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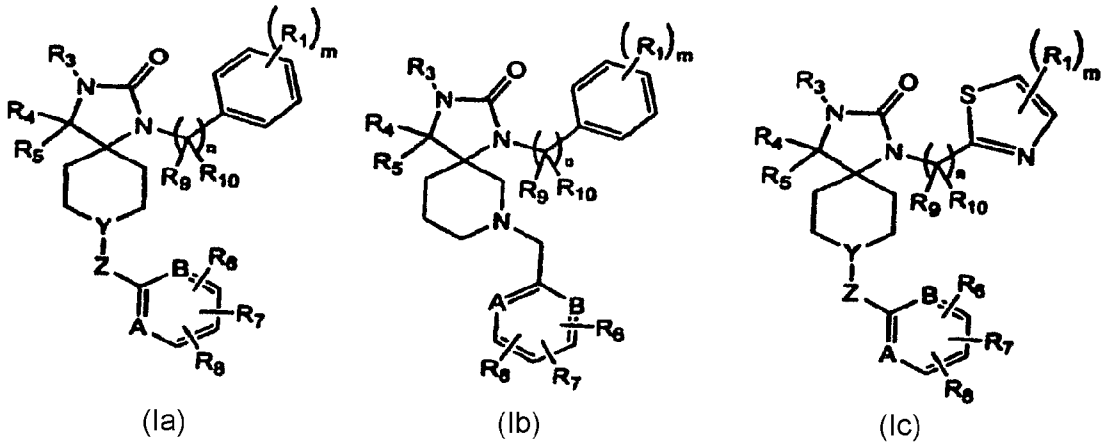
(54) Title: SPIRO IMIDAZOLE DERIVATIVES AS PPAR MODULATORS



(57) Abstract: The invention provides compounds (Ia), (Ib) and (Ic), pharmaceutical compositions comprising such compounds and methods of using such compounds to treat or prevent diseases or disorders associated with the activity of the Peroxisome Proliferator-Activated Receptor (PPAR) families.

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SPIRO IMIDAZOLE DERIVATIVES AS PPAR MODULATORS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This patent application claims the benefit of priority under 35 U.S.C. §119(e) to U.S. Provisional Patent Application No. 60/763,557, filed January 30, 2006. The disclosure of the priority application is incorporated herein by reference in its entirety and for all purposes.

BACKGROUND OF THE INVENTION

Field of the Invention

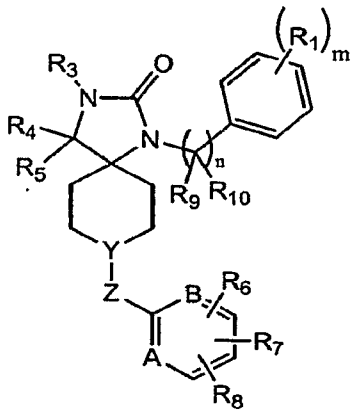
[0002] The invention provides compounds, pharmaceutical compositions comprising such compounds and methods of using such compounds to treat or prevent diseases or disorders associated with the activity of the Peroxisome Proliferator-Activated Receptor (PPAR) families.

Background

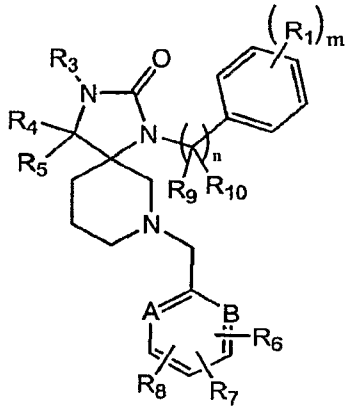
[0003] Peroxisome Proliferator Activated Receptors (PPARs) are members of the nuclear hormone receptor super family, which are ligand-activated transcription factors regulating gene expression. Certain PPARs are associated with a number of disease states including dyslipidemia, hyperlipidemia, hypercholesteremia, atherosclerosis, atherogenesis, hypertriglyceridemia, heart failure, myocardial infarction, vascular diseases, cardiovascular diseases, hypertension, obesity, inflammation, arthritis, cancer, Alzheimer's disease, skin disorders, respiratory diseases, ophthalmic disorders, IBDs (irritable bowel disease), ulcerative colitis and Crohn's disease. Accordingly, molecules that modulate the activity of PPARs are useful as therapeutic agents in the treatment of such diseases.

SUMMARY OF THE INVENTION

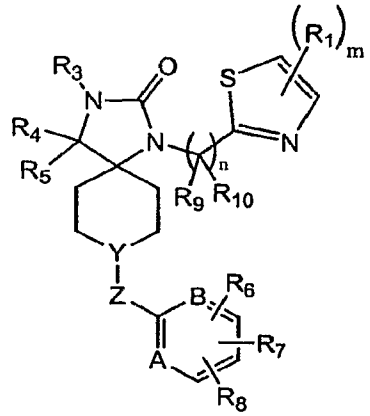
[0004] In one aspect, the present invention provides compounds selected from Formula Ia, Ib and Ic:



Ia



Ib



Ic

in which

n is selected from 1, 2, 3, 4 and 5;

m is selected from 1, 2, 3, 4 and 5; each

R_1 is independently selected from hydrogen, halo, C_{1-6}alkyl, halo-substituted C_{1-6}alkyl, C_{1-6}alkoxy and halo-substituted-C_{1-6}alkoxy;

R_3 is selected from C_{1-8}alkyl, C_{2-8}alkenyl, halo-substituted-C_{1-6}alkyl, halo-substituted-C_{2-6}alkenyl, $-X_1C(O)R_2$, C_{5-10}heteroaryl-C_{0-4}alkyl and C_{3-12}cycloalkyl-C_{0-4}alkyl; wherein R_2 is selected from hydrogen and C_{1-6}alkyl;

R_4 is selected from hydrogen and C_{1-6}alkyl;

R_5 is selected from hydrogen and C_{1-6}alkyl; or R_4 and R_5 together with the carbon atom to which R_4 and R_5 are both attached form carbonyl;

Y is selected from N and CH;

Z is selected from a bond, $-S(O)_{0-2}-$ and $-CR_{11}R_{12}-$; wherein R_{11} and R_{12} are independently selected from hydrogen and C_{1-6}alkyl;

A and B are independently selected from CH and N;

R_6 and R_7 are independently selected from hydrogen, halo, C_{1-6}alkyl, halo-substituted C_{1-6}alkyl, C_{1-6}alkoxy and halo-substituted-C_{1-6}alkoxy;

R_8 is selected from $-X_2CO_2R_{13}$, $-X_2CR_{14}R_{15}X_3CO_2R_{13}$, $-X_2SCR_{14}R_{15}X_3CO_2R_{13}$ and $-X_2OCR_{14}R_{15}X_3CO_2R_{13}$; wherein X_2 and X_3 are independently selected from a bond and C_{1-4}alkylene; and R_{14} and R_{15} are independently selected from hydrogen, C_{1-4}alkyl and C_{1-4}alkoxy; or R_{14} and R_{15} together with the carbon atom to which R_{14} and R_{15} are attached form C_{3-12}cycloalkyl; and R_{13} is selected from hydrogen and C_{1-6}alkyl;

R_9 and R_{10} are independently selected from hydrogen, C_{1-6}alkyl and $-OR_{16}$; wherein R_{16} is selected from hydrogen and C_{1-6}alkyl; and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixture of isomers thereof; and the pharmaceutically acceptable salts and solvates (e.g. hydrates) of such compounds.

[0005] In a second aspect, the present invention provides a pharmaceutical composition that contains a compound of Formula I or a N-oxide derivative, individual isomers and mixture of isomers thereof; or a pharmaceutically acceptable salt thereof, in admixture with one or more suitable excipients.

[0006] In a third aspect, the present invention provides a method of treating a disease in an animal in which modulation of PPAR activity can prevent, inhibit or ameliorate the pathology and/or symptomology of the diseases, which method comprises administering to the animal a therapeutically effective amount of a compound of Formula I or a N-oxide derivative, individual isomers and mixture of isomers thereof, or a pharmaceutically acceptable salt thereof.

[0007] In a fourth aspect, the present invention provides the use of a compound of Formula I in the manufacture of a medicament for treating a disease in an animal in which PPAR activity activity contributes to the pathology and/or symptomology of the disease.

[0008] In a fifth aspect, the present invention provides a process for preparing compounds of Formula I and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixture of isomers thereof, and the pharmaceutically acceptable salts thereof.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

[0009] "Alkyl" as a group and as a structural element of other groups, for example halo-substituted-alkyl and alkoxy, can be either straight-chained or branched. C_{1-6}alkoxy includes, methoxy, ethoxy, and the like. Halo-substituted alkyl includes trifluoromethyl, pentafluoroethyl, and the like.

[0010] "Aryl" means a monocyclic or fused bicyclic aromatic ring assembly containing six to ten ring carbon atoms. For example, aryl can be phenyl or naphthyl, preferably phenyl. "Arylene" means a divalent radical derived from an aryl group. "Heteroaryl" is as defined for aryl where one or more of the ring members are a heteroatom. For example heteroaryl includes pyridyl, indolyl, indazolyl, quinoxalinyl, quinolinyl, benzofuranyl, benzopyranyl, benzothiopyranyl, benzo[1,3]dioxole, imidazolyl, benzo-imidazolyl, pyrimidinyl, furanyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl, pyrazolyl, thienyl, etc. "C_{6-10}arylC_{0-4}alkyl" means an aryl as described above connected via a alkylene grouping. For example, C_{6-10}arylC_{0-4}alkyl includes phenethyl, benzyl, etc.

[0011] "Cycloalkyl" means a saturated or partially unsaturated, monocyclic, fused bicyclic or bridged polycyclic ring assembly containing the number of ring atoms indicated. For example, C_{3-10}cycloalkyl includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc. "Heterocycloalkyl" means cycloalkyl, as defined in this application, provided that one or more of the ring carbons indicated, are replaced by a moiety selected from -O-, -N=, -NR-, -C(O) -, -S-, -S(O) - or -$S(O)_2$-, wherein R is hydrogen, C_{1-4}alkyl or a nitrogen protecting group. For example, C_{3-8}heterocycloalkyl as used in this application to describe compounds of the invention includes morpholino, pyrrolidinyl, piperazinyl, piperidinyl, piperidinylone, 1,4-dioxa-8-aza-spiro[4.5]dec-8-yl, etc.

[0012] "Halogen" (or halo) preferably represents chloro or fluoro, but can also be bromo or iodo.

[0013] "Treat", "treating" and "treatment" refer to a method of alleviating or abating a disease and/or its attendant symptoms.

Description of the Preferred Embodiments

[0014] The present invention provides compounds, compositions and methods for the treatment of diseases in which modulation of one or more PPARs can prevent, inhibit or ameliorate the pathology and/or symptomology of the diseases, which method comprises administering to the animal a therapeutically effective amount of a compound of Formula I.

[0015] In one embodiment, with reference to compounds of Formula Ia, Ib and Ic: n is selected from 1, 2, 3 and 4; m is selected from 1, 2 and 3; each R_1 is independently selected from hydrogen, halo, C_{1-6}alkyl, halo-substituted C_{1-6}alkyl, C_{1-6}alkoxy and halo-substituted-C_{1-6}alkoxy; R_3 is selected from C_{1-8}alkyl, C_{2-8}alkenyl, halo-substituted-C_{1-6}alkyl, halo-substituted-C_{2-6}alkenyl, $-X_1C(O)R_2$, C_{5-10}heteroaryl-C_{0-4}alkyl and C_{3-12}cycloalkyl-C_{0-4}alkyl; wherein R_2 is selected from hydrogen and C_{1-6}alkyl; R_4 is selected from hydrogen and C_{1-6}alkyl; R_5 is selected from hydrogen and C_{1-6}alkyl; or R_4 and R_5 together with the carbon atom to which R_4 and R_5 are both attached form carbonyl; Y is selected from N and CH; Z is selected from a bond, $-S(O)_{0-2}-$ and $-CR_{11}R_{12}-$; wherein R_{11} and R_{12} are independently selected from hydrogen and C_{1-6}alkyl; A and B are independently selected from CH and N; R_6 and R_7 are independently selected from hydrogen, halo, C_{1-6}alkyl, halo-substituted C_{1-6}alkyl and C_{1-6}alkoxy; R_8 is selected from $-X_2CO_2R_{13}$, $-X_2CR_{14}R_{15}X_3CO_2R_{13}$ and $-X_2OCR_{14}R_{15}X_3CO_2R_{13}$; wherein X_2 and X_3 are independently selected from a bond and C_{1-4}alkylene; and R_{14} and R_{15} are independently selected from hydrogen and C_{1-4}alkyl; R_{13} is selected from hydrogen and C_{1-6}alkyl; and R_9 and R_{10} are independently selected from hydrogen, C_{1-6}alkyl and $-OR_{16}$; wherein R_{16} is selected from hydrogen and C_{1-6}alkyl.

[0016] In another embodiment, R_1 is independently selected from hydrogen, halo, methoxy, trifluormethoxy and trifluoromethyl; R_3 is selected from isobutyl, cyclopropyl-methyl, cyclobutyl-methyl, isopentyl, butyl, cyclopentyl-methyl, 3-methyl-but-2-enyl, pentyl, 2,2-dimethyl-propyl, 4-fluoro-butyl, 2-ethyl-butyl, 2-methyl-pentyl, cyclohexyl-methyl, 3,3-dimethyl-2-oxo-butyl, pyrrolyl-propyl, 3-trifluoromethyl-propyl, cyclohexyl-ethyl, 2-ethyl-hexyl, 2-methyl-butyl, 3,4,4-trifluoro-but-3-enyl and 3,3-dimethyl-butyl; R_4 and R_5 are each hydrogen or R_4 and R_5 together with the carbon atom to which R_4 and R_5 are both attached form carbonyl; and Z is selected from a bond, $-S(O)_2-$ and $-CH_2-$.

[0017] In another embodiment, R_8 is selected from $-CH_2C(O)OH$, $-CH(CH_2)C(O)OH$, $-OC(CH_2)_2C(O)OH$, $-(CH_2)_2C(O)OH$ and $-OCH_2C(O)OH$; and R_9 and R_{10} are independently selected from hydrogen, halo, methyl, methoxy and trifluoromethyl.

[0018] Preferred compounds of the invention are selected from: (3-{3-Isobutyl-1-[2-(4-methoxy-phenyl)-ethyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-ylmethyl}-phenyl)-acetic acid; (3-{3-Isobutyl-1-[2-(4-methoxy-phenyl)-ethyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]decane-8-sulfonyl}-4-methyl-phenyl)-acetic acid; (3-{3-Isobutyl-1-[2-(4-methoxy-phenyl)-ethyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl}-phenyl)-acetic acid; 2-(4-{3-Isobutyl-1-[2-(4-methoxy-phenyl)-ethyl]-2,4-dioxo-1,3-diaza-spiro[4.5]dec-7-ylmethyl}-phenyl)-propionic acid; (3-{3-Cyclopropylmethyl-1-[2-(4-methoxy-phenyl)-ethyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl}-phenyl)-acetic acid; {3-[3-Isobutyl-2,4-dioxo-1-(4-trifluoromethoxy-benzyl)-1,3,8-triaza-spiro[4.5]dec-8-yl]-phenyl}-acetic acid; 2-(2-{3-Isobutyl-1-[2-(4-methoxy-phenyl)-ethyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl}-pyrimidin-4-yloxy)-2-methyl-propionic acid; 2-(3-{3-Cyclobutylmethyl-1-[2-(2,4-dichloro-phenyl)-ethyl]-2,4-dioxo-1,3-diaza-spiro[4.5]dec-8-yl}-phenoxy)-2-methyl-propionic acid; {3-[3-Cyclopropylmethyl-2,4-dioxo-1-(4-trifluoromethoxy-benzyl)-1,3,8-triaza-spiro[4.5]dec-8-yl]-phenyl}-acetic acid; (3-{3-Cyclobutylmethyl-2,4-dioxo-1-[2-(4-trifluoromethyl-phenyl)-ethyl]-1,3,8-triaza-spiro[4.5]dec-8-yl}-phenyl)-acetic acid; (3-{3-Cyclobutylmethyl-1-[4-(4-methoxy-phenyl)-butyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl}-phenyl)-acetic acid; 3-{3-Isobutyl-1-[2-(4-methoxy-phenyl)-ethyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-ylmethyl}-benzoic acid; (2-{3-Isobutyl-1-[2-(4-methoxy-phenyl)-ethyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-ylmethyl}-phenyl)-acetic acid; (3-{3-Isobutyl-1-[2-(4-methoxy-phenyl)-ethyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]decane-8-sulfonyl}-4-methoxy-phenyl)-acetic acid; 3-(3-{3-Isobutyl-1-[2-(4-methoxy-phenyl)-ethyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl}-phenyl)-propionic acid; (3-{3-Isobutyl-1-[2-(4-methoxy-phenyl)-ethyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl}-phenoxy)-acetic acid; 2-(3-{3-Isobutyl-1-[2-(4-methoxy-phenyl)-ethyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl}-phenoxy)-2-methyl-propionic acid; (5-{3-Isobutyl-1-[2-(4-methoxy-phenyl)-ethyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl}-2-methyl-phenyl)-acetic acid; (3-{3-Isobutyl-1-[2-(4-methoxy-phenyl)-ethyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl}-5-methyl-phenyl)-acetic acid; (2-Fluoro-5-{3-isobutyl-1-[2-(4-methoxy-phenyl)-ethyl]-

