7. A compound of formula (I), the *N*-oxide forms, the pharmaceutically acceptable
 addition salts and the stereochemically isomeric forms thereof, wherein;
 n is 1, 2, 3, or 4;

Z represents O, S, NR⁶ or SO₂; in particular O or NR⁶;

R¹ represents hydrogen or C₁₋₄alkyl;

R² represents hydrogen or C₁₋₄alkyl;

5 R³ represents hydrogen, C₁₋₄alkyl, C₁₋₄alkyloxy- or R³ combined with R² form together a divalent radical selected from the group consisting of -O-CH₂- (a), -NR⁷-CH₂- (b), -(CR⁸R⁹)_m- (c) and -CR¹⁰= (d) wherein m represents 1 or 2 and R⁷, R⁸, R⁹ and R¹⁰ are each independently selected from hydrogen or C₁₋₄alkyl;

10 R⁴ represents hydrogen, halo, hydroxy, amino, -NR¹¹R¹², C₁₋₄alkyloxy-, C₁₋₄alkyloxycarbonyl-, hydroxycarbonyl-, or C₁₋₄alkyl optionally substituted with one or where possible two or three halo substituents;

R⁵ represents hydrogen, halo, amino, phenyl, hydroxy, hydroxycarbonyl, Het¹, NR¹³R¹⁴, -O-(C=O)-C₁₋₄alkyl, -carbonyl-NR²³R²⁴ or R⁵ represents C₁₋₄alkyloxy optionally substituted with one or more substituents selected from NR¹⁷R¹⁸ or R⁵ represents -O(=O)-C₁₋₄alkyl substituted with halo or Het³;

R¹¹ and R¹² each independently represent hydrogen, C₁₋₄alkyl or C₁₋₄alkylcarbonyl-;

20 R¹³ and R¹⁴ each independently represent hydrogen, C₁₋₄alkyl, C₁₋₆alkyl-SO₂-, mono- or di(C₁₋₄alkyl)amino-SO₂-, Ar¹-SO₂-, mono- or di(C₁₋₄alkyl)amino-carbonyl-, C₁₋₄alkyl-oxycarbonyl or C₁₋₄alkylcarbonyl- wherein said C₁₋₆alkyl-SO₂-, C₁₋₄alkyl-oxycarbonyl or C₁₋₄alkylcarbonyl- are each independently and optionally substituted with one, two or three substituents selected from halo, C₁₋₄alkyloxycarbonyl, NR¹⁹R²⁰ and Het²;

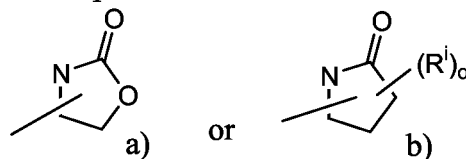
25 R¹⁷ and R¹⁸ each independently represent C₁₋₄alkyl;

R¹⁹ and R²⁰ each independently represent hydrogen or C₁₋₄alkyl optionally substituted with hydroxy;

R²¹ and R²² each independently represent hydrogen or Ar²;

30 R²³ and R²⁴ each independently represent hydrogen or Het⁴;

Het¹ represents a radical of formula



wherein Rⁱ represents hydrogen or C₁₋₄alkyl and o is 1 or 2;

Het² represents morpholinyl;

Het³ represents morpholinyl;

Het⁴ represents piperidinyl;

Ar¹ and Ar² each independently represent phenyl optionally substituted with C₁₋₄alkyl, for use as a medicine, provided however that said compound of formula (I) is other than N-adamantyl-2-yl-2-ortho-tolyloxy-acetamide.