2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl}-phenyl)-acetic acid; (5-{3-Isobutyl-1-[2-(4-methoxy-phenyl)-ethyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl}-2-trifluoromethyl-phenyl)-acetic acid; (5-{3-Isobutyl-1-[2-(4-methoxy-phenyl)-ethyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl}-2-methoxy-phenyl)-acetic acid; 2-(3-{3-Isobutyl-1-[2-(4-methoxy-phenyl)-ethyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl}-phenyl)-2-methyl-propionic acid; (5-{3-Isobutyl-1-[2-(4-methoxy-phenyl)-ethyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl}-2-methyl-phenoxy)-acetic acid; (2-Chloro-5-{3-isobutyl-1-[2-(4-methoxy-phenyl)-ethyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl}-phenoxy)-acetic acid; 2-(5-{3-Isobutyl-1-[2-(4-methoxy-phenyl)-ethyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl}-2-methyl-phenoxy)-2-methyl-propionic acid; 2-(2-Chloro-5-{3-isobutyl-1-[2-(4-methoxy-phenyl)-ethyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl}-phenoxy)-2-methyl-propionic acid; 2-(2,3-Difluoro-5-{3-isobutyl-1-[2-(4-methoxy-phenyl)-ethyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl}-phenoxy)-2-methyl-propionic acid; (3-{3-Isobutyl-1-[2-(4-methoxy-phenyl)-ethyl]-2-oxo-1,3,8-triaza-spiro[4.5]dec-8-yl}-phenyl)-acetic acid; (6-{3-Isobutyl-1-[2-(4-methoxy-phenyl)-ethyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl}-pyridin-2-yl)-acetic acid; (2-{3-Isobutyl-1-[2-(4-methoxy-phenyl)-ethyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl}-pyridin-4-yl)-acetic acid; (5-{3-Cyclobutylmethyl-1-[2-(2,4-dichloro-phenyl)-ethyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl}-2-methyl-phenyl)-acetic acid; 2-(5-{3-Cyclobutylmethyl-1-[2-(2,4-dichloro-phenyl)-ethyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl}-2-methyl-phenoxy)-2-methyl-propionic acid; (2-Chloro-5-{3-cyclobutylmethyl-1-[2-(2,4-dichloro-phenyl)-ethyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl}-phenoxy)-acetic acid; 2-(2-Chloro-5-{3-cyclobutylmethyl-1-[2-(2,4-dichloro-phenyl)-ethyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl}-phenoxy)-2-methyl-propionic acid; (6-{3-Cyclobutylmethyl-1-[2-(2,4-dichloro-phenyl)-ethyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl}-pyridin-2-yl)-acetic acid; (4-{3-Isobutyl-1-[2-(4-methoxy-phenyl)-ethyl]-2,4-dioxo-1,3,7-triaza-spiro[4.5]dec-7-ylmethyl}-phenoxy)-acetic acid; (3-{3-Cyclobutylmethyl-1-[2-(4-methoxy-phenyl)-ethyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl}-phenyl)-acetic acid; {3-[1-[2-(4-Methoxy-phenyl)-ethyl]-3-(3-methyl-butyl)-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl]-phenyl}-acetic acid; (3-{3-Butyl-1-[2-(4-methoxy-phenyl)-ethyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl}-phenyl)-acetic acid; 2-(4-{3-Isobutyl-1-[2-(4-methoxy-phenyl)-ethyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl}-

pyrimidin-2-yloxy)-2-methyl-propionic acid; 2-(6-{3-Isobutyl-1-[2-(4-methoxy-phenyl)-ethyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl}-pyrimidin-4-yloxy)-2-methyl-propionic acid; 2-(4-{3-Cyclobutylmethyl-1-[2-(2,4-dichloro-phenyl)-ethyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl}-pyrimidin-2-yloxy)-2-methyl-propionic acid; 2-(2-{3-Cyclobutylmethyl-1-[2-(2,4-dichloro-phenyl)-ethyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl}-pyrimidin-4-yloxy)-2-methyl-propionic acid; 2-(6-{3-Cyclobutylmethyl-1-[2-(2,4-dichloro-phenyl)-ethyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl}-pyrimidin-4-yloxy)-2-methyl-propionic acid; {3-[3-Cyclobutylmethyl-2,4-dioxo-1-(4-trifluoromethoxy-benzyl)-1,3,8-triaza-spiro[4.5]dec-8-yl]-phenyl}-acetic acid; {3-[3-Cyclobutylmethyl-2,4-dioxo-1-(4-trifluoromethyl-benzyl)-1,3,8-triaza-spiro[4.5]dec-8-yl]-phenyl}-acetic acid; {3-[3-Cyclopentylmethyl-2,4-dioxo-1-(4-trifluoromethyl-benzyl)-1,3,8-triaza-spiro[4.5]dec-8-yl]-phenyl}-acetic acid; {3-[3-Cyclopentylmethyl-2,4-dioxo-1-(4-trifluoromethoxy-benzyl)-1,3,8-triaza-spiro[4.5]dec-8-yl]-phenyl}-acetic acid; {3-[1-(2,4-Bis-trifluoromethyl-benzyl)-3-cyclopentylmethyl-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl]-phenyl}-acetic acid; {3-[3-Cyclobutylmethyl-2,4-dioxo-1-(3-trifluoromethoxy-benzyl)-1,3,8-triaza-spiro[4.5]dec-8-yl]-phenyl}-acetic acid; (3-{3-Cyclobutylmethyl-2,4-dioxo-1-[4-(4-trifluoromethyl-phenyl)-thiazol-2-ylmethyl]-1,3,8-triaza-spiro[4.5]dec-8-yl}-phenyl)-acetic acid; (3-{3-Cyclopropylmethyl-2,4-dioxo-1-[4-(4-trifluoromethyl-phenyl)-thiazol-2-ylmethyl]-1,3,8-triaza-spiro[4.5]dec-8-yl}-phenyl)-acetic acid; {3-[3-(3-Methyl-but-2-enyl)-2,4-dioxo-1-(4-trifluoromethoxy-benzyl)-1,3,8-triaza-spiro[4.5]dec-8-yl]-phenyl}-acetic acid; {3-[1-[2-(4-Bromo-phenyl)-2-hydroxy-ethyl]-3-(3-methyl-butyl)-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl]-phenyl}-acetic acid; {3-[1-[2-(4-Chloro-phenyl)-2-hydroxy-ethyl]-3-(3-methyl-butyl)-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl]-phenyl}-acetic acid; {3-[2,4-Dioxo-3-pentyl-1-(4-trifluoromethoxy-benzyl)-1,3,8-triaza-spiro[4.5]dec-8-yl]-phenyl}-acetic acid; {3-[3-(2,2-Dimethyl-propyl)-2,4-dioxo-1-(4-trifluoromethoxy-benzyl)-1,3,8-triaza-spiro[4.5]dec-8-yl]-phenyl}-acetic acid; {3-[3-(2-Ethyl-butyl)-2,4-dioxo-1-(4-trifluoromethoxy-benzyl)-1,3,8-triaza-spiro[4.5]dec-8-yl]-phenyl}-acetic acid; {3-[3-(4-Fluoro-butyl)-2,4-dioxo-1-(4-trifluoromethoxy-benzyl)-1,3,8-triaza-spiro[4.5]dec-8-yl]-phenyl}-acetic acid; {3-[3-(4-Methyl-pentyl)-2,4-dioxo-1-(4-trifluoromethoxy-benzyl)-1,3,8-triaza-spiro[4.5]dec-8-yl]-phenyl}-acetic acid; {3-[3-Cyclohexylmethyl-2,4-dioxo-1-(4-trifluoromethoxy-benzyl)-1,3,8-triaza-spiro[4.5]dec-8-

yl]-phenyl}-acetic acid; {3-[2,4-Dioxo-3-(3-pyrrol-1-yl-propyl)-1-(4-trifluoromethoxy-benzyl)-1,3,8-triaza-spiro[4.5]dec-8-yl]-phenyl}-acetic acid; {3-[3-(3,3-Dimethyl-2-oxo-butyl)-2,4-dioxo-1-(4-trifluoromethoxy-benzyl)-1,3,8-triaza-spiro[4.5]dec-8-yl]-phenyl}-acetic acid; {3-[2,4-Dioxo-3-(4,4,4-trifluoro-butyl)-1-(4-trifluoromethoxy-benzyl)-1,3,8-triaza-spiro[4.5]dec-8-yl]-phenyl}-acetic acid; {3-[3-(2-Cyclohexyl-ethyl)-2,4-dioxo-1-(4-trifluoromethoxy-benzyl)-1,3,8-triaza-spiro[4.5]dec-8-yl]-phenyl}-acetic acid; {3-[3-(2-Ethyl-hexyl)-2,4-dioxo-1-(4-trifluoromethoxy-benzyl)-1,3,8-triaza-spiro[4.5]dec-8-yl]-phenyl}-acetic acid; {3-[3-(2-Methyl-butyl)-2,4-dioxo-1-(4-trifluoromethoxy-benzyl)-1,3,8-triaza-spiro[4.5]dec-8-yl]-phenyl}-acetic acid; {3-[2,4-Dioxo-3-(3,4,4-trifluoro-but-3-enyl)-1-(4-trifluoromethoxy-benzyl)-1,3,8-triaza-spiro[4.5]dec-8-yl]-phenyl}-acetic acid; {3-[3-(3,3-Dimethyl-butyl)-2,4-dioxo-1-(4-trifluoromethoxy-benzyl)-1,3,8-triaza-spiro[4.5]dec-8-yl]-phenyl}-acetic acid; {3-[1-(2,4-Dichloro-5-fluoro-benzyl)-3-(3,3-dimethyl-butyl)-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl]-phenyl}-acetic acid; {3-[1-(2,4-Dichloro-5-fluoro-benzyl)-3-(4-fluoro-butyl)-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl]-phenyl}-acetic acid; (3-{3-Cyclobutylmethyl-1-[2-(2,4-dichloro-phenyl)-ethyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl}-phenyl)-acetic acid; (3-{3-Cyclopentylmethyl-2,4-dioxo-1-[2-(4-trifluoromethyl-phenyl)-ethyl]-1,3,8-triaza-spiro[4.5]dec-8-yl}-phenyl)-acetic acid; (3-{3-Cyclopentylmethyl-1-[2-(2,4-dichloro-phenyl)-ethyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl}-phenyl)-acetic acid; (3-{3-Cyclohexylmethyl-1-[2-(2,4-dichloro-phenyl)-ethyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl}-phenyl)-acetic acid; and (3-{1-[2-(4-Chloro-phenyl)-ethyl]-3-cyclopentylmethyl-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl}-phenyl)-acetic acid.

[0019] Further preferred compounds and intermediates of the invention are detailed in the Examples, *infra*.

Pharmacology and Utility

[0020] Compounds of the invention modulate the activity of PPARs and, as such, are useful for treating diseases or disorders in which PPARs contributes to the pathology and/or symptomology of the disease. This invention further provides compounds of this invention for use in the preparation of medicaments for the treatment of diseases or

disorders in which PPARs contributes to the pathology and/or symptomology of the disease.

[0021] Such compounds may therefore be employed for the treatment of prophylaxis, dyslipidemia, hyperlipidemia, hypercholesteremia, atherosclerosis, atherogenesis, hypertriglyceridemia, heart failure, hyper cholesteremia, myocardial infarction, vascular diseases, cardiovascular diseases, hypertension, obesity, cachexia, HIV wasting syndrome, inflammation, arthritis, cancer, Alzheimer's disease, anorexia, anorexia nervosa, bulimia, skin disorders, respiratory diseases, ophthalmic disorders, IBDs (irritable bowel disease), ulcerative colitis and Crohn's disease. Preferably for the treatment of prophylaxis, dyslipidemia, hyperlipidemia, hypercholesteremia, atherosclerosis, atherogenesis, hypertriglyceridemia, cardiovascular diseases, hypertension, obesity, inflammation, cancer, skin disorders, IBDs (irritable bowel disease), ulcerative colitis and Crohn's disease.

[0022] Compounds of the invention can also be employed to treat long term critical illness, increase muscle mass and/or muscle strength, increase lean body mass, maintain muscle strength and function in the elderly, enhance muscle endurance and muscle function, and reverse or prevent frailty in the elderly.

[0023] Further, the compounds of the present invention may be employed in mammals as hypoglycemic agents for the treatment and prevention of conditions in which impaired glucose tolerance, hyperglycemia and insulin resistance are implicated, such as type-1 and type-2 diabetes, Impaired Glucose Metabolism (IGM), Impaired Glucose Tolerance (IGT), Impaired Fasting Glucose (IFG), and Syndrome X. Preferably type-1 and type-2 diabetes, Impaired Glucose Metabolism (IGM), Impaired Glucose Tolerance (IGT) and Impaired Fasting Glucose (IFG).

[0024] In accordance with the foregoing, the present invention further provides a method for preventing or treating any of the diseases or disorders described above in a subject in need of such treatment, which method comprises administering to said subject a therapeutically effective amount (*See, "Administration and Pharmaceutical Compositions", infra*) of a compound of the invention or a pharmaceutically acceptable salt thereof. For any of the above uses, the required dosage will vary depending on the mode of administration, the particular condition to be treated and the effect desired. The

present invention also concerns: i) a compound of the invention or a pharmaceutically acceptable salt thereof for use as a medicament; and ii) the use of a compound of the invention or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for preventing or treating any of the diseases or disorders described above.

Administration and Pharmaceutical Compositions

[0025] In general, compounds of the invention will be administered in therapeutically effective amounts via any of the usual and acceptable modes known in the art, either singly or in combination with one or more therapeutic agents. A therapeutically effective amount can vary widely depending on the severity of the disease, the age and relative health of the subject, the potency of the compound used and other factors. In general, satisfactory results are indicated to be obtained systemically at daily dosages of from about 0.03 to 2.5mg/kg per body weight. An indicated daily dosage in the larger mammal, e.g. humans, is in the range from about 0.5mg to about 100mg, conveniently administered, e.g. in divided doses up to four times a day or in retard form. Suitable unit dosage forms for oral administration comprise from ca. 1 to 50mg active ingredient.

[0026] Compounds of the invention can be administered as pharmaceutical compositions by any conventional route, in particular enterally, e.g., orally, e.g., in the form of tablets or capsules, or parenterally, e.g., in the form of injectable solutions or suspensions, topically, e.g., in the form of lotions, gels, ointments or creams, or in a nasal or suppository form. Pharmaceutical compositions comprising a compound of the present invention in free form or in a pharmaceutically acceptable salt form in association with at least one pharmaceutically acceptable carrier or diluent can be manufactured in a conventional manner by mixing, granulating or coating methods. For example, oral compositions can be tablets or gelatin capsules comprising the active ingredient together with a) diluents, e.g., lactose, dextrose, sucrose, mannitol, sorbitol, cellulose and/or glycine; b) lubricants, e.g., silica, talcum, stearic acid, its magnesium or calcium salt and/or polyethyleneglycol; for tablets also c) binders, e.g., magnesium aluminum silicate, starch paste, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose and or polyvinylpyrollidone; if desired d) disintegrants, e.g., starches, agar, alginic acid or its sodium salt, or effervescent mixtures; and/or e) absorbents, colorants, flavors and

sweeteners. Injectable compositions can be aqueous isotonic solutions or suspensions, and suppositories can be prepared from fatty emulsions or suspensions. The compositions can be sterilized and/or contain adjuvants, such as preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure and/or buffers. In addition, they can also contain other therapeutically valuable substances. Suitable formulations for transdermal applications include an effective amount of a compound of the present invention with a carrier. A carrier can include absorbable pharmacologically acceptable solvents to assist passage through the skin of the host. For example, transdermal devices are in the form of a bandage comprising a backing member, a reservoir containing the compound optionally with carriers, optionally a rate controlling barrier to deliver the compound to the skin of the host at a controlled and predetermined rate over a prolonged period of time, and means to secure the device to the skin. Matrix transdermal formulations can also be used. Suitable formulations for topical application, e.g., to the skin and eyes, are preferably aqueous solutions, ointments, creams or gels well-known in the art. Such can contain solubilizers, stabilizers, tonicity enhancing agents, buffers and preservatives.

[0027] This invention also concerns a pharmaceutical composition comprising a therapeutically effective amount of a compound as described herein in combination with one or more pharmaceutically acceptable carriers.

[0028] Compounds of the invention can be administered in therapeutically effective amounts in combination with one or more therapeutic agents (pharmaceutical combinations).

[0029] Thus, the present invention also relates to pharmaceutical combinations, such as a combined preparation or pharmaceutical composition (fixed combination), comprising: 1) a compound of the invention as defined above or a pharmaceutical acceptable salt thereof; and 2) at least one active ingredient selected from:

a) anti-diabetic agents such as insulin, insulin derivatives and mimetics; insulin secretagogues such as the sulfonylureas, e.g., Glipizide, glyburide and Amaryl; insulinotropic sulfonylurea receptor ligands such as meglitinides, e.g., nateglinide and repaglinide; insulin sensitizer such as protein tyrosine phosphatase-1B (PTP-1B) inhibitors such as PTP-112; GSK3 (glycogen synthase kinase-3) inhibitors such as SB-517955, SB-

4195052, SB-216763, NN-57-05441 and NN-57-05445; RXR ligands such as GW-0791 and AGN-194204; sodium-dependent glucose co-transporter inhibitors such as T-1095; glycogen phosphorylase A inhibitors such as BAY R3401; biguanides such as metformin; alpha-glucosidase inhibitors such as acarbose; GLP-1 (glucagon like peptide-1), GLP-1 analogs such as Exendin-4 and GLP-1 mimetics; DPPIV (dipeptidyl peptidase IV) inhibitors such as DPP728, LAF237 (vildagliptin - Example 1 of WO 00/34241), MK-0431, saxagliptin, GSK23A ; an AGE breaker; a thiazolidone derivative (glitazone) such as pioglitazone, rosiglitazone, or *(R)*-1-{4-[5-methyl-2-(4-trifluoromethyl-phenyl)-oxazol-4-ylmethoxy]-benzenesulfonyl}-2,3-dihydro-1*H*-indole-2-carboxylic acid described in the patent application WO 03/043985, as compound 19 of Example 4, a non-glitazone type PPARγ agonist e.g. GI-262570;

b) hypolipidemic agents such as 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase inhibitors, e.g., lovastatin, pitavastatin, simvastatin, pravastatin, cerivastatin, mevastatin, velostatin, fluvastatin, dalvastatin, atorvastatin, rosuvastatin and rivastatin; squalene synthase inhibitors; FXR (farnesoid X receptor) and LXR (liver X receptor) ligands; cholestyramine; fibrates; nicotinic acid and aspirin;

c) an anti-obesity agent or appetite regulating agent such as phentermine, leptin, bromocriptine, dexamphetamine, amphetamine, fenfluramine, dexfenfluramine, sibutramine, orlistat, dexfenfluramine, mazindol, phentermine, phendimetrazine, diethylpropion, fluoxetine, bupropion, topiramate, diethylpropion, benzphetamine, phenylpropanolamine or ecopipam, ephedrine, pseudoephedrine or cannabinoid receptor antagonists;

d) anti-hypertensive agents, e.g., loop diuretics such as ethacrynic acid, furosemide and torsemide; diuretics such as thiazide derivatives, chlorithiazide, hydrochlorothiazide, amiloride; angiotensin converting enzyme (ACE) inhibitors such as benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perinodopril, quinapril, ramipril and trandolapril; inhibitors of the Na-K-ATPase membrane pump such as digoxin; neutralendopeptidase (NEP) inhibitors e.g. thiorphan, terteo-thiorphan, SQ29072; ECE inhibitors e.g. SLV306; ACE/NEP inhibitors such as omapatrilat, sampatrilat and fasidotril; angiotensin II antagonists such as candesartan, eprosartan, irbesartan, losartan, telmisartan and valsartan, in particular valsartan; renin inhibitors such as aliskiren, terlakiren, ditekiren,

RO 66-1132, RO-66-1168; β-adrenergic receptor blockers such as acebutolol, atenolol, betaxolol, bisoprolol, metoprolol, nadolol, propranolol, sotalol and timolol; inotropic agents such as digoxin, dobutamine and milrinone; calcium channel blockers such as amlodipine, bepridil, diltiazem, felodipine, nicardipine, nimodipine, nifedipine, nisoldipine and verapamil; aldosterone receptor antagonists; and aldosterone synthase inhibitors;

e) a HDL increasing compound;

f) Cholesterol absorption modulator such as Zetia® and KT6-971;

g) Apo-A1 analogues and mimetics;

h) thrombin inhibitors such as Ximelagatran;

i) aldosterone inhibitors such as anastrazole, fadrazole, eplerenone;

j) Inhibitors of platelet aggregation such as aspirin, clopidogrel bisulfate;

k) estrogen, testosterone, a selective estrogen receptor modulator, a selective androgen receptor modulator;

l) a chemotherapeutic agent such as aromatase inhibitors e.g. femara, anti-estrogens, topoisomerase I inhibitors, topoisomerase II inhibitors, microtubule active agents, alkylating agents, antineoplastic antimetabolites, platin compounds, compounds decreasing the protein kinase activity such as a PDGF receptor tyrosine kinase inhibitor preferably Imatinib ({ N-{5-[4-(4-methyl-piperazino-methyl)-benzoylamido]-2-methylphenyl}-4-(3-pyridyl)-2-pyrimidine-amine }) described in the European patent application EP-A-0 564 409 as example 21 or 4-Methyl-N-[3-(4-methyl-imidazol-1-yl)-5-trifluoromethyl-phenyl]-3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-benzamide described in the patent application WO 04/005281 as example 92; and

m) an agent interacting with a 5-HT_3 receptor and/or an agent interacting with 5-HT_4 receptor such as tegaserod described in the US patent No. 5510353 as example 13, tegaserod hydrogen maleate, cisapride, cilansetron;

or, in each case a pharmaceutically acceptable salt thereof; and optionally a pharmaceutically acceptable carrier.

[0030] Most preferred combination partners are tegaserod, imatinib, vildagliptin, metformin, a thiazolidone derivative (glitazone) such as pioglitazone, rosiglitazone, or *(R)*-1-{4-[5-methyl-2-(4-trifluoromethyl-phenyl)-oxazol-4-ylmethoxy]-benzenesulfonyl}-

2,3-dihydro-1*H*-indole-2-carboxylic acid, a sulfonylurea receptor ligand, aliskiren, valsartan, orlistat or a statin such as pitavastatin, simvastatin, fluvastatin or pravastatin.

[0031] Preferably the pharmaceutical combinations contains a therapeutically effective amount of a compound of the invention as defined above, in a combination with a therapeutically effective amount of another therapeutic agent as described above, e.g., each at an effective therapeutic dose as reported in the art. Combination partners (1) and (2) can be administered together, one after the other or separately in one combined unit dosage form or in two separate unit dosage forms. The unit dosage form may also be a fixed combination.

[0032] The structure of the active agents identified by generic or trade names may be taken from the actual edition of the standard compendium "The Merck Index" or the Physician's Desk Reference or from databases, e.g. Patents International (e.g. IMS World Publications) or Current Drugs. The corresponding content thereof is hereby incorporated by reference. Any person skilled in the art is fully enabled to identify the active agents and, based on these references, likewise enabled to manufacture and test the pharmaceutical indications and properties in standard test models, both in vitro and in vivo.

[0033] In another preferred aspect the invention concerns a pharmaceutical composition (fixed combination) comprising a therapeutically effective amount of a compound as described herein, in combination with a therapeutically effective amount of at least one active ingredient selected from the above described group a) to m), or, in each case a pharmaceutically acceptable salt thereof.

[0034] A pharmaceutical composition or combination as described herein for the manufacture of a medicament for the treatment of for the treatment of dyslipidemia, hyperlipidemia, hypercholesteremia, atherosclerosis, hypertriglyceridemia, heart failure, myocardial infarction, vascular diseases, cardiovascular diseases, hypertension, obesity, inflammation, arthritis, cancer, Alzheimer's disease, skin disorders, respiratory diseases, ophthalmic disorders, inflammatory bowel diseases, IBDs (irritable bowel disease), ulcerative colitis, Crohn's disease, conditions in which impaired glucose tolerance, hyperglycemia and insulin resistance are implicated, such as type-1 and type-2 diabetes,

Impaired Glucose Metabolism (IGM), Impaired Glucose Tolerance (IGT), Impaired Fasting Glucose (IFG), and Syndrome-X.

[0035] Such therapeutic agents include estrogen, testosterone, a selective estrogen receptor modulator, a selective androgen receptor modulator, insulin, insulin derivatives and mimetics; insulin secretagogues such as the sulfonylureas, e.g., Glipizide and Amaryl; insulinotropic sulfonylurea receptor ligands, such as meglitinides, e.g., nateglinide and repaglinide; insulin sensitizers, such as protein tyrosine phosphatase-1B (PTP-1B) inhibitors, GSK3 (glycogen synthase kinase-3) inhibitors or RXR ligands; biguanides, such as metformin; alpha-glucosidase inhibitors, such as acarbose; GLP-1 (glucagon like peptide-1), GLP-1 analogs, such as Exendin-4, and GLP-1 mimetics; DPPIV (dipeptidyl peptidase IV) inhibitors, e.g. isoleucin-thiazolidide; DPP728 and LAF237, hypolipidemic agents, such as 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase inhibitors, e.g., lovastatin, pitavastatin, simvastatin, pravastatin, cerivastatin, mevastatin, velostatin, fluvastatin, dalvastatin, atorvastatin, rosuvastatin, fluindostatin and rivastatin, squalene synthase inhibitors or FXR (liver X receptor) and LXR (farnesoid X receptor) ligands, cholestyramine, fibrates, nicotinic acid and aspirin. A compound of the present invention may be administered either simultaneously, before or after the other active ingredient, either separately by the same or different route of administration or together in the same pharmaceutical formulation.

[0036] The invention also provides for pharmaceutical combinations, e.g. a kit, comprising: a) a first agent which is a compound of the invention as disclosed herein, in free form or in pharmaceutically acceptable salt form, and b) at least one co-agent. The kit can comprise instructions for its administration.

[0037] The terms "co-administration" or "combined administration" or the like as utilized herein are meant to encompass administration of the selected therapeutic agents to a single patient, and are intended to include treatment regimens in which the agents are not necessarily administered by the same route of administration or at the same time.

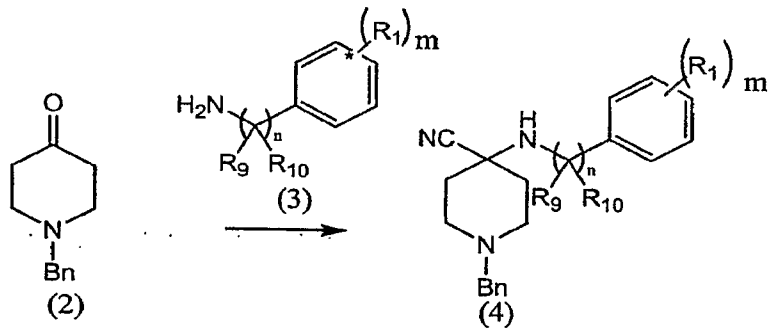
The term "pharmaceutical combination" as used herein means a product that results from the mixing or combining of more than one active ingredient and includes both fixed and non-fixed combinations of the active ingredients. The term "fixed combination" means that the active ingredients, e.g. a compound of Formula I and a co-agent, are both administered to a

patient simultaneously in the form of a single entity or dosage. The term "non-fixed combination" means that the active ingredients, e.g. a compound of Formula I and a co-agent, are both administered to a patient as separate entities either simultaneously, concurrently or sequentially with no specific time limits, wherein such administration provides therapeutically effective levels of the 2 compounds in the body of the patient. The latter also applies to cocktail therapy, e.g. the administration of 3 or more active ingredients.

Processes for Making Compounds of the Invention

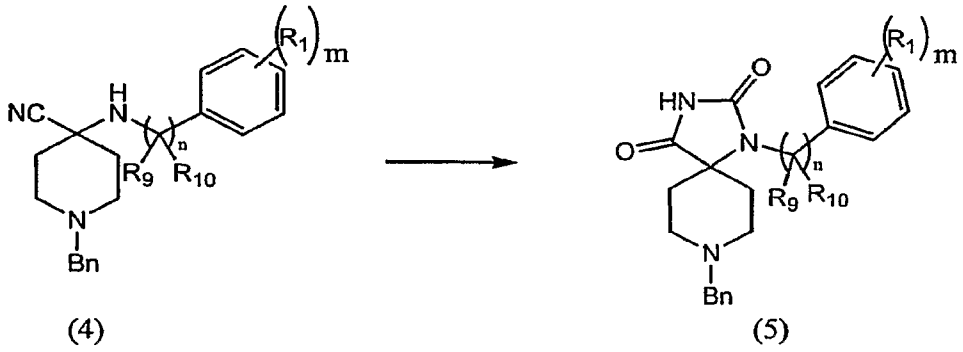
[0038] The present invention also includes processes for the preparation of compounds of the invention. In the reactions described, it can be necessary to protect reactive functional groups, for example hydroxy, amino, imino, thio or carboxy groups, where these are desired in the final product, to avoid their unwanted participation in the reactions. Conventional protecting groups can be used in accordance with standard practice, for example, see T.W. Greene and P. G. M. Wuts in "Protective Groups in Organic Chemistry", John Wiley and Sons, 1991.

[0039] Compounds of Formula 4 can be prepared by proceeding as in reaction scheme 1:



in which m, R_1, R_9, R_{10} and n are as defined for Formula I. Compounds of Formula 4 are prepared by reacting a compound of formula 2 with a compound of formula 3 in the presence of a suitable solvent (for example, Acetic Acid, and the like) and a suitable reagent (for example, trimethyl-silyl-cyanide, and the like). The reaction is carried out in the temperature range of about 0 to about 50°C and takes up to about 24 hours to complete.

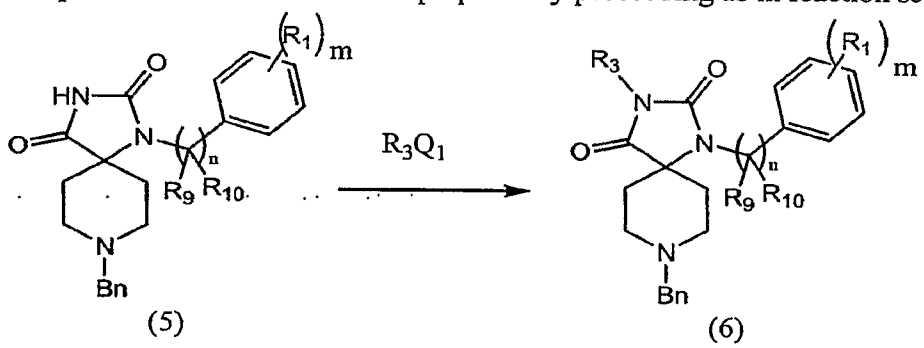
[0040] Compounds of Formula 5 can be prepared by proceeding as in reaction scheme 2:



(4) (5)

in which m, R_1, R_9, R_{10} and n are as defined for Formula I. Compounds of Formula 5 are prepared by first forming an intermediate by reacting a compound of formula 4 with a suitable reagent (for example, chlorosulfonylisocyanate, and the like) and a suitable solvent (for example, DCM, and the like). The reaction is carried out at a temperature range of about 0 to about 50°C and takes up to about 2 hours to complete. Secondly, the intermediate is treated with a suitable acid (for example, 1M HCl in water, and the like) in a temperature range of about 80 to about 120°C and takes up to about 6 hours to complete.

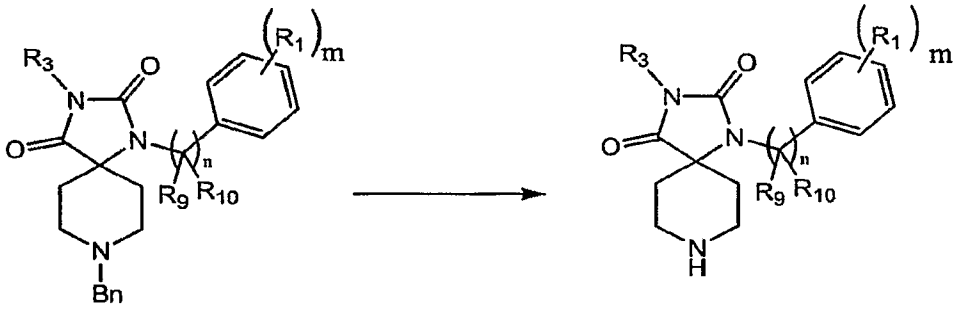
Compounds of Formula 6 can be prepared by proceeding as in reaction scheme 3:



(5) (6)

in which m, R_1, R_3, R_9, R_{10} and n are as defined for Formula I; and Q_1 is a halogen, preferably Cl, I or Br. Compounds of formula 6 are formed by reacting a compound of formula 5 with R_3Q_1 in the presence of a suitable solvent (for example, DMSO, and the like) and a suitable base (for example, potassium carbonate, and the like). The reaction is carried out in the temperature range of about 25 to about 75°C and takes up to about 24 hours to complete.

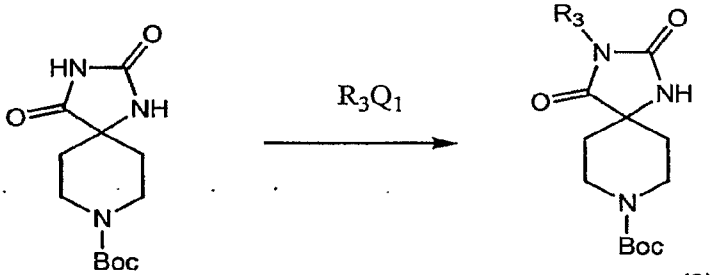
[0041] Compounds of Formula 7 can be prepared by proceeding as in reaction scheme 4:



(6) (7)

in which m, R_1, R_3, R_9, R_{10} and n are as defined for Formula I. Compounds of Formula 7 are prepared by deprotecting a compound of formula 6 in the presence of a suitable solvent (for example, methanol, and the like), a suitable catalyst (for example, palladium on charcoal, and the like), a suitable acid (for example, HCl, and the like) and a suitable reducing agent (for example, hydrogen, and the like). The reaction is carried out in the temperature range of about 0 to about 50°C and takes up to about 24 hours to complete.

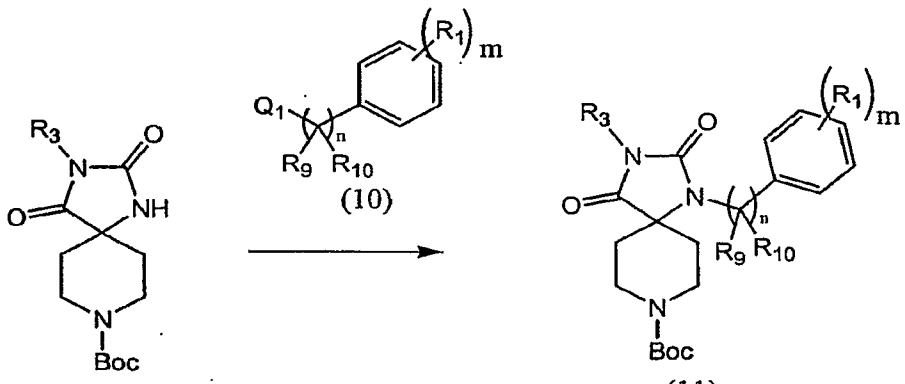
Compounds of Formula 9 can be prepared by proceeding as in reaction scheme 5:



(8) (9)

in which R_3 is as defined for Formula I; and Q_1 is a halogen, preferably Cl, I or Br. Compounds of formula 9 are formed by reacting a compound of formula 8 with R_3Q_1 in the presence of a suitable solvent (for example, DMF, and the like) and a suitable base (for example, cesium bicarbonate, and the like). The reaction is carried out in the temperature range of about 25 to about 75°C and takes up to about 24 hours to complete.

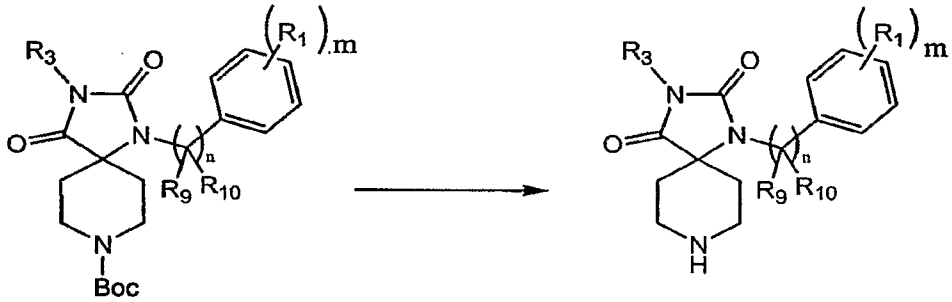
[0042] Compounds of Formula 11 can be prepared by proceeding as in reaction scheme 6:



(9) (10) (11)

in which m, R_1, R_3, R_9, R_{10} and n are as defined for Formula I; and Q_1 is a halogen, preferably Cl, I or Br. Compounds of formula 11 are formed by reacting a compound of formula 9 with a compound of formula 10 in the presence of a suitable solvent (for example, DMF, DME, and the like) and a suitable base (for example, cesium carbonate, KF-Al_2O_3, and the like). The reaction mixture can be subjected to microwave radiation. The reaction is carried out in the temperature range of about 100 to about 150°C and takes up to about 30 minutes to complete.

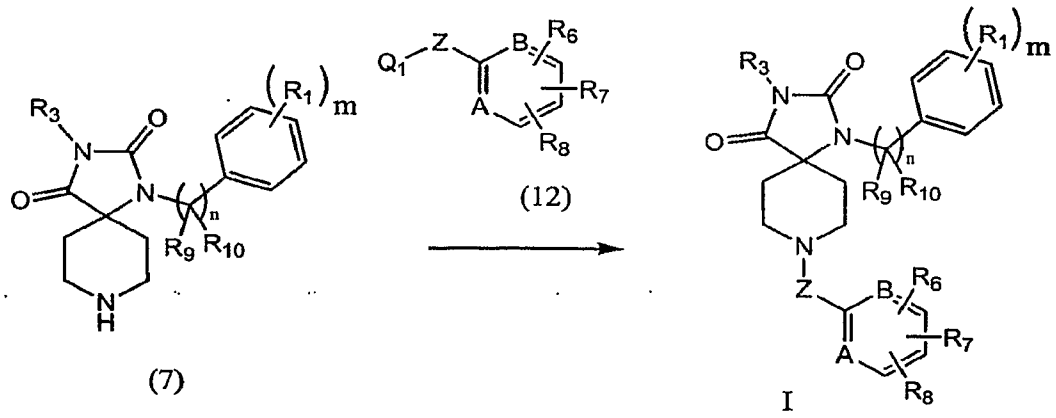
[0043] Compounds of Formula 7 can be prepared by proceeding as in reaction scheme 6:



(11) (7)

in which R_1, R_2, R_3, R_9, R_{10} and n are as defined for Formula I. Compounds of Formula 7 are prepared by deprotecting a compound of formula 11 in the presence of a suitable solvent (for example, DCM, and the like) and a suitable acid (for example, TFA, and the like). The reaction is carried out in the temperature range of about 0 to about 50°C and takes up to about 5 hours to complete.

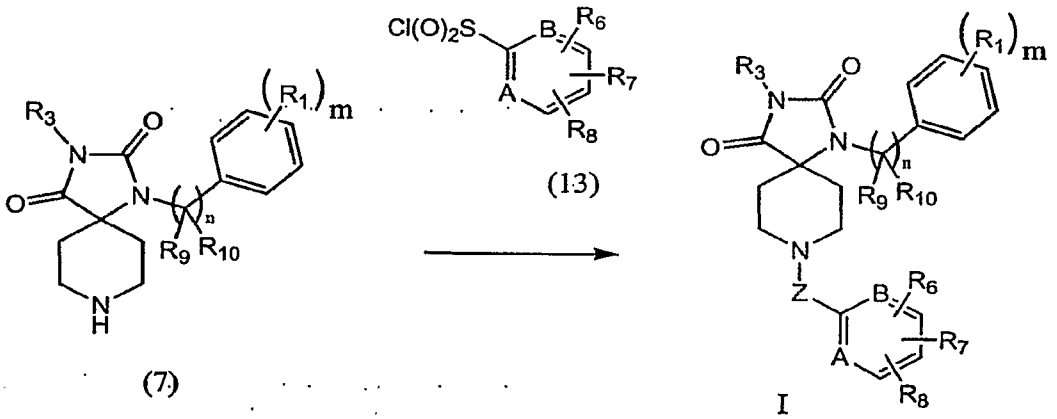
[0044] Compounds of Formula I, wherein Z is a bond, can be prepared by proceeding as in reaction scheme 7:



(7) (12) I

in which n, m, A, B, R_1, R_3, R_6, R_7, R_8, R_9 and R_{10} are as defined for Formula I; and Q_1 is preferably chloro, iodo or bromo. Compounds of Formula I are prepared by reacting a compound of formula 7 with a compound of formula 12 in the presence of a suitable solvent (for example, 1,4-dioxane, and the like), a suitable catalyst (for example, $Pd_2(dba)_3$, and the like), a suitable ligand (for example, phosphine ligands such as $(tBU)_3PHBF_3$, and the like), a suitable inorganic base (for example, Cesium carbonate, and the like) under a suitable protective atmosphere (for example, argon, and the like). The reaction is carried out in the temperature range of about 80 to about 150°C and takes up to about 24 hours to complete.