8. A compound of formula (I), the *N*-oxide forms, the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof, wherein;

n is 1, 2, 3, or 4;

Z represents O, S or SO₂; in particular O;

R¹ represents hydrogen or C₁₋₄alkyl;

R² represents hydrogen or C₁₋₄alkyl;

R³ represents hydrogen, C₁₋₄alkyl, C₁₋₄alkyloxy- or R³ combined with R² form together a divalent radical selected from the group consisting of

-O-CH₂- (a), -NR⁷-CH₂- (b), -(CR⁸R⁹)_m- (c) and -CR¹⁰= (d) wherein m represents 1 or 2 and R⁷, R⁸, R⁹ and R¹⁰ are each independently selected from hydrogen or C₁₋₄alkyl;

R⁴ represents hydrogen, hydroxy, amino, -NR¹¹R¹², C₁₋₄alkyloxy- or C₁₋₄alkyl optionally substituted with one or where possible two or three halo substituents;

R⁵ represents hydrogen or hydroxy; in particular hydroxy; and

R¹¹ and R¹² each independently represent hydrogen, C₁₋₄alkyl or C₁₋₄alkylcarbonyl-, for use as a medicine, provided however that said compound of formula (I) is other than N-adamantyl-2-yl-2-ortho-tolyloxy-acetamide.
9. A compound of formula (I), the *N*-oxide forms, the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof, wherein;

n is 1, 2, 3, or 4;

Z represents O;

R¹ represents a hydrogen or C₁₋₄alkyl, in particular hydrogen or methyl;

R³ combined with R² form together a divalent radical selected from the group consisting of -O-CH₂- (a), -NR⁷-CH₂- (b), -(CR⁸R⁹)_m- (c) and -CR¹⁰= (d) wherein m represents 1 or 2 and R⁷, R⁸, R⁹ and R¹⁰ are each independently selected from hydrogen or C₁₋₄alkyl;

R⁴ represents hydrogen, halo, hydroxy, C₁₋₄alkyloxy-, or C₁₋₄alkyl; in particular R⁴ represents methyl, ethyl, methoxy, fluor, chloro or bromo; and

R⁵ represents hydrogen, amino or hydroxy; in particular amino or hydroxy.

10. A compound according to claim 9, wherein;
 n is 1, 2, 3, or 4;
 R¹ represents a hydrogen;
 R³ combined with R² form together a divalent radical selected from the group
 5 consisting of
 -O-CH₂- (a), -NR⁷-CH₂- (b), -(CR⁸R⁹)_m- (c) and -CR¹⁰= (d) wherein m
 represents 1 or 2 and R⁷, R⁸, R⁹ and R¹⁰ are each independently selected from
 hydrogen or C₁₋₄alkyl;
 R⁴ represents hydrogen, halo, hydroxy, C₁₋₄alkyloxy-, or C₁₋₄alkyl; in particular R⁴
 10 represents methyl, ethyl, methoxy, fluor, chloro or bromo; and
 R⁵ represents hydrogen or hydroxy; in particular hydroxy.
11. A compound of formula (I), the *N*-oxide forms, the pharmaceutically acceptable
 addition salts and the stereochemically isomeric forms thereof, wherein;
 15 n is 1, 2 or 3;
 R¹ represents a C₁₋₄alkyl, in particular methyl;
 R² represents a C₁₋₄alkyl, in particular methyl;
 R³ represents hydrogen, C₁₋₄alkyl or C₁₋₄alkyloxy, in particular hydrogen, methyl
 or methoxy;
 20 R⁴ represents hydrogen, halo, -NR¹¹R¹², C₁₋₄alkyloxy-, C₁₋₄alkyloxycarbonyl,
 hydroxycarbonyl or C₁₋₄alkyl optionally substituted with one or where possible
 two or three halo substituents; in particular R⁴ represents methyl, ethyl,
 dimethylamine, trifluoromethyl, methoxycarbonyl, methoxy, fluor, chloro or
 bromo;
 25 R⁵ represents hydrogen, halo, amino, phenyl, hydroxy, hydroxycarbonyl, Het¹,
 -NR¹³R¹⁴, -O-(C=O)-NR²¹R²², -O-(C=O)-C₁₋₄alkyl, -carbonyl-NR²³R²⁴ or
 C₁₋₄alkyloxy optionally substituted with NR¹⁷R¹⁸ or R⁵ represents
 -O-(C=O)-C₁₋₄alkyl substituted with one or more Het³ or halo substituents; in
 particular R⁵ represents hydroxy, amino, methylsulfonylamine, ethylsulfonyl-
 30 amine, methylcarbonylamine, ethylcarbonylamine, dimethylaminosulfonyl-
 amine, chloromethylcarbonylamine, trifluoroethylsulfonylamine or methyl-
 phenylsulfonylamine;
 R¹¹ and R¹² each independently represent hydrogen, C₁₋₄alkyl or C₁₋₄alkylcarbonyl;
 in particular R¹¹ and R¹² represent methyl;
 35 R¹³ and R¹⁴ each independently represent hydrogen, C₁₋₄alkyl, C₁₋₆alkyl-SO₂-,
 mono- or di(C₁₋₄alkyl)amino-SO₂-, Ar¹-SO₂-, mono- or di(C₁₋₄alkyl)amino-
 carbonyl-, C₁₋₄alkyl-oxycarbonyl or C₁₋₄alkylcarbonyl- wherein said