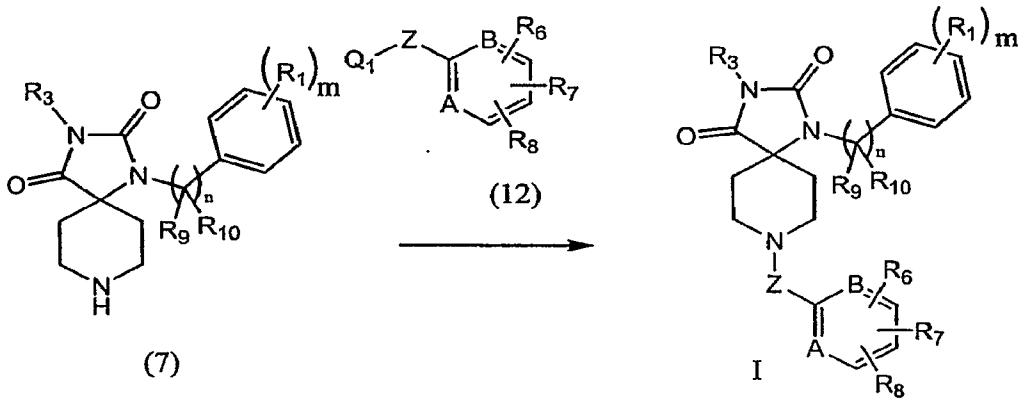
[0045] Compounds of Formula I, in which Z is $-S(O)_{0-2}-$ (SO_2 shown), can be prepared by proceeding as in reaction scheme 8:



(7) (13) I

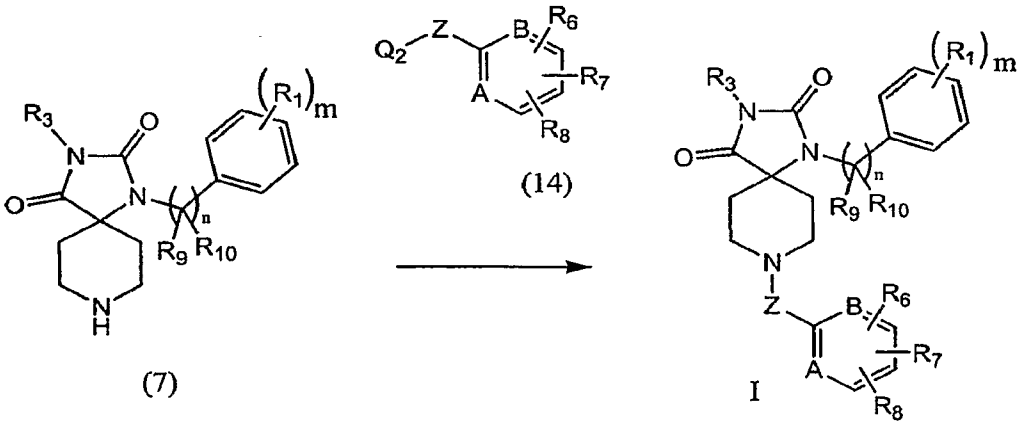
in which n, m, A, B, R_1, R_3, R_6, R_7, R_8, R_9 and R_{10} are as defined for Formula I. Compounds of Formula I are prepared by reacting a compound of formula 7 with a compound of formula 13 in the presence of a suitable solvent (for example, DCM, and the like), a suitable organic base (for example, triethylamine, and the like). The reaction is carried out in the temperature range of about 0 to about 50°C and takes up to about 24 hours to complete.

[0046] Compounds of Formula I, wherein Z is methylene, can be prepared by proceeding as in reaction scheme 9:



in which n, m, A, B, R_1, R_3, R_6, R_7, R_8, R_9 and R_{10} are as defined for Formula I; and Q_1 is chloro, bromo or iodo. Compounds of Formula I are prepared by reacting a compound of formula 7 with a compound of formula 12 in the presence of a suitable solvent (for example, DCM, and the like) and a suitable base (for example, triethylamine, and the like). The reaction is carried out in the temperature range of about 0 to about 50°C and takes up to about 24 hours to complete.

[0047] Compounds of Formula I, wherein Z is a bond, can be prepared by proceeding as in reaction scheme 10:



(7) (14) I

in which n, m, A, B, R_1, R_3, R_6, R_7, R_8, R_9 and R_{10} are as defined for Formula I; and Q_2 is chloro, bromo, iodo or SO_2Me. Compounds of Formula I are prepared by reacting a compound of formula 7 with a compound of formula 14 in the presence of a suitable solvent (for example, n-butanol, and the like) and a suitable base (for example, diisopropylethylamine, and the like). The reaction is carried out in the temperature range of about 25 to about 75°C and takes up to about 24 hours to complete.

[0048] Compounds of Formula I, where R_1 is selected from $-X_1CO_2R_{13}$, $-X_1CR_{11}R_{12}X_2CO_2R_{13}$, $-X_1SCR_{11}R_{12}X_2CO_2R_{13}$ and $-X_1OCR_{11}R_{12}X_2CO_2R_{13}$ (and R_{13} is C_{1-6}alkyl), are converted to their corresponding acids (where R_{13} is hydrogen) via a saponification reaction. The reacting proceeds in the presence of a suitable base (e.g., lithium hydroxide, or the like) and a suitable solvent mixture (e.g., THF/water, or the like) and is carried out in the temperature range of about 0°C to about 50°C, taking up to about 30 hours to complete.

[0001] Detailed reaction conditions are described in the examples, *infra*.

Additional Processes for Making Compounds of the Invention

[0002] A compound of the invention can be prepared as a pharmaceutically acceptable acid addition salt by reacting the free base form of the compound with a pharmaceutically acceptable inorganic or organic acid. Alternatively, a pharmaceutically acceptable base addition salt of a compound of the invention can be prepared by reacting the free acid form of the compound with a pharmaceutically acceptable inorganic or organic

base. Alternatively, the salt forms of the compounds of the invention can be prepared using salts of the starting materials or intermediates.

[0003] The free acid or free base forms of the compounds of the invention can be prepared from the corresponding base addition salt or acid addition salt from, respectively. For example a compound of the invention in an acid addition salt form can be converted to the corresponding free base by treating with a suitable base (e.g., ammonium hydroxide solution, sodium hydroxide, and the like). A compound of the invention in a base addition salt form can be converted to the corresponding free acid by treating with a suitable acid (e.g., hydrochloric acid, etc.).

[0004] Compounds of the invention in unoxidized form can be prepared from N-oxides of compounds of the invention by treating with a reducing agent (e.g., sulfur, sulfur dioxide, triphenyl phosphine, lithium borohydride, sodium borohydride, phosphorus trichloride, tribromide, or the like) in a suitable inert organic solvent (e.g. acetonitrile, ethanol, aqueous dioxane, or the like) at 0 to 80°C.

[0005] Prodrug derivatives of the compounds of the invention can be prepared by methods known to those of ordinary skill in the art (e.g., for further details see Saulnier et al., (1994), Bioorganic and Medicinal Chemistry Letters, Vol. 4, p. 1985). For example, appropriate prodrugs can be prepared by reacting a non-derivatized compound of the invention with a suitable carbamylating agent (e.g., 1,1-acyloxyalkylcarbanochloridate, para-nitrophenyl carbonate, or the like).

[0006] Protected derivatives of the compounds of the invention can be made by means known to those of ordinary skill in the art. A detailed description of techniques applicable to the creation of protecting groups and their removal can be found in T. W. Greene, "Protecting Groups in Organic Chemistry", 3rd edition, John Wiley and Sons, Inc., 1999.

[0007] Compounds of the present invention can be conveniently prepared, or formed during the process of the invention, as solvates (e.g., hydrates). Hydrates of compounds of the present invention can be conveniently prepared by recrystallization from an aqueous/organic solvent mixture, using organic solvents such as dioxin, tetrahydrofuran or methanol.

[0008] Compounds of the invention can be prepared as their individual stereoisomers by reacting a racemic mixture of the compound with an optically active resolving agent to form a pair of diastereoisomeric compounds, separating the diastereomers and recovering the optically pure enantiomers. While resolution of enantiomers can be carried out using covalent diastereomeric derivatives of the compounds of the invention, dissociable complexes are preferred (e.g., crystalline diastereomeric salts). Diastereomers have distinct physical properties (e.g., melting points, boiling points, solubilities, reactivity, etc.) and can be readily separated by taking advantage of these dissimilarities. The diastereomers can be separated by chromatography, or preferably, by separation/resolution techniques based upon differences in solubility. The optically pure enantiomer is then recovered, along with the resolving agent, by any practical means that would not result in racemization. A more detailed description of the techniques applicable to the resolution of stereoisomers of compounds from their racemic mixture can be found in Jean Jacques, Andre Collet, Samuel H. Wilen, "Enantiomers, Racemates and Resolutions", John Wiley And Sons, Inc., 1981.

[0009] In summary, the compounds of Formula I can be made by a process, which involves:

(a) that of the reaction schemes detailed above; and

(b) optionally converting a compound of the invention into a pharmaceutically acceptable salt;

(c) optionally converting a salt form of a compound of the invention to a non-salt form;

(d) optionally converting an unoxidized form of a compound of the invention into a pharmaceutically acceptable N-oxide;

(e) optionally converting an N-oxide form of a compound of the invention to its unoxidized form;

(f) optionally resolving an individual isomer of a compound of the invention from a mixture of isomers;

(g) optionally converting a non-derivatized compound of the invention into a pharmaceutically acceptable prodrug derivative; and

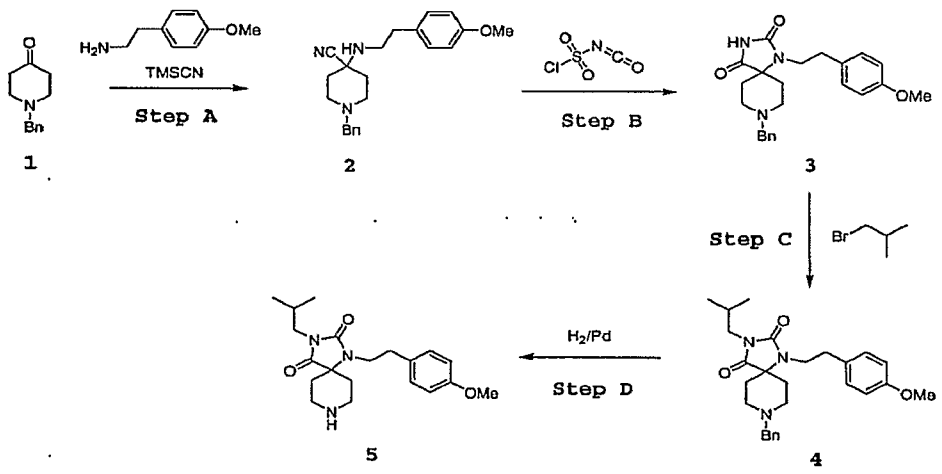
(h) optionally converting a prodrug derivative of a compound of the invention to its non-derivatized form.

[0010] Insofar as the production of the starting materials is not particularly described, the compounds are known or can be prepared analogously to methods known in the art or as disclosed in the Examples hereinafter.

[0011] One of skill in the art will appreciate that the above transformations are only representative of methods for preparation of the compounds of the present invention, and that other well known methods can similarly be used.

Examples

[0012] The present invention is further exemplified, but not limited, by the following intermediates and examples that illustrate the preparation of compounds of Formula I according to the invention.



Intermediate 5. 3-Isobutyl-1-[2-(4-methoxy-phenyl)-ethyl]-1,3,8-triaza-spiro[4.5]decane-2,4-dione.

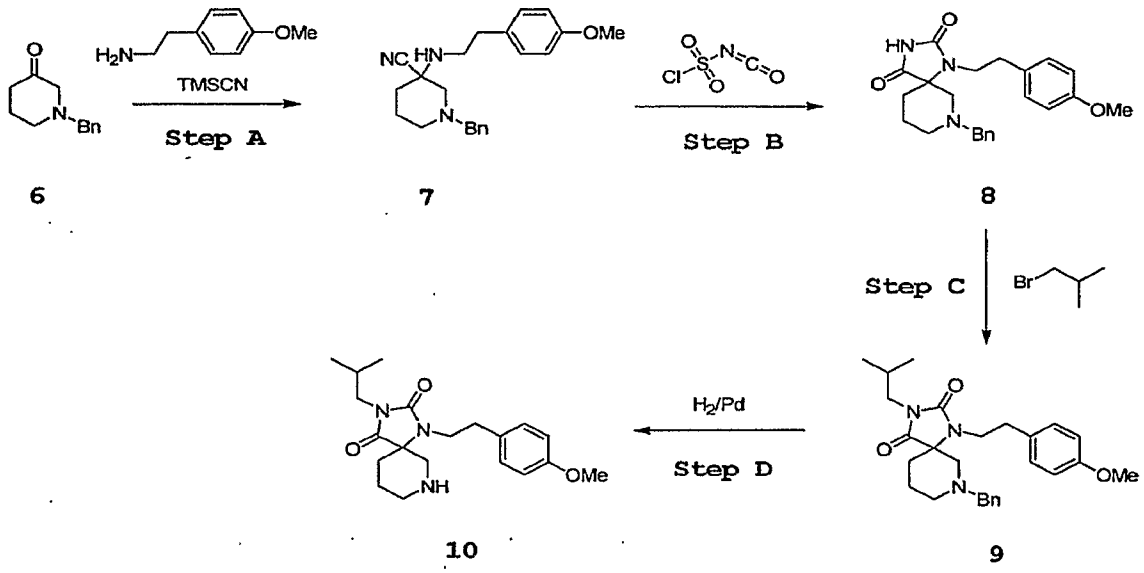
[0013] Step A: 1-Benzyl-piperidine-4-one 1 (9.5 g, 50 mmol) is dissolved in AcOH (75 mL) and cooled to 0°C. 4-Methoxyphenethylamine (8.1 mL, 55 mmol) is added followed by trimethylsilylcyanide (6.7 mL, 50 mmol). The ice-bath is removed and the

mixture is stirred at rt for 20 h. Then the mixture is poured on ice-water, adjusted to pH 9 with aqueous ammonia and extracted with DCM twice. The organic layers are combined and concentrated. Recrystallization from ether affords 2 as a white solid. ^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.26 (m, 5H), 7.07 (d, J = 8.5 Hz, 2H), 6.77 (d, J = 8.5 Hz, 2H), 3.72 (s, 3H), 3.46 (s, 2H), 2.90 (t, J = 6.9 Hz, 2H), 2.70 (m, 4H), 2.27 (m, 2H), 1.91 (m, 2H), 1.69 (m, 2H). MS calcd. for $C_{22}H_{28}N_3O$ ($M+H^+$) 350.2, found 350.3.

[0014] Step B: 1-Benzyl-4-[2-(4-methoxy-phenyl)-ethylamino]-piperidine-4-carbonitrile 2 (8.0 g, 23 mmol) is dissolved in DCM (100 mL) and cooled to 0°C. Chlorosulfonylisocyanate (2.2 mL, 25 mmol) is added, the ice-bath is removed and the mixture is stirred at rt for 1 h. Then the solvent is removed, 1 M HCl (100 mL) is added and the mixture is heated to reflux for 3 h. After adjusting the pH to 7, the mixture is extracted with DCM three times. The solvent is removed, and the remainder is triturated with MeCN to yield 8-benzyl-1-[2-(4-methoxy-phenyl)-ethyl]-1,3,8-triaza-spiro[4.5]decane-2,4-dione 3 as a colorless solid. ^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.33 (m, 5H), 7.15 (d, J = 8.5 Hz, 2H), 6.84 (d, J = 8.5 Hz, 2H), 3.79 (s, 3H), 3.58 (s, 2H), 3.36 (t, J = 7.9 Hz, 2H), 2.91 (t, J = 7.9 Hz, 2H), 2.76 (m, 4H), 1.88 (m, 2H), 1.60 (m, 2H). MS calcd. for $C_{23}H_{28}N_3O_3$ ($M+H^+$) 394.3, found 394.2.

[0015] **Step C:** The hydantoin **3** (8.2 g, 20.8 mmol), 1-bromo-2-methylpropane (2.83 mL, 26.1 mmol) and potassium carbonate (3.7 g, 27.1 mmol) in DMSO (50 mL) are stirred for 12 h at 50°C. The mixture is cooled to rt, diluted with EtOAc and washed with H_2O three times and with brine once. The organic layer is dried ($MgSO_4$), filtered and concentrated. The remainder is purified by flash chromatography (EtOAc/Hexanes gradient) to afford 8-benzyl-3-isobutyl-1-[2-(4-methoxy-phenyl)-ethyl]-1,3,8-triaza-spiro[4.5]decane-2,4-dione **4** () as a white solid: ^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.32 (m, 5H), 7.13 (d, J = 8.7 Hz, 2H), 6.83 (d, J = 8.7 Hz, 2H), 3.78 (s, 3H), 3.58 (s, 2H), 3.38 (t, J = 7.8 Hz, 2H), 3.30 (d, J = 7.4 Hz, 2H), 2.92 (t, J = 7.8 Hz, 2H), 2.75 (m, 4H), 2.08 (m, 1H), 1.87 (m, 2H), 1.49 (m, 2H), 0.90 (d, J = 6.7 Hz, 6H). MS calcd. for $C_{27}H_{36}N_3O_3$ ($M+H^+$) 450.3, found 450.2.

[0016] **Step D:** The hydantoin **4** (0.25 g, 0.56 mmol) is dissolved in MeOH (25 mL). A catalytic amount of palladium (10% on charcoal, 50 mg) is added followed by a catalytic amount (3 drops) of HCl conc. The mixture is put under 1 atm of hydrogen and stirred at rt for 20 h. The mixture is filtered over celite, washed with MeOH and dried in vacuo to yield 3-isobutyl-1-[2-(4-methoxy-phenyl)-ethyl]-1,3,8-triaza-spiro[4.5]decane-2,4-dione **5** (220 mg, quant.) as a colorless glass: ^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.14 (d, J = 8.5 Hz, 2H), 6.78 (d, J = 8.5 Hz, 2H), 3.72 (s, 3H), 3.57 (m, 2H), 3.42 (t, J = 7.3 Hz, 2H), 3.34 (m, 2H), 3.27 (d, J = 7.4 Hz, 2H), 2.93 (t, J = 7.3 Hz, 2H), 2.36 (m, 2H), 2.04 (m, 1H), 1.45 (m, 2H), 0.86 (d, J = 6.7 Hz, 6H). MS calcd. for $C_{20}H_{30}N_3O_3$ ($M+H^+$) 360.2, found 360.2.



Intermediate 10. 3-Isobutyl-1-[2-(4-methoxy-phenyl)-ethyl]-1,3,7-triaza-spiro[4.5]decane-2,4-dione.

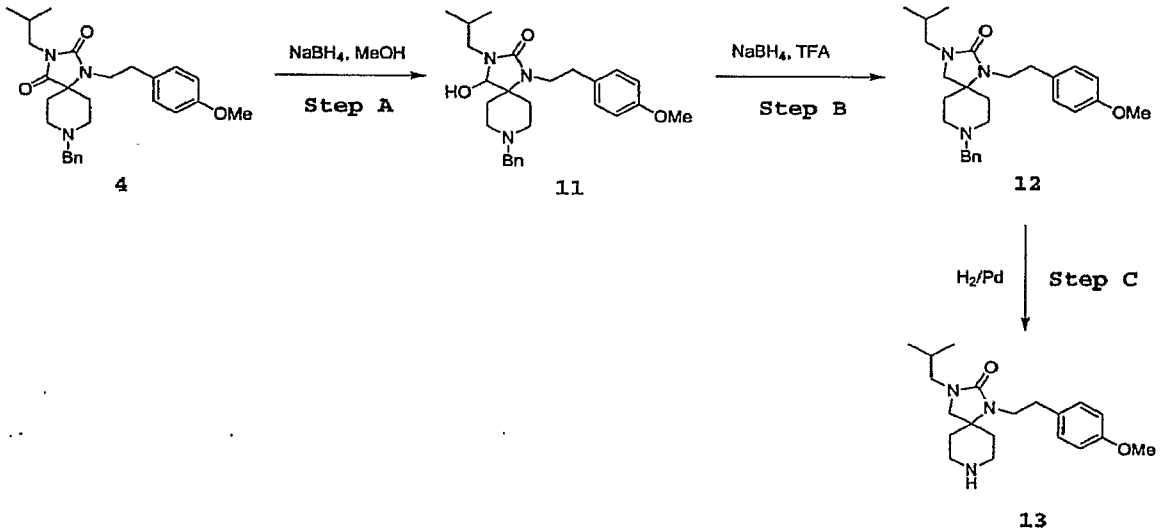
[0017] Step A: 1-Benzyl-3-piperidinone hydrochloride hydrate **6** (3.0 g, 13.3 mmol) is dissolved in AcOH (30 mL) and cooled to 0°C. 4-Methoxyphenethylamine (2.1 mL, 14.6 mmol) is added followed by trimethylsilylcyanide (2.4 mL, 13.3 mmol). The ice-bath is removed and the mixture is stirred at rt for 20 h. Then the mixture is poured on ice-

water, adjusted to pH 9 with aqueous ammonia and extracted with DCM twice. The organic layers are combined and concentratedto give a brown oil which is used directly in the next step without purification. MS calcd. for $C_{22}H_{28}N_3O$ ($M+H^+$) 350.2, found 350.2.

[0018] Step B: 1-Benzyl-3-[2-(4-methoxy-phenyl)-ethylamino]-piperidine-3-carbonitrile 7 (13.3 mmol) is dissolved in DCM (50 mL) and cooled to 0°C. Chlorosulfonylisocyanate (1.3 mL, 14.6 mmol) is added, the ice-bath is removed and the mixture is stirred at rt for 2 h. Then the solvent is removed, 1 M HCl (100 mL) is added and the mixture is heated to reflux for 3 h. After adjusting the pH to 7, the mixture is extracted with DCM three times. The solvent is removed, and the residue is purified on reverse phase HPLC (H_2O/MeCN gradient) to afford 7-Benzyl-1-[2-(4-methoxy-phenyl)-ethyl]-1,3,7-triaza-spiro[4.5]decane-2,4-dione 8 as a colorless oil. ^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.16 (m, 5H), 7.08 (d, J = 8.8 Hz, 2H), 6.76 (d, J = 8.8 Hz, 2H), 3.98 (m, 1H), 3.70 (s, 3H), 3.65 (m, 1H), 3.39 (d, J = 13.3 Hz, 1H), 3.33 (d, J = 13.3 Hz, 1H), 2.90 (m, 1H), 2.78 (m, 1H), 2.67 (m, 1H), 2.53 (d, J = 12.0 Hz, 1H), 2.46 (d, J = 12.0 Hz, 1H), 2.13 (m, 1H), 1.79 (m, 3H), 1.62 (m, 1H). MS calcd. for $C_{23}H_{28}N_3O_3$ ($M+H^+$) 394.3, found 394.2.

[0019] **Step C:** The hydantoin **8** (1.2 g, 3.0 mmol), 1-bromo-2-methylpropane (0.39 mL, 3.6 mmol) and potassium carbonate (0.54 g, 3.9 mmol) in DMSO (10 mL) are stirred for 12 h at 50°C. The mixture is cooled to rt, diluted with EtOAc and washed with H_2O three times and with brine once. The organic layer is dried ($MgSO_4$), filtered and concentrated to afford 7-Benzyl-3-isobutyl-1-[2-(4-methoxy-phenyl)-ethyl]-1,3,7-triaza-spiro[4.5]decane-2,4-dione **9** as a colorless oil which is used directly in Step D: ^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.26 (m, 5H), 7.16 (d, J = 8.4 Hz, 2H), 6.84 (d, J = 8.4 Hz, 2H), 4.00 (m, 1H), 3.80 (s, 3H), 3.79 (m, 1H), 3.52 (d, J = 13.2 Hz, 1H), 3.40 (d, J = 13.2 Hz, 1H), 3.29 (d, J = 7.6 Hz, 2H), 3.00 (m, 1H), 2.89 (m, 1H), 2.76 (m, 1H), 2.55 (m, 2H), 2.05 (m, 1H), 1.91 (m, 3H), 1.62 (m, 2H), 0.87 (d, J = 6.4 Hz, 6H). MS calcd. for $C_{27}H_{36}N_3O_3$ ($M+H^+$) 450.3, found 450.3.

[0020] **Step D:** The hydantoin 9 (0.25 g, 0.56 mmol) is dissolved in AcOH (20 mL). A catalytic amount of palladium (10% on charcoal, 50 mg) is added and the mixture is pressurized to 60 psi of hydrogen and shaken for 20 h. The mixture is filtered over celite, neutralized with aqueous sodium bicarbonate and extracted with ethyl acetate. The organic fraction is washed with brine, dried ($MgSO_4$), filtered, and evaporated to yield 3-Isobutyl-1-[2-(4-methoxy-phenyl)-ethyl]-1,3,7-triaza-spiro[4.5]decane-2,4-dione **10** as a colorless glass: ^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.06 (d, J = 8.8 Hz, 2H), 6.77 (d, J = 8.8 Hz, 2H), 3.72 (s, 3H), 3.63 (s, 1H), 3.35 (m, 2H), 3.28 (d, J = 7.2 Hz, 2H), 3.02 (m, 1H), 2.85 (t, J = 7.6 Hz, 2H), 2.68 (m, 2H), 2.47 (m, 1H), 2.05 (m, 2H), 1.65 (m, 2H), 0.83 (d, J = 6.8 Hz, 6H). MS calcd. for $C_{20}H_{30}N_3O_3$ ($M+H^+$) 360.2, found 360.2.



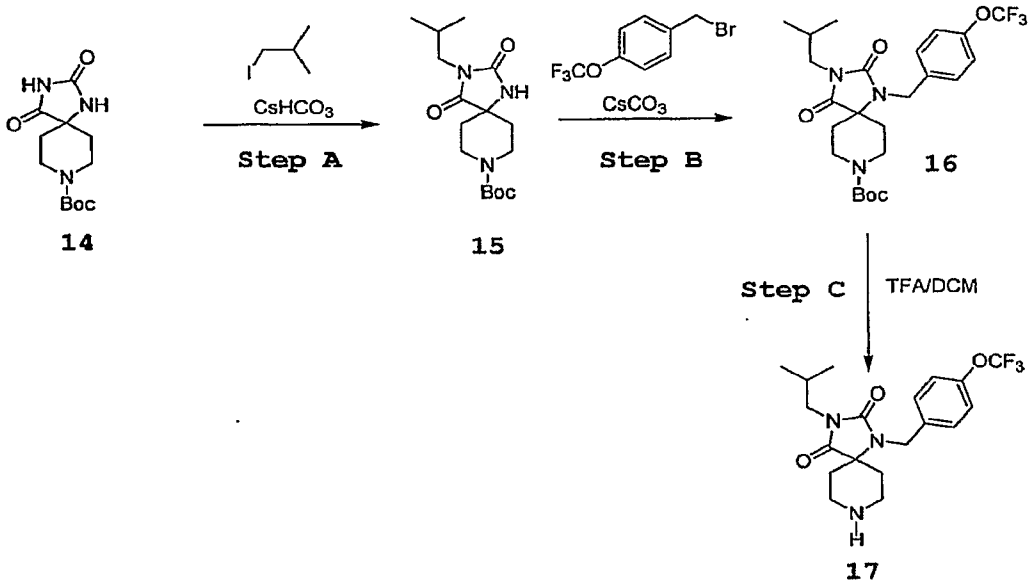
Intermediate 13. 3-Isobutyl-1-[2-(4-methoxy-phenyl)-ethyl]-1,3,8-triaza-spiro[4.5]decan-2-one.

[0021] Step A: Intermediate 4 (45 mg, 0.1 mmol) is dissolved in MeOH (1.5 mL) and cooled to 0°C. Sodium borohydride (100 mg, 2.5 mmol) is added, and the mixture is stirred at 0°C for 30 min, then stirred for 48 h at room temperature. The crude 8-benzyl-4-hydroxy-3-isobutyl-1-[2-(4-methoxy-phenyl)-ethyl]-1,3,8-triaza-spiro[4.5]decan-2-one 11 is

used in the next step without further purification. MS calcd. for $C_{27}H_{38}N_3O_3$ ($M+H^+$) 452.3, found 452.3.

[0022] Step B: Intermediate 11 is dissolved in trifluoroacetic acid (1.5 mL) and cooled to 0°C. Sodium borohydride (40 mg, 1.0 mmol) is added, and the mixture is stirred at room temperature for 5 h. Then the reaction mixture is poured into ice water and extracted with EtOAc twice. The organic layers are combined, washed with water and concentrated to afford 12 as a white solid. ^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.38-7.30 (m, 5H), 7.14 (d, J = 8.6 Hz, 2H), 6.81 (d, J = 8.6 Hz, 2H), 3.77 (s, 3H), 3.52 (s, 2H), 3.21 (t, J = 8.0 Hz, 2H), 3.09 (s, 2H), 2.98 (d, J = 7.5 Hz, 2H), 2.88 (m, 2H), 2.80 (d, J = 8.0 Hz, 2H), 1.99 (m, 2H), 1.84 (m, 3H), 1.37 (m, 2H), 0.90 (d, J = 6.7 Hz, 6H). MS calcd. for $C_{22}H_{28}N_3O$ ($M+H^+$) 436.3, found 436.3.

[0023] **Step C:** The hydantoin **12** (35 mg, 0.08 mmol) is dissolved in MeOH. A catalytic amount of palladium (10% on charcoal, 50 mg) is added followed by a catalytic amount (3 drops) of HCl conc. The mixture is put under 1 atm of hydrogen and stirred at rt for 20 h. The mixture is filtered over celite, washed with MeOH and dried in vacuo to yield 3-Isobutyl-1-[2-(4-methoxy-phenyl)-ethyl]-1,3,8-triaza-spiro[4.5]decan-2-one **13** (22 mg, quant.) as a colorless glass: MS calcd. for $C_{20}H_{32}N_3O_2$ ($M+H^+$) 346.2, found 346.2.



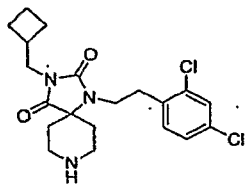
Intermediate 17. 3-Propyl-1-(4-trifluoromethoxy-benzyl)-1,3,8-triaza-spiro[4.5]decane-2,4-dione.

[0024] **Step A.** A well stirred solution of **14** (2 g, 7.4 mmol) in anhydrous DMF (10 mL) is treated with $CsHCO_3$ (2.16 g, 11.1 mmol) and 1-Iodo-2-methyl-propane (2.0 g, 11.1 mmol). The reaction mixture is heated at 65°C for 8 hours. The reaction mixture is cooled down and quenched with water and extracted with EtOAc. The organic layer is washed once with 3N NaOH, water, brine, dried over Na_2SO_4, and concentrated to afford 3-Isobutyl-2,4-dioxo-1,3,8-triaza-spiro[4.5]decane-8-carboxylic acid tert-butyl ester **15** as white solid. LC/MS ($M+H^+$) = 326.2.

[0025] **Step B.** A well stirred solution of **15** (0.15 g, 0.46 mmol) in anhydrous DMF (1 mL) is treated with Cs_2CO_3 (0.18 g, 0.55 mmol) and 1-bromomethyl-4-trifluoromethoxy-benzene (0.176 g, 0.69 mmol). The reaction mixture is irradiated in a microwave oven at 120 °C for 20 min. The reaction mixture is directly purified by preparative LC/MS using a MeCN/water gradient 90-10%. The solvent is removed under vacuum to afford 3-Isobutyl-2,4-dioxo-1-(4-trifluoromethoxy-benzyl)-1,3,8-triaza-spiro[4.5]decane-8-carboxylic acid *tert*-butyl ester **16**. ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.23 (d, J = 8.0 Hz, 2H), 7.10 (d, J = 8.0 Hz, 2H), 4.42 (s, 2H), 3.97-3.94 (bm, 2H), 3.42-3.30 (m,

2H), 3.30 (d, J = 8.0 Hz, 2H) 2.05 (quint, J = 8.0 Hz, 1H), 1.68-1.64 (m, 2H) 1.49-1.46 (m, 2H), 1.38 (s, 9H), 0.85 (d, J = 8.0Hz, 6H). MS ($M+H^+$) = 500.3.

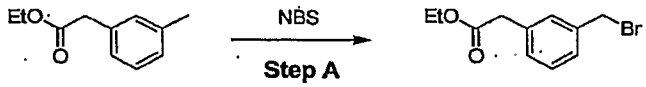
[0026] **Step C.** 3-Isobutyl-2,4-dioxo-1-(4-trifluoromethoxy-benzyl)-1,3,8-triaza-spiro[4.5]decane-8-carboxylic acid *tert*-butyl ester **16** (0.15 g, 0.3 mmol), is dissolved in DCM (1 mL) and treated with a 50% solution of TFA /DCM (2 mL). The reaction mixture is stirred at room temperature for 1 h. The solvent is removed under vacuum to afford **17** as a TFA salt in quantitative yield. LC/MS($M+H^+$)= 400.2.



18

Intermediate 18. 3-Cyclobutylmethyl-1-[2-(2,4-dichloro-phenyl)-ethyl]-1,3,8-triaza-spiro[4.5]decane-2,4-dione.

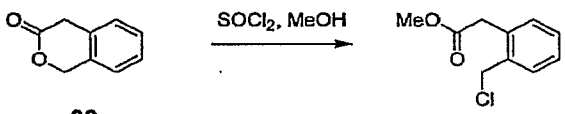
[0027] Following the procedure of Intermediate 5, except substituting 2,4-dichlorophenethylamine for 4-methoxyphenethylamine, and substituting (bromomethyl)cyclobutane for 1-bromo-2-methylpropane the title compound is prepared as a clear liquid: ^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.38 (s, 1H), 7.18 (s, 2H), 3.52 (d, J = 7.4 Hz, 2H), 3.41 (t, J = 7.5 Hz, 2H), 3.34 (m, 2H), 3.11 (t, J = 7.3 Hz, 2H), 2.97 (m, 2H), 2.68 (m, 1H), 1.99 (m, 4H), 1.75 (m, 4H), 1.44 (d, J = 13.7 Hz, 2H). MS calcd. for $C_{20}H_{26}Cl_2N_3O_2$ ($M+H^+$) 410.1, found 410.1.



30 31

Intermediate 31. (3-Bromomethyl-phenyl)-acetic acid ethyl ester.

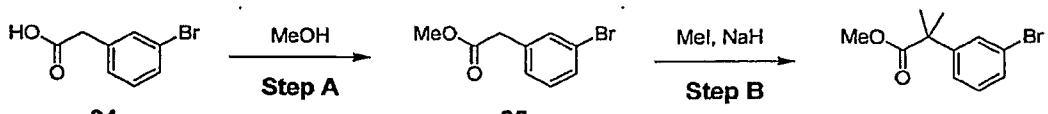
[0028] Ethyl-m-tolylacetate 30 (2.00 g, 11.2 mmol) is dissolved in carbontetrachloride (30 mL). NBS (1.90 g, 10.7 mmol) is added followed by benzoyl peroxide (266 mg, 1.1 mmol). The mixture is heated to 75°C overnight. The mixture is diluted with DCM and washed with water and saturated aqueous $NaHCO_3$. The remainder is purified by flash chromatography (EtOAc/Hexanes gradient) to afford (3-bromomethyl-phenyl)-acetic acid ethyl ester 31 as a colorless oil: ^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.36-7.22 (m, 4H), 4.48 (s, 2H), 4.16 (q, J = 7.1 Hz, 2H), 3.61 (s, 2H), 1.26 (t, J = 7.1 Hz, 3H). MS calcd. for $C_{11}H_{13}BrO_2$ ($M+H^+$) 257.0, found 257.0.



32 33

Intermediate 33. (2-Chloromethyl-phenyl)-acetic acid methyl ester.

[0029] Isochromanone 32 (1.9 g, 13 mmol) is dissolved in MeOH (15 mL) and cooled to 0°C. Thionyl chloride (2 mL, 27.3 mmol) is added and the solution is stirred at rt for 48 h. The solvent is removed in vacuo, the remainder is dissolved in DCM and washed with water and saturated aqueous $NaHCO_3$. The organic layer is dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (EtOAc/Hexanes gradient) affords the (2-chloromethyl-phenyl)-acetic acid methyl ester 33 as a colorless oil: ^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.39-7.26 (m, 4H), 4.68 (s, 2H), 3.82 (s, 2H), 3.70 (s, 3H). MS calcd. for $C_{10}H_{11}O_2$ ($M-Cl^+$) 163.1, found 163.1.

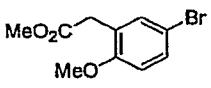


34 35 36

Intermediate 36. 2-(3-Bromo-phenyl)-2-methyl-propionic acid methyl ester.

[0030] Step A: 3-Bromophenyl acetic acid 34 (1.17 g, 5.44 mmol) is dissolved in MeOH (15 mL) containing catalytic amounts of thionyl chloride (0.2 mL). The solution is stirred at rt overnight. The solvent is evaporated, the remainder is dissolved in DCM and washed with water and saturated aqueous $NaHCO_3$. The organic layer is dried ($MgSO_4$), filtered and concentrated to afford the methyl ester 35 as an oil: ^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.44 (s, 1H), 7.40 (ddd, J = 2.0, 2.4, 6.8 Hz, 1H), 7.20 (m, 2H), 3.70 (s, 3H), 3.59 (s, 2H). MS calcd. for $C_9H_{10}BrO_2$ ($M+H^+$) 229.1, found 229.0.