C_{1-6} alkyl-SO₂-, C_{1-4} alkyl-oxycarbonyl or C_{1-4} alkylcarbonyl- are each independently and optionally substituted with one, two or three substituents selected from halo, C_{1-4} alkyloxycarbonyl, NR¹⁹R²⁰ and Het²;
 R¹⁷ and R¹⁸ each independently represent hydrogen or C_{1-4} alkyl; in particular R¹⁷ and R¹⁸ represent methyl;
 R¹⁹ and R²⁰ each independently represent hydrogen or C_{1-4} alkyl optionally substituted with hydroxy; in particular R¹⁹ and R²⁰ each independently represent hydrogen, methyl or hydroxyethyl;
 R²¹ and R²² each independently represent hydrogen or Ar²; in particular R²¹ and R²² each independently represent hydrogen or methylphenyl;
 R²³ and R²⁴ each independently represent hydrogen or Het⁴; in particular R²³ and R²⁴ each independently represent hydrogen or piperidinyl;
 Het² represents morpholinyl;
 Het³ represents morpholinyl;
 Het⁴ represents piperidinyl;
 Ar¹ represents phenyl substituted with C_{1-4} alkyl; and
 Ar² represents phenyl substituted with C_{1-4} alkyl.

12. A compound according to claim 11, wherein;
 n is 1 or 2;
 R¹ represents a C_{1-4} alkyl, in particular methyl;
 R² represents a C_{1-4} alkyl, in particular methyl;
 R³ represents hydrogen;
 R⁴ represents hydrogen, halo, -NR¹¹R¹², C_{1-4} alkyloxy-, or C_{1-4} alkyl; in particular
 R⁴ represents methyl, ethyl, methoxy, fluor, chloro or bromo;
 R⁵ represents hydrogen or hydroxy; in particular hydroxy; and
 R¹¹ and R¹² each independently represent hydrogen, C_{1-4} alkyl or C_{1-4} alkylcarbonyl.

13. A compound as claimed in claim 1 wherein the compound is selected from the group consisting of;

2,3-dihydro-*N*-[(1R,3S)-5-hydroxytricyclo[3.3.1.1^{3,7}]dec-2-yl]-1,4-benzodioxin-2-carboxamide,
N-[(1R,3S)-5-hydroxytricyclo[3.3.1.1^{3,7}]dec-2-yl]-2-methyl-2-(2-methylphenoxy)-propanamide,
N-[(1R,3S)-5-hydroxytricyclo[3.3.1.1^{3,7}]dec-2-yl]-2-methyl-2-(4-methylphenoxy)-propanamide,