[0031] Step B: Intermediate 35 (1.0 g, 4.4 mmol) is dissolved in DMF (10 mL) and cooled to 0°C. Sodium hydride (60% dispersion, 1.6 g, 22.0 mmol) is added slowly and the mixture is stirred at 0°C until the gas evolution ceases. Then methyl iodide (1.5 mL, 22.0 mmol) is added, and the mixture is stirred at ambient temperature for 2 h. The reaction mixture is carefully quenched with MeOH (5 mL) while stirring on an ice-bath. Water is added and the mixture is extracted with EtOAc twice. The combined organic layers are washed with water and brine, dried over MgSO4 and concentrated. The crude remainder is purified by flash silica chromatography (EtOAc/hexanes gradient) to afford 2-(3-bromo-phenyl)-2-methyl-propionic acid methyl ester 36 as a clear liquid: ^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.48 (t, J = 1.9 Hz, 1H), 7.37 (m, 1H), 7.25 (m, 1H), 7.19 (t, J = 7.8 Hz, 1H), 3.66 (s, 3H), 1.56 (s, 6H). MS calcd. for $C_{11}H_{14}BrO_2$ ($M+H^+$) 257.0, found 257.0.

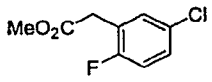


37

Intermediate 37. (5-Bromo-2-methoxy-phenyl)-acetic acid methyl ester.

[0032] Following the procedure of Intermediate 36, Step A, except substituting (5-bromo-2-methoxy-phenyl)-acetic acid for 3-bromophenyl acetic acid, the title compound is prepared as a clear liquid: ^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.35 (dd, J = 2.5 Hz, J = 8.7 Hz,

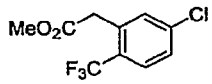
1H), 7.30 (d, J = 2.5 Hz, 1H), 6.74 (d, J = 8.7 Hz, 1H), 3.80 (s, 3H), 3.69 (s, 3H), 3.59 (s, 2H). MS calcd. for $C_{10}H_{12}BrO_3$ ($M+H^+$) 259.0, found 259.0.



38

Intermediate 38. (5-Chloro-2-fluoro-phenyl)-acetic acid methyl ester.

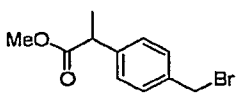
[0033] Following the procedure of Intermediate 36, Step A, except substituting (5-chloro-2-fluoro-phenyl)-acetic acid for 3-bromophenyl acetic acid, the title compound is prepared as a clear liquid: ^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.27-7.20 (m, 2H), 7.00 (t, J = 8.9 Hz, 1H), 3.72 (s, 3H), 3.64 (s, 2H). MS calcd. for $C_9H_9ClFO_2$ ($M+H^+$) 203.0, found 203.0.



39

Intermediate 39. (5-Chloro-2-trifluoromethyl-phenyl)-acetic acid methyl ester.

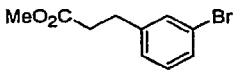
[0034] Following the procedure of Intermediate 36, Step A, except substituting (5-chloro-2-trifluoromethyl-phenyl)-acetic acid for 3-bromophenyl acetic acid, the title compound is prepared as a clear liquid: ^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.59 (d, J = 8.4 Hz, 1H), 7.40 (s, 1H), 7.37 (d, J = 8.4 Hz, 1H), 3.80 (s, 2H), 3.72 (s, 3H). MS calcd. for $C_{10}H_9ClF_2O_2$ ($M-F^+$) 233.0, found 233.0.



40

Intermediate 40. 2-(4-Bromomethyl-phenyl)-propionic acid methyl ester.

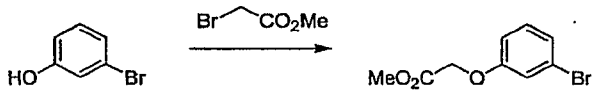
[0035] Following the procedure of Intermediate 36, Step A, except substituting 2-(4-bromomethyl-phenyl)-propionic acid for 3-bromophenyl acetic acid, the title compound is prepared as a clear liquid: ^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.31 (d, J = 8.1 Hz, 2H), 7.23 (d, J = 8.1 Hz, 2H), 4.43 (s, 2H), 3.68 (q, J = 7.2 Hz, 1H), 3.61 (s, 3H), 1.45 (d, J = 7.2 Hz, 3H). MS calcd. for $C_{11}H_{13}BrO_2$ ($M+H^+$) 257.0, found 257.0.



41

Intermediate 41. 3-(3-Bromo-phenyl)-propionic acid methyl ester.

[0036] Following the procedure of Intermediate 36, Step A, except substituting 3-(3-bromo-phenyl)-propionic acid for 3-bromophenyl acetic acid, the title compound is prepared as a clear liquid: MS calcd. for $C_{10}H_{11}BrO_2$ ($M+H^+$) 243.0, found 243.0.

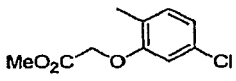


42 **43**

Intermediate 43. (3-Bromo-phenoxy)-acetic acid methyl ester.

[0037] 3-Bromo-phenol 42 (1.72 g, 10 mmol) together with methyl-bromoacetate (1.01 mL, 11 mmol) are dissolved in MeCN (600 mL). K_2CO_3 (2.07 g, 15 mmol) is added and the mixture is stirred at 50°C overnight. After insoluble salts are filtered and washed with MeCN, the solvent is removed and the remainder is taken up in EtOAc and washed subsequently with water and brine. The organic layer is dried ($MgSO_4$), filtered and

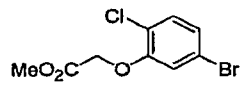
concentrated to afford 43 as a colorless semi-solid: MS calcd. for $C_9H_{10}BrO_3$ ($M+H^+$) 245.0, found 244.9.



44

Intermediate 44. (5-Chloro-2-methyl-phenoxy)-acetic acid methyl ester.

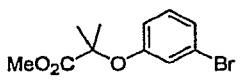
[0038] Following the procedure of Intermediate 43, except substituting 5-chloro-2-methyl-phenol for 3-bromo-phenol, the title compound is prepared as a white solid: ^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.07 (d, J = 8.0 Hz, 1H), 6.89 (dd, J = 1.9 Hz, J = 8.0 Hz, 1H), 6.68 (d, J = 1.9 Hz, 1H), 4.64 (s, 2H), 3.82 (s, 3H), 2.24 (s, 3H). MS calcd. for $C_{10}H_{12}ClO_3$ ($M+H^+$) 215.0, found 215.0.



45

Intermediate 45. (5-Bromo-2-chloro-phenoxy)-acetic acid methyl ester.

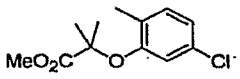
[0039] Following the procedure of Intermediate 43, except substituting 5-bromo-2-chloro-phenol for 3-bromo-phenol, the title compound is prepared as a white solid: ^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.27 (d, J = 8.4 Hz, 1H), 7.11 (dd, J = 2.1 Hz, J = 8.4 Hz, 1H), 6.99 (d, J = 2.1 Hz, 1H), 4.73 (s, 2H), 3.85 (s, 3H). MS calcd. for $C_9H_9BrClO_3$ ($M+H^+$) 278.9, found 279.0.



46

Intermediate 46. 2-(3-Bromo-phenoxy)-2-methyl-propionic acid methyl ester.

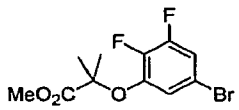
[0040] Following the procedure of Intermediate 43, except substituting □,□-dimethyl-methyl-bromoacetate for methyl-bromoacetate and heating to reflux, the title compound is prepared as a clear liquid: MS calcd. for $C_{11}H_{14}BrO_3$ ($M+H^+$) 273.0, found 273.0.



47

Intermediate 47. 2-(5-Chloro-2-methyl-phenoxy)-2-methyl-propionic acid methyl ester.

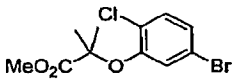
[0041] Following the procedure of Intermediate 43, except substituting □,□-dimethyl-methyl-bromoacetate for methyl-bromoacetate and heating to reflux, the title compound is prepared as a clear liquid: ^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.06 (d, J = 8.0 Hz, 1H), 6.87 (dd, J = 2.0 Hz, J = 8.0 Hz, 1H), 6.62 (d, J = 2.0 Hz, 1H), 3.80 (s, 3H), 2.18 (s, 3H), 1.60 (s, 6H). MS calcd. for $C_{12}H_{16}ClO_3$ ($M+H^+$) 243.1, found 243.1.



48

Intermediate 48. 2-(5-Bromo-2,3-difluoro-phenoxy)-2-methyl-propionic acid methyl ester.

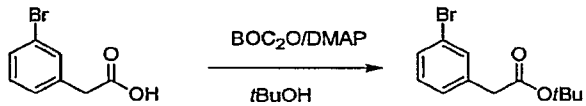
[0042] Following the procedure of Intermediate 43, except substituting 5-bromo-2,3-difluoro-phenol for 5-chloro-2-methyl-phenol, the title compound is prepared as a clear liquid: ^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.05 (m, 1H), 6.91 (m, 1H), 3.80 (s, 3H), 1.60 (s, 6H). MS calcd. for $C_{11}H_{12}BrF_2O_3$ ($M+H^+$) 309.0, found 309.0.



49

Intermediate 49. 2-(5-Bromo-2-chloro-phenoxy)-2-methyl-propionic acid methyl ester.

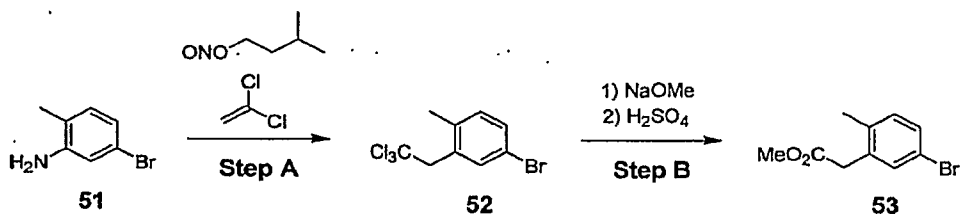
[0043] Following the procedure of Intermediate 43, except substituting 5-bromo-2-chloro-phenol for 5-chloro-2-methyl-phenol, the title compound is prepared as a clear liquid: ^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.23 (d, J = 8.5 Hz, 1H), 7.09 (dd, J = 2.0 Hz, J = 8.5 Hz, 1H), 7.03 (d, J = 2.0 Hz, 1H), 3.81 (s, 3H), 1.62 (s, 6H). MS calcd. for $C_{11}H_{13}BrClO_3$ ($M+H^+$) 307.0, found 307.0.



34 Step A 50

Intermediate 50. (3-Bromo-phenyl)-acetic acid *tert*-butyl ester.

[0044] To a solution of **34** (11.2 g, 51.6 mmol) and Boc_2O (25 g, 114.5 mmol) in 525 mL of *t*BuOH is added DMAP (1.9 g). The reaction mixture is stirred overnight and checked by TLC till completion. After evaporation of the solvent the product is purified by a short column of silica gel (5-10 cm) up to 10% EtOAc to afford pure (3-bromo-phenyl)-acetic acid *tert*-butyl ester **50** as a colorless oil. ^{1}H-NMR (400MHz, $CDCl_3$) δ 7.36(m, 1H),7.34-7.30 (m, 1H),7.15-7.11 (m, 2H), 3.42 (s, 2H), 1.17 (s, 9H).

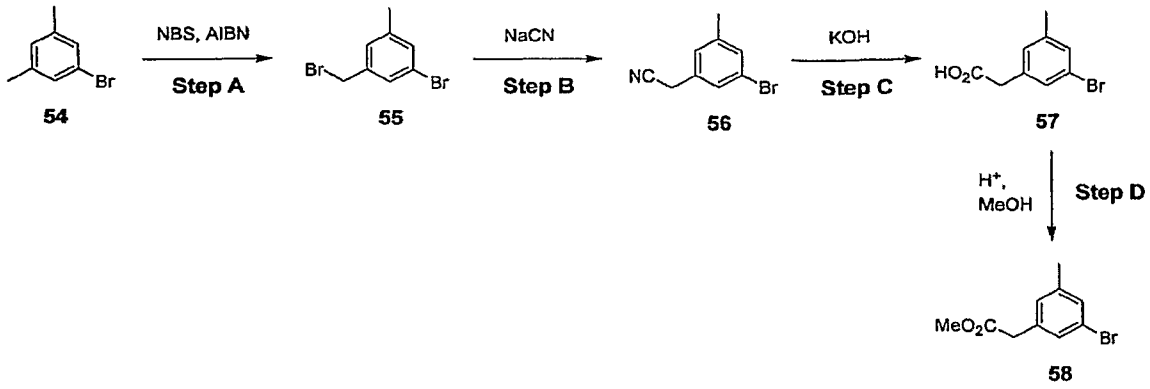


51 52 53

Intermediate 53. (5-Bromo-2-methyl-phenyl)-acetic acid methyl ester.

[0045] Step A: In a flame-dried flask isoamyl nitrate (2.16 mL, 16 mmol) is dissolved in dry MeCN (6 mL). Then copper chloride ($Cu(II)Cl_2$, 1.74 g, 13 mmol) and vinylidene chloride (12.9 mL, 16 mmol) are added. 5-Bromo-2-methyl-aniline 51 (2.00 g, 11 mmol) is added slowly over a period of 10 min, while the mixture is kept at ambient temperature with a waterbath. The reaction mixture is stirred at room temperature overnight, then poured into ice-cold 20% aqueous HCl (80 mL). After stirring for 30 min it is extracted with ether twice, the combined organic layers are washed with 20% aqueous HCl, water and brine, dried over $MgSO_4$ and concentrated.

[0046] Step B: The crude 4-bromo-1-methyl-2-(2,2,2-trichloro-ethyl)-benzene 52 from Step A is dissolved in MeOH (2 mL) and cooled to 0°C. A solution of 30% NaOMe in MeOH (8.5 mL) is added slowly, then the mixture is heated to reflux for 5 h. After cooling back down to 0°C, H_2SO_4 conc. (1.6 mL) is added, and the mixture is heated to reflux for 1 h. The reaction mixture is cooled to room temperature, water is added and it is extracted with DCM three times. The combined organic layers are washed with water and brine, dried over $MgSO_4$ and concentrated. The residue is purified by flash silica chromatography (EtOAc/hexanes gradient) to yield (5-bromo-2-methyl-phenyl)-acetic acid methyl ester 53 as an oil: ^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.34 (d, J = 2.0 Hz, 1H), 7.30 (dd, J = 2.0 Hz, J = 8.1 Hz, 1H), 7.05 (d, J = 8.1 Hz, 1H), 3.70 (s, 3H), 3.60 (s, 2H), 2.25 (s, 3H). MS calcd. for $C_{10}H_{12}BrO_2$ ($M+H^+$) 243.0, found 243.0.



Intermediate 58. (3-Bromo-5-methyl-phenyl)-acetic acid methyl ester.

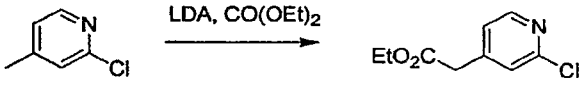
[0047] **Step A:** 5-Bromo-meta-xylene **54** (1.85 g, 10 mmol), N-bromosuccinimide (1.78 g, 10 mmol) and AIBN (0.11 g, 0.7 mmol) are suspended in CCl_4 (20 mL). The reaction mixture is heated to reflux for 2 h, then the solids are filtered and the remainder is concentrated to give 1-bromo-3-bromomethyl-5-methyl-benzene **55** (2.7 g, quant.) as a white solid: MS calcd. for $C_8H_9Br_2$ ($M+H^+$) 262.9, found 281.0.

[0048] **Step B:** Intermediate **55** (2.70 g, 10 mmol) is dissolved in DMSO (10 mL) and cooled to 0°C. Then sodium cyanide (0.98 g, 20 mmol) is added and the mixture is stirred at room temperature for 1 h. Acetonitrile (10 mL) is added and the mixture is heated to reflux for 90 min. Then it is diluted with H_2O and extracted with ether three times. The combined organic layers are washed with H_2O and brine, dried over $MgSO_4$ and concentrated to yield (3-bromo-5-methyl-phenyl)-acetonitrile **56** as a reddish oil. MS calcd. for C_9H_9BrN ($M+H^+$) 210.0, found 210.0.

[0049] **Step C:** A high pressure tube is charged with KOH (2.24 g, 40 mmol) dissolved in H_2O (20 mL). Intermediate **56** (~10 mmol) dissolved in isopropanol (10 mL) is added, the tube is sealed and heated to 120°C overnight. The mixture is then stirred at room temperature for 62 h. After the isopropanol is evaporated, the remainder is acidified with 6 M HCl to pH 2 and extracted with ether three times. The combined organic layers are

washed with H_2O, dried over $MgSO_4$ and concentrated to yield (3-bromo-5-methyl-phenyl)-acetic acid **57** as a reddish solid. MS calcd. for $C_9H_{10}BrO_2$ ($M+H^+$) 229.0, found 228.9.

[0050] Step D: (3-Bromo-5-methyl-phenyl)-acetic acid 57 is dissolved in MeOH (20 mL) containing catalytic amounts of thionyl chloride (0.2 mL). The solution is stirred at rt overnight. The solvent is evaporated, the remainder is dissolved in DCM and washed with water and saturated aqueous $NaHCO_3$. The organic layer is dried ($MgSO_4$), filtered and concentrated. The remainder is purified by flash silica chromatography (EtOAc/hexanes gradient) to afford (3-bromo-5-methyl-phenyl)-acetic acid methyl ester 58 as an oil: ^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.24 (s, 2H), 7.02 (s, 1H), 3.71 (s, 3H), 3.56 (s, 2H), 2.32 (s, 3H). MS calcd. for $C_{10}H_{12}BrO_2$ ($M+H^+$) 243.0, found 243.0.

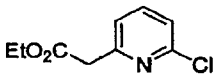


59 **60**

Intermediate 59. (2-Chloro-pyridin-4-yl)-acetic acid ethyl ester.

[0051] 2-Chloro-4-methyl-pyridine **59** (1.06 g, 8.33 mmol) is dissolved in THF (18 mL) and cooled to -78°C. LDA (10 mL, 20 mmol) is slowly added over a period of 15 min and stirred at -78°C for another 15 min. Then diethylcarbonate (1.2 mL, 10 mmol) is slowly added over a period of 5 min and stirred at -78°C for another 15 min. The mixture is then warmed to 0°C and stirred at that temperature for 4 h. After quenching with saturated ammonium chloride solution (250 mL) the solution is extracted with EtOAc three times. The combined organic layers are washed with H_2O, dried over Na_2SO_4 and concentrated. The remainder is purified by flash silica chromatography (EtOAc/hexanes gradient) to afford (2-chloro-pyridin-4-yl)-acetic acid ethyl ester **60** as an orange liquid: ^{1}H-NMR (400MHz, $CDCl_3$) δ = 8.32 (d, J = 5.1 Hz, 1H), 7.27 (d, J = 4.0 Hz, 1H), 7.15 (d, J = 5.0 Hz, 1H), 4.17

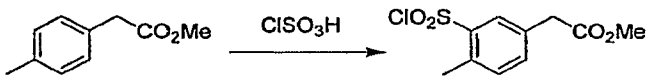
(q, J = 7.1 Hz, 2H), 3.60 (s, 2H), 1.26 (t, J = 7.1 Hz, 3H). MS calcd. for $C_9H_{11}ClNO_2$ ($M+H^+$) 200.0, found 200.1.



61

Intermediate 61. (6-Chloro-pyridin-2-yl)-acetic acid ethyl ester.

[0052] Following the procedure of Intermediate **60**, except substituting 6-Chloro-2-methyl-pyridine for 2-Chloro-4-methyl-pyridine, the title compound is prepared as a clear liquid: ^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.63 (t, J = 7.8 Hz, 1H), 7.24 (m, 2H), 4.18 (q, J = 7.1 Hz, 2H), 3.82 (s, 2H), 1.26 (t, J = 7.1 Hz, 3H). MS calcd. for $C_9H_{11}ClNO_2$ ($M+H^+$) 200.0, found 200.1.

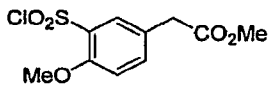


62 63

Intermediate 63. (3-Chlorosulfonyl-4-methyl-phenyl)-acetic acid methyl ester.

[0053] p-Tolyl-acetic acid methyl ester **62** (1.0 g, 6.09 mmol) is dissolved in dichloromethane (4 mL) and cooled to 0°C. Chlorosulfonic acid (10 mL) is added dropwise while stirring during the period of 1 h. The mixture is warmed to rt and stirred for 1 h. The reaction mixture is diluted with EtOAc, and washed with saturated Na_2CO_3 and brine. The organic layer is separated, dried ($MgSO_4$), filtered and concentrated to give crude product, which is purified from silic gel chromatography (EtOAc/hexane gradient) to give the title compound **63** as an oil: ^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.89 (d, J=1.6 Hz, 1H), 7.48 (dd, J =

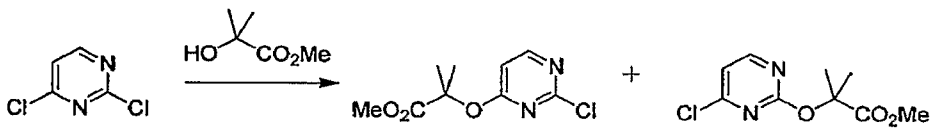
1.6 Hz, J=7.6 Hz, 1H), 7.32 (d, J=7.6 Hz, 1H), 3.66 (s, 3H), 3.63 (s, 2H), 2.70 (s, 3H); MS calcd. for $C_{10}H_{11}O_4S$ ($M-Cl^+$) 227.04, found 227.00.



64

Intermediate 64. (3-Chlorosulfonyl-4-methoxy-phenyl)-acetic acid methyl ester.

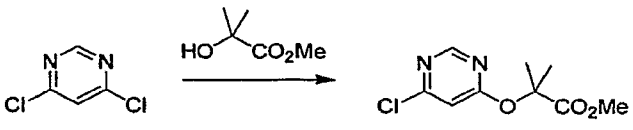
Intermediate **64** is prepared according to patent literature GB 2378179.



65 66 67

Intermediates 66 and 67. 2-(2-Chloro-pyrimidin-4-yloxy)-2-methyl-propionic acid methyl ester and. 2-(4-Chloro-pyrimidin-2-yloxy)-2-methyl-propionic acid methyl ester.

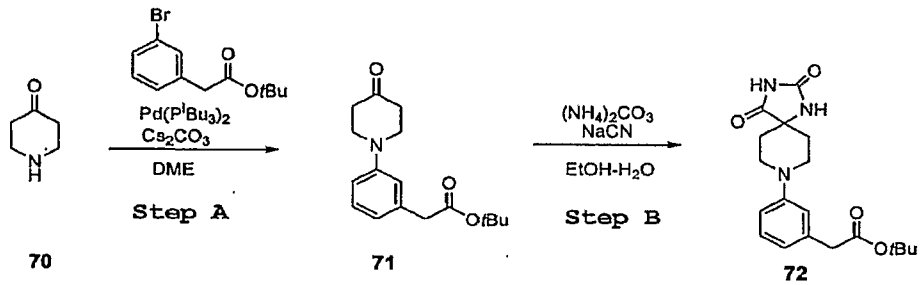
[0054] 2,4-Dichloropyrimidine **65** (0.90 g, 6.0 mmol) is dissolved in DMF (36 mL). 2-Hydroxy isobutyrate methylester (2.13 g, 18.0 mmol) and Cs2CO3 (7.8 g, 24 mmol) are added and the mixture is subjected to microwave irradiation (120°C, 5 min). Then it is diluted with EtOAc and washed with H_2O three times, then with brine. The organic layer is dried over $MgSO_4$ and concentrated. The remainder is purified by flash silica chromatography (EtOAc/hexanes gradient) to afford regioisomers **66** and **67** in a 3:1 ratio as clear oils: **66:** ^{1}H-NMR (400MHz, $CDCl_3$) δ = 8.24 (d, J = 5.8 Hz, 1H), 6.61 (d, J = 5.8 Hz, 1H), 3.66 (s, 3H), 1.63 (s, 6H). MS calcd. for $C_9H_{12}ClN_2O_3$ ($M+H^+$) 231.1, found 231.0. **67:** ^{1}H-NMR (400MHz, $CDCl_3$) δ = 8.26 (d, J = 5.4 Hz, 1H), 6.90 (d, J = 5.4 Hz, 1H), 3.61 (s, 3H), 1.65 (s, 6H). MS calcd. for $C_9H_{12}ClN_2O_3$ ($M+H^+$) 231.1, found 231.0.



68 69

Intermediate 69. 2-(6-Chloro-pyrimidin-4-yloxy)-2-methyl-propionic acid methyl ester.

[0055] 4,6-Dichloropyrimidine **68** (0.90 g, 6.0 mmol) is dissolved in DMF (36 mL). 2-Hydroxy isobutyrate methylester (2.13 g, 18.0 mmol) and Cs_2CO_3 (7.8 g, 24 mmol) are added and the mixture is heated to 50°C for 12 h. Then it is diluted with EtOAc and washed with H_2O three times, then with brine. The organic layer is dried over $MgSO_4$ and concentrated. The remainder is purified by flash silica chromatography (EtOAc/hexanes gradient) to afford **69** as a clear oil: ^{1}H-NMR (400MHz, $CDCl_3$) δ = 8.48 (s, 1H), 6.79 (s, 1H), 3.67 (s, 3H), 1.68 (s, 6H). MS calcd. for $C_9H_{12}ClN_2O_3$ ($M+H^+$) 231.1, found 231.0.



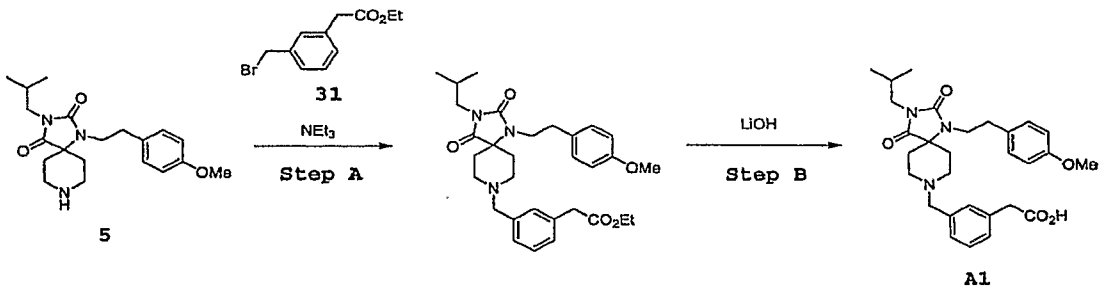
70 71 72

Intermediate 72. [3-(2,4-Dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl)-phenyl]-acetic acid tert-butyl ester.

[0056] **Step A:** To a solution of 4-piperidone monohydrate hydrochloride **70** (2.5 g, 16.42 mmol) in anydrous dioxane (50 mL) and under a nitrogen atmosphere, Cs_2CO_3 (11.75g, 36.13 mmol), (3-Bromo-phenyl)-acetic acid *tert*-butyl ester (4.9 g, 18.1 mmol), and bis (tri t-butyl phosphine) palladium are added. The flask is capped with septa and evacuated

three times. The reaction mixture is stirred in oil bath at 85°C for 12 hours, after this time the reaction mix is cooled down, diluted with a saturated solution of NH_4Cl (80 mL) and extracted with EtOAc (2x100 mL). The combined organic layers are washed once with NH_4Cl, brine and dried over Na_2SO_4. The crude is purified by short SiO_2 chromatography (hexane-EtOAc 9:1 to 8:2 as eluant) to afford 1.27g [3-(4-Oxo-piperidin-1-yl)-phenyl]-acetic acid *tert*-butyl ester **71** as a yellow oil. ^{1}HNMR (400MHz, $CDCl_3$) δ 7.24 (t, J = 8.0Hz, 1H), 6.92-6.86 (m, 2H), 6.80 (d, J = 4.0 Hz, 1H), 3.61 (t, J = 8.0 Hz, 4H), 3.49 (s, 2H), 2.55 (t, J = 8.0 Hz, 4H). MS (m/z) $(M+1)^+$ 290.2.

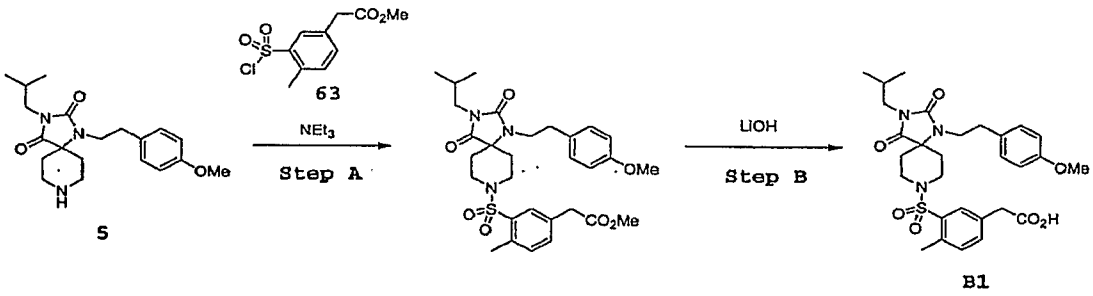
[0057] **Step B:** A well stirred solution of **71** (0.3g, 1.04 mmol) in 6.5 mL of 95% EtOH and 0.5 mL of H_2O, is treated with $(NH_4)_2CO_3$ (1.84g, 19.2 mmol) and NaCN (0.2g, 4.1 mmol). The reaction mix is heated in a sealed tube at 85°C for 12 hours. After this time the reaction is let to cool down, diluted with H_2O, and extracted with EtOAc (2x 60 mL). The combined organic layers are washed once with brine, dried over Na_2SO_4, and evaporated to yield 0.36g of **72** as a white solid that is used without further purification. ^{1}HNMR (400MHz, CD_3OD) δ 7.19 (t, J = 8.0Hz, 1H), 6.93-6.90 (m, 2H), 6.75 (d, J = 8.0 Hz, 1H), 3.68-3.63 (m, 2H), 3.48 (s, 2H), 3.12 (m, 2H), 2.17-2.09 (m, 2H), 1.43 (s, 9H). MS (m/z) $(M+1)^+$ 360.2.



Example A1. (3-{3-Isobutyl-1-[2-(4-methoxy-phenyl)-ethyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-ylmethyl}-phenyl)-acetic acid.

[0058] **Step A:** The 3-isobutyl-1-[2-(4-methoxy-phenyl)-ethyl]-1,3,8-triaza-spiro[4.5]decane-2,4-dione **5** (30 mg, 0.08 mmol) is dissolved in DCM (2.5 mL). Triethylamine (53 uL, 0.24 mmol) and (3-bromomethyl-phenyl)-acetic acid methyl ester **31** (22 mg, 0.09 mmol) are added successively and the mixture is stirred at rt overnight. The solvent is removed in vacuo to afford crude (3-{3-isobutyl-1-[2-(4-methoxy-phenyl)-ethyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-ylmethyl}-phenyl)-acetic acid ethyl ester which is used without further purification in Step B.

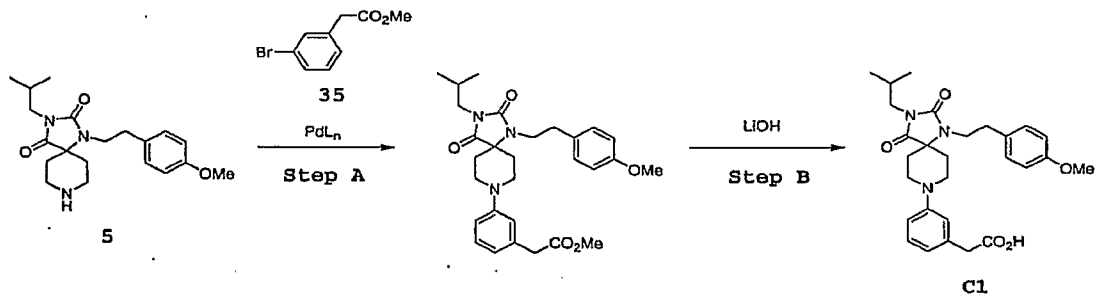
Step B: The crude (3-{3-isobutyl-1-[2-(4-methoxy-phenyl)-ethyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-ylmethyl}-phenyl)-acetic acid ethyl ester is dissolved in THF (1 mL), a solution of 1 M LiOH in H_2O (0.6 mL) is added and the mixture is stirred for 12 h at 50°C. The mixture is acidified with 1 M HCl (0.8 mL) and extracted with DCM twice. The organic layer is washed with brine, dried ($MgSO_4$), filtered, concentrated and purified on reverse phase HPLC (H_2O/MeCN gradient) to afford the title compound as a colorless solid: ^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.35 (m, 3H), 7.23 (s, 1H), 7.07 (d, J = 8.6 Hz, 2H), 6.79 (d, J = 8.6 Hz, 2H), 4.11 (s, 2H), 3.75 (s, 3H), 3.62 (s, 2H), 3.44 (m, 4H), 3.35 (t, J = 7.1 Hz, 2H), 3.30 (d, J = 7.4 Hz, 2H), 2.90 (m, 2H), 2.33 (m, 2H), 2.06 (m, 1H), 1.40 (m, 2H), 0.89 (d, J = 6.7 Hz, 6H). MS calculated for $C_{29}H_{38}N_3O_5$ ($M+H^+$) 508.3, found 508.4.



Example B1. (3-{3-Isobutyl-1-[2-(4-methoxy-phenyl)-ethyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]decane-8-sulfonyl}-4-methyl-phenyl)-acetic acid.

[0059] **Step A:** The 3-isobutyl-1-[2-(4-methoxy-phenyl)-ethyl]-1,3,8-triaza-spiro[4.5]decane-2,4-dione **5** (18 mg, 0.05 mmol) is dissolved in DCM (0.5 mL). Triethylamine (14 uL, 0.10 mmol) and (3-Chlorosulfonyl-4-methyl-phenyl)-acetic acid methyl ester **63** (16 mg, 0.06 mmol) are added successively and the mixture is stirred at rt for 8 h. The solvent is removed in vacuo to afford crude (3-{3-Isobutyl-1-[2-(4-methoxy-phenyl)-ethyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]decane-8-sulfonyl}-4-methyl-phenyl)-acetic acid methyl ester which is used without further purification in Step B.

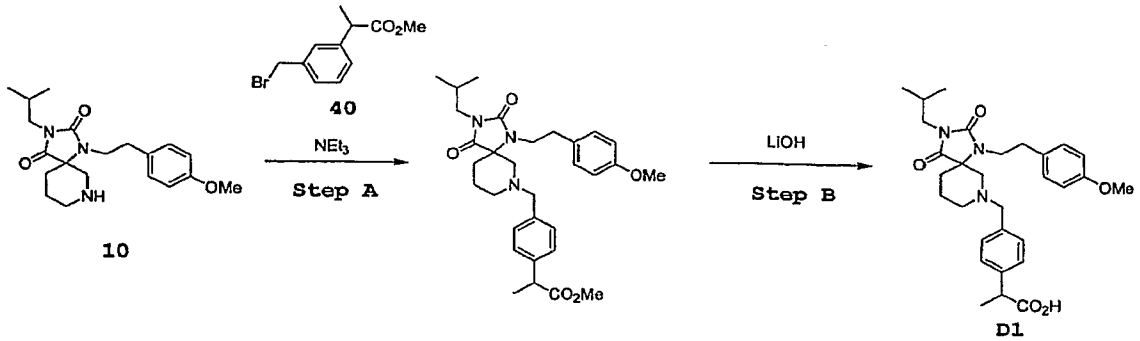
[0060] **Step B:** The crude (3-{3-Isobutyl-1-[2-(4-methoxy-phenyl)-ethyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]decane-8-sulfonyl}-4-methyl-phenyl)-acetic acid methyl ester is dissolved in THF (1 mL), a solution of 1 M LiOH in H_2O (0.6 mL) is added and the mixture is stirred for 12 h at rt. The mixture is acidified with 1 M HCl (0.8 mL) and extracted with DCM twice. The organic layer is washed with brine, dried ($MgSO_4$), filtered, concentrated and purified on reverse phase HPLC (H_2O/MeCN gradient) to afford the title compound as a colorless solid: ^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.80 (d, J = 1.6 Hz, 1H), 7.37 (dd, J = 1.6 Hz, J = 7.8 Hz, 1H), 7.28 (d, J = 7.8 Hz, 1H), 7.12 (d, J = 8.5 Hz, 2H), 6.84 (d, J = 8.5 Hz, 2H), 3.79 (s, 3H), 3.75 (m, 2H), 3.68 (s, 2H), 3.40 (m, 2H), 3.34 (t, J = 7.0 Hz, 2H), 3.28 (d, J = 7.4 Hz, 2H), 2.93 (t, J = 7.4 Hz, 2H), 2.58 (s, 3H), 2.04 (m, 1H), 1.90 (m, 2H), 1.43 (d, J = 13.7 Hz, 2H), 0.87 (d, J = 6.7 Hz, 6H). MS calculated for $C_{29}H_{38}N_3O_7S$ ($M+H^+$) 572.2, found 572.2.



Example C1. (3-{3-Isobutyl-1-[2-(4-methoxy-phenyl)-ethyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl}-phenyl)-acetic acid.

[0061] **Step A:** A flame-dried, sealed tube is charged with 3-isobutyl-1-[2-(4-methoxy-phenyl)-ethyl]-1,3,8-triaza-spiro[4.5]decane-2,4-dione **5** (75 mg, 0.21 mmol), (3-bromo-phenyl)-acetic acid methyl ester **35** (72 mg, 0.31 mmol), $(tBu)_3PHBF_3$ (6 mg, 0.021 mmol) and Cs_2CO_3 (137 mg, 0.42 mmol). 1,4-Dioxane (1.1 mL) is added and the tube is purged with argon. Then $Pd_2(dba)_3$ (10 mg, 0.011 mmol) is added and the mixture is heated at 120°C overnight. The mixture containing crude (3-{3-isobutyl-1-[2-(4-methoxy-phenyl)-ethyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl}-phenyl)-acetic acid methyl ester is used without further purification in Step B.