2-(3,5-dimethylphenoxy)-*N*-[(1*R*,3*S*)-5-hydroxytricyclo[3.3.1.1^{3,7}]dec-2-yl]-2-methyl-propanamide,
N-[(1*R*,3*S*)-5-hydroxytricyclo[3.3.1.1^{3,7}]dec-2-yl]-3-methyl-2-benzofuran-carboxamide,
3,4-dihydro-*N*-[(1*R*,3*S*)-5-hydroxytricyclo[3.3.1.1^{3,7}]dec-2-yl]-2*H*-1-benzopyran-2-carboxamide,
2-(4-chloro-2-methylphenoxy)-*N*-[(1*R*,3*S*)-5-hydroxytricyclo[3.3.1.1^{3,7}]dec-2-yl]-2-methyl-propanamide,
2-(4-Chloro-2-methyl-phenoxy)-*N*-[(1*R*,3*S*)-5-methanesulfonylaminotricyclo[3.3.1.1^{3,7}]dec-2-yl]-2-methyl-propionamide,
2-(4-Chloro-2-methyl-phenoxy)-*N*-[(1*R*,3*S*)-5-(dimethylamino)sulfonylaminotricyclo[3.3.1.1^{3,7}]dec-2-yl]-2-methyl-propionamide,
2-(4-Chloro-phenoxy)-*N*-[(1*R*,3*S*)-5-hydroxytricyclo[3.3.1.1^{3,7}]dec-2-yl]-2-methyl-propionamide,
N-[(1*R*,3*S*)-5-(dimethylamino)sulfonylaminotricyclo[3.3.1.1^{3,7}]dec-2-yl]-2-methyl-2-(3-trifluoromethyl-phenoxy)-propionamide,
N-[(1*R*,3*S*)-5-methanesulfonylaminotricyclo[3.3.1.1^{3,7}]dec-2-yl]-2-methyl-2-(3-trifluoromethyl-phenoxy)-propionamide,
N-[(1*R*,3*S*)-5-aminotricyclo[3.3.1.1^{3,7}]dec-2-yl]-2-(2-chloro-phenoxy)-2-methyl-propionamide,
N-[(1*R*,3*S*)-5-aminotricyclo[3.3.1.1^{3,7}]dec-2-yl]-2-methyl-2-(2-trifluoromethyl-phenoxy)-propionamide,
N-[(1*R*,3*S*)-5-Ethanesulfonylaminotricyclo[3.3.1.1^{3,7}]dec-2-yl]-2-methyl-2-(3-trifluoromethyl-phenoxy)-propionamide,
(3*R*,5*S*)-4-[2-(4-Chloro-2-methyl-phenoxy)-2-methyl-propionylamino]tricyclo[3.3.1.1^{3,7}]decane-1-carboxylic acid,
N-[(1*R*,3*S*)-5-aminotricyclo[3.3.1.1^{3,7}]dec-2-yl]-2-(4-chloro-2-methyl-phenoxy)-2-methyl-propionamide,
2-(4-Chloro-2-methyl-phenoxy)-2-methyl-*N*-[(1*R*,3*S*)-5-(3-methyl-2-oxo-pyrrolidin-1-yl)tricyclo[3.3.1.1^{3,7}]dec-2-yl]-propionamide,
2-(3-Bromo-phenoxy)-2-methyl-*N*-[(1*R*,3*S*)-5-(2-oxo-oxazolidin-3-yl)tricyclo[3.3.1.1^{3,7}]dec-2-yl]-propionamide,
2-(3-Bromo-phenoxy)-*N*-[(1*R*,3*S*)-5-methanesulfonylaminotricyclo[3.3.1.1^{3,7}]dec-2-yl]-2-methyl-propionamide, or
2-(4-Chloro-phenoxy)-*N*-[(1*R*,3*S*)-5-methanesulfonylaminotricyclo[3.3.1.1^{3,7}]dec-2-yl]-2-methyl-propionamide.

14. 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 13.
- 5
15. A process of preparing a pharmaceutical composition as defined in claim 14, 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 13.
- 10
16. A compound as claimed in any one of claims 3, 4, 5, 6, 9, 10, 11 or 12 for use as a medicine.
- 15
17. Use of a compound as claimed in any one of claims 1 to 13 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, stress and glaucoma.
- 20
18. Use of a compound as claimed in any one of claims 1 to 13 in combination with an antihypertensive agent in the manufacture of a medicament for the treatment of insulin resistance, dyslipidemia, obesity and hypertension.
- 25
19. Use of a compound as claimed in any one of claims 1 to 13 in combination with a glucocorticoid receptor agonist in the manufacture of a medicament for the reduction of undesirable side effects occurring during glucocorticoid receptor agonist therapy and for treating some forms of cancer, diseases and disorders having inflammation as a component.