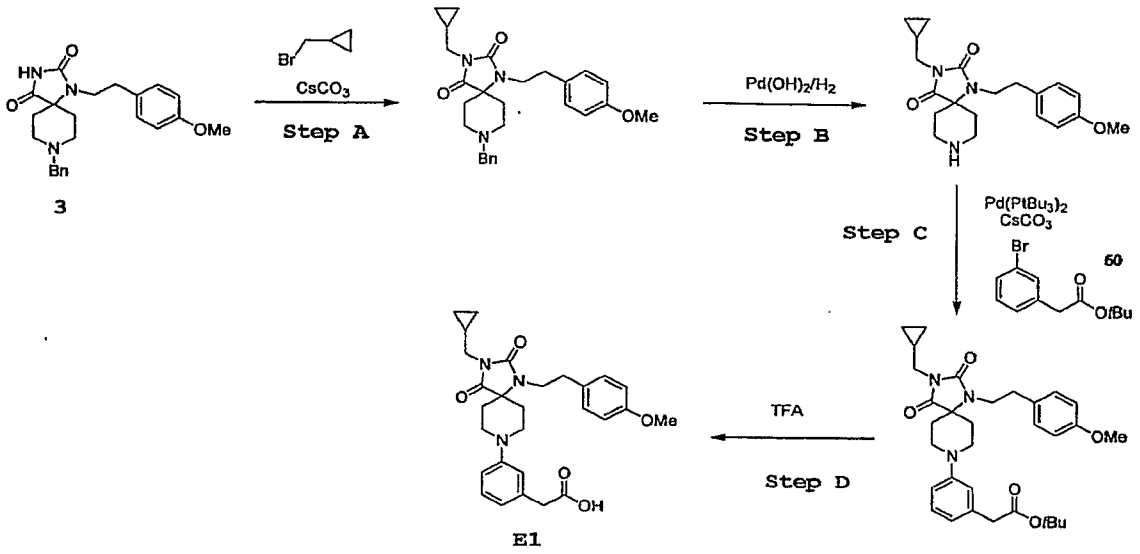
[0062] **Step B:** To the reaction mixture of Step A is added THF (3 mL), a solution of 1 M LiOH in H_2O (1 mL) is added and the mixture is stirred for 12 h at rt. The mixture is acidified with 1 M HCl (1.2 mL) and extracted with DCM twice. The organic layer is washed with brine, dried ($MgSO_4$), filtered, concentrated and purified on reverse phase HPLC (H_2O/MeCN gradient) to afford the title compound as a colorless solid: ^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.40-7.18 (m, 4H), 7.13 (d, J = 8.5 Hz, 2H), 6.82 (d, J = 8.5 Hz, 2H), 3.93 (t, J = 11.9 Hz, 2H), 3.77 (s, 3H), 3.65 (s, 2H), 3.54 (m, 2H), 3.43 (t, J = 7.1 Hz, 2H), 3.34 (d, J = 7.4 Hz, 2H), 2.96 (t, J = 7.4 Hz, 2H), 2.43 (m, 2H), 2.11 (m, 1H), 1.51 (d, J = 14.0 Hz, 2H), 0.92 (d, J = 6.7 Hz, 6H). MS calculated for $C_{28}H_{36}N_3O_5$ ($M+H^+$) 494.3, found 494.2.



Example D1. 2-(4-{3-Isobutyl-1-[2-(4-methoxy-phenyl)-ethyl]-2,4-dioxo-1,3-diaza-spiro[4.5]dec-7-ylmethyl}-phenyl)-propionic acid.

[0063] **Step A:** The 3-Isobutyl-1-[2-(4-methoxy-phenyl)-ethyl]-1,3,7-triaza-spiro[4.5]decane-2,4-dione **10** (15 mg, 0.04 mmol) is dissolved in DCM (2.5 mL). Triethylamine (17 uL, 0.12 mmol) and 2-(3-bromomethyl-phenyl)-propionic acid methyl ester **40** (12 mg, 0.04 mmol) are added successively and the mixture is stirred at rt overnight. The solvent is removed in vacuo to afford crude 2-(4-{3-Isobutyl-1-[2-(4-methoxy-phenyl)-ethyl]-2,4-dioxo-1,3-diaza-spiro[4.5]dec-7-ylmethyl}-phenyl)-propionic acid methyl ester which is used without further purification in Step B.

[0064] **Step B:** The crude 2-(4-{3-Isobutyl-1-[2-(4-methoxy-phenyl)-ethyl]-2,4-dioxo-1,3-diaza-spiro[4.5]dec-7-ylmethyl}-phenyl)-propionic acid methyl ester is dissolved in THF (1 mL), a solution of 1 M LiOH in H_2O (0.6 mL) is added and the mixture is stirred for 12 h at 50°C. The mixture is acidified with 1 M HCl (0.8 mL) and extracted with DCM twice. The organic layer is washed with brine, dried ($MgSO_4$), filtered, concentrated and purified on reverse phase HPLC (H_2O/MeCN gradient) to afford the title compound as a colorless solid: ^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.40 (d, J = 6.8 Hz, 2H), 7.27 (d, J = 6.0 Hz, 2H), 7.13 (d, J = 6.8 Hz, 2H), 6.85 (d, J = 6.0 Hz, 2H), 4.45 (m, 1H), 4.33 (m, 1H), 3.87 (s, 3H), 3.64 (m, 1H), 3.40 (m, 4H), 3.10 (m, 2H), 2.93 (m, 1H), 2.78 (s, 3H), 2.52 (m, 1H), 2.15 (m, 1H), 2.00 (m, 2H), 1.72 (m, 1H), 1.61 (m, 3H), 0.95 (s, 6H). MS calculated for $C_{30}H_{40}N_3O_5$ ($M+H^+$) 522.3, found 522.3.



Example E1. (3-{3-Cyclopropylmethyl-1-[2-(4-methoxy-phenyl)-ethyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl}-phenyl)-acetic acid.

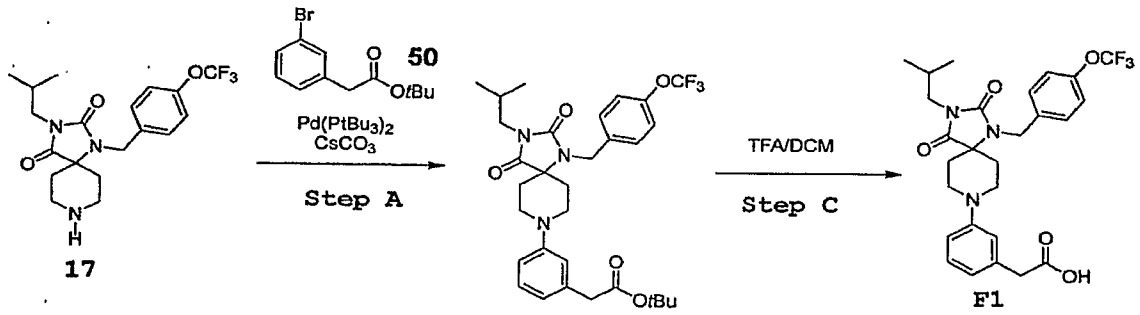
[0065] **Step A:** 8-Benzyl-1-[2-(4-methoxy-phenyl)-ethyl]-1,3,8-triaza-spiro[4.5]decane-2,4-dione (39 mg, 0.1 mmol) is dissolved in acetonitrile (0.5 mL). Cyclopropylmethyl bromide (0.2 mmol), sodium iodide (30 mg, 0.2 mmol) and cesium carbonate (65 mg, 0.2 mmol) are added at ambient temperature. The mixture is heated in oil at 80 °C for 16 h. The reaction is judged complete by LC/MS. Solid is filtered off and solvent is removed from the mixture to afford the crude 8-Benzyl-3-cyclopropylmethyl-1-[2-(4-methoxy-phenyl)-ethyl]-1,3,8-triaza-spiro[4.5]decane-2,4-dione which is used without further purification in Step B.

[0066] **Step B:** The crude 8-Benzyl-3-cyclopropylmethyl-1-[2-(4-methoxy-phenyl)-ethyl]-1,3,8-triaza-spiro[4.5]decane-2,4-dione is dissolved in MeOH (1 mL) and stirred with $Pd(OH)_2$ (~10 mg) in the presence of 1 atm hydrogen for 16 h at ambient temperature. After filtration and concentration, the crude product 3-Cyclopropylmethyl-1-

[2-(4-methoxy-phenyl)-ethyl]-1,3,8-triaza-spiro[4.5]decane-2,4-dione is obtained and used without further purification in Step C.

[0067] **Step C:** The crude 3-Cyclopropylmethyl-1-[2-(4-methoxy-phenyl)-ethyl]-1,3,8-triaza-spiro[4.5]decane-2,4-dione is dissolved in 1,4-dioxane (0.3 mL). *tert*-Butyl 3-bromophenylacetate **50** (40 mg, 0.15 mmol) and cesium carbonate (65 mg, 0.2 mmol) are added at ambient temperature. The resultant mixture is purged under a stream of nitrogen and $Pd(PtBu_3)_2$ (5 mg, 0.01 mmol) is introduced under nitrogen. The reaction mixture is heated in oil at 110 °C for 16 h. The mixture is purified by silica gel flash chromatography (15% EtOAc/hexanes) to yield (3-{3-Cyclopropylmethyl-1-[2-(4-methoxy-phenyl)-ethyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl}-phenyl)-acetic acid *tert*-butyl ester as colorless oil.

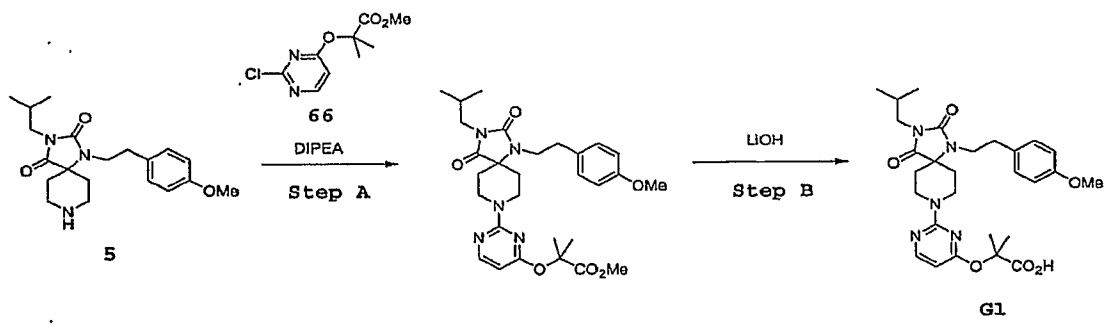
[0068] **Step D:** The (3-{3-Cyclopropylmethyl-1-[2-(4-methoxy-phenyl)-ethyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl}-phenyl)-acetic acid *tert*-butyl ester is treated with trifluoroacetic acid at ambient temperature to afford (3-{(3-{3-Cyclopropylmethyl-1-[2-(4-methoxy-phenyl)-ethyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl}-phenyl)-acetic acid as a trifluoroacetic acid salt which is purified by preparative LC/MS (20-100 %MeCN/H_2O).^{1}H NMR (400 MHz, $CDCl_3$) □ 7.62 (s, 1H), 7.53 (d, J= 8.3 Hz, 1H), 7.48 (t, J= 8.2 Hz, 1H), 7.39 (d, J= 7.6 Hz, 1H), 7.15 (d, J= 8.5 Hz, 2H), 6.83 (d, J= 8.5 Hz, 2H), 4.16 (t, J= 11.7 Hz, 2H), 3.77 (s, 3H), 3.72 (s, 2H), 3.58 (d, J= 12 Hz, 2H), 3.47 (t, , J= 7.2 Hz, 2H), 3.41 (d, J= 7.3 Hz, 2H), 2.99 (t, J= 7 Hz, 2H), 2.64 (t, J= 13 Hz, 2H), 1.56 (dt, J= 14.2, 2 Hz, 2H), 1.2 (m, 1H), 0.55 (m, 2H), 0.37 (m, 2H). LC/MS ($M+H^+$): 492.2.



Example F1. {3-[3-Isobutyl-2,4-dioxo-1-(4-trifluoromethoxy-benzyl)-1,3,8-triaza-spiro[4.5]dec-8-yl]-phenyl}-acetic acid.

[0069] **Step A.** To a solution of **17**, (0.103 g, 0.19 mmol) in anhydrous dioxane (1 mL) and under a nitrogen atmosphere, Cs_2CO_3 (0.16 g, 0.49 mmol), (3-Bromo-phenyl)-acetic acid *tert*-butyl ester **50** (0.074 g, 0.27 mmol), and $Pd(PtBu_3)_2$ (0.03 g, 0.06 mmol) are added. The vial is capped with septa and evacuated three times. The reaction mixture is stirred in an oil bath at 85°C for 12 hours. The reaction mix is cooled down, diluted with a saturated solution of ammonium chloride (5 mL) and extracted with EtOAc (2x10 mL). The organic layer is washed once with NH_4Cl, brine and dried over Na_2SO_4. The crude is purified by preparative LC/MS (20-100 % MeCN/H_2O) to afford {3-[3-Isobutyl-2,4-dioxo-1-(4-trifluoromethoxy-benzyl)-1,3,8-triaza-spiro[4.5]dec-8-yl]-phenyl}-acetic acid *tert* butyl ester. LC/MS ($M+H^+$) = 590.3.

[0070] **Step B.** 3-[3-Isobutyl-2,4-dioxo-1-(4-trifluoromethoxy-benzyl)-1,3,8-triaza-spiro[4.5]dec-8-yl]-phenyl}-acetic acid *tert* butyl ester is dissolved in DCM (1 mL) and treated with a 50% solution of TFA /DCM (2 mL). The reaction mixture is stirred at room temperature for 3h. The solvent is removed under vacuum to afford **F1** as a TFA salt in quantitative yield. ^{1}HNMR (400 MHz, CD_3OD) δ 7.45-7.21 (m, 8H), 4.63 (s, 2H), 4.04-3.98 (bm, 2H), 3.67 (m, 4H).3.40 (d, J = 8.0 Hz, 2H), 2.38 (dt, J = 4.0 and 16.0 Hz, 2H), 2.10 (quint, J = 8.0 Hz, 1H), 1.94-1.90 (m, 2H), 0.95 (d, J = 8.0Hz, 6H). LC/MS ($M+H^+$)= 534.3.

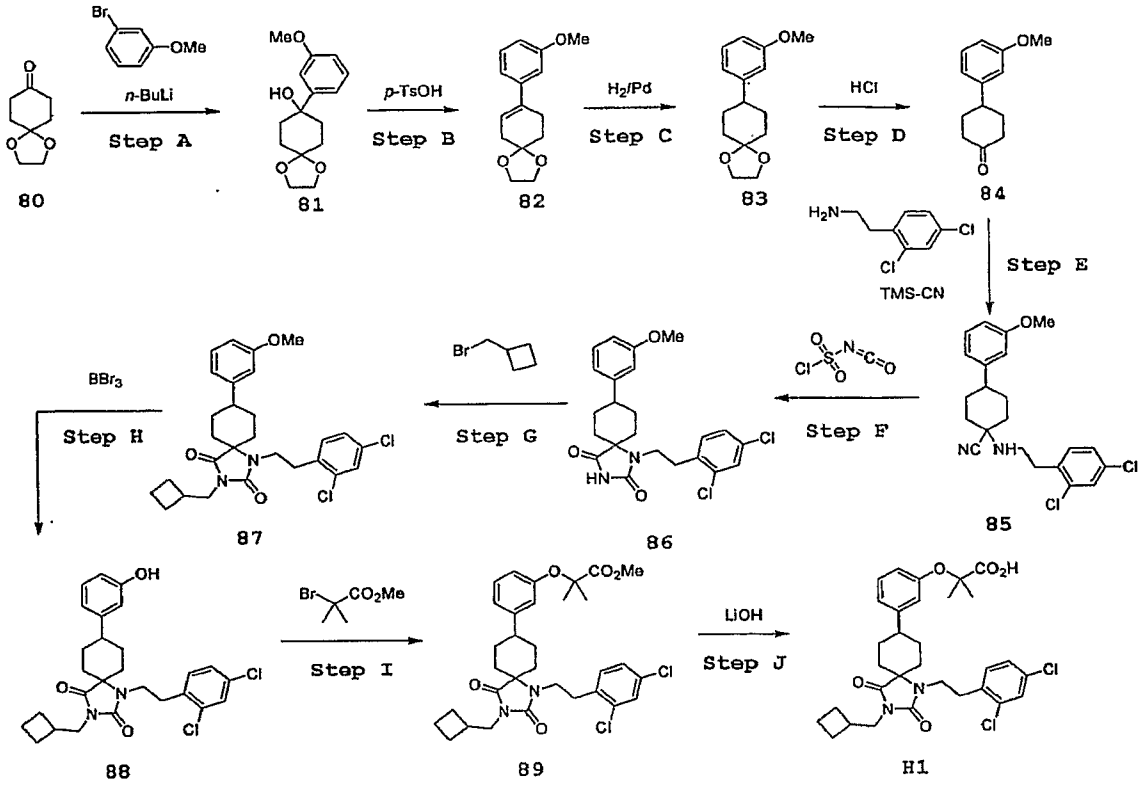


Example G1. 2-(2-{3-Isobutyl-1-[2-(4-methoxy-phenyl)-ethyl]-2,4-dioxo-1,3,8-triaza-

spiro[4.5]dec-8-yl}-pyrimidin-4-yloxy)-2-methyl-propionic acid.

[0071] **Step A:** 3-Isobutyl-1-[2-(4-methoxy-phenyl)-ethyl]-1,3,8-triaza-spiro[4.5]decane-2,4-dione **5** (72 mg, 0.20 mmol) is dissolved together with 2-(2-Chloro-pyrimidin-4-yloxy)-2-methyl-propionic acid methyl ester **66** (48 mg, 0.20 mmol) and diisopropylethylamine (52 □L, 0.30 mmol) in n-butanol (0.8 mL). The solution is heated to 50°C for 12 h, then diluted with EtOAc and washed with water twice. The organic layer is seperated and concentrated to give crude 2-(2-{3-isobutyl-1-[2-(4-methoxy-phenyl)-ethyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl}-pyrimidin-4-yloxy)-2-methyl-propionic acid methyl ester.

[0072] **Step B:** To the crude product of Step A is added THF (3 mL), a solution of 1 M LiOH in H_2O (1 mL) is added and the mixture is stirred for 12 h at rt. The mixture is acidified with 1 M HCl (1.2 mL) and extracted with DCM twice. The organic layer is washed with brine, dried ($MgSO_4$), filtered, concentrated and purified on reverse phase HPLC (H_2O/MeCN gradient) to afford the title compound as a white solid: ^{1}H-NMR (400MHz, $CDCl_3$) δ = 8.12 (d, J = 6.4 Hz, 1H), 7.08 (d, J = 8.5 Hz, 2H), 6.84 (d, J = 8.5 Hz, 2H), 6.21 (d, J = 6.4 Hz, 1H), 4.34 (m, 2H), 3.80 (s, 3H), 3.65 (m, 2H), 3.50-3.00 (m, 4H), 2.95 (m, 2H), 2.07 (m, 1H), 2.00-1.20 (m, 4H), 1.70 (s, 6H), 0.91 (d, J = 6.7 Hz, 6H). MS calculated for $C_{28}H_{38}N_5O_6$ ($M+H^+$) 540.3, found 540.3.



Example H1. 2-(3-{3-Cyclobutylmethyl-1-[2-(2,4-dichloro-phenyl)-ethyl]-2,4-dioxo-1,3-diaza-spiro[4.5]dec-8-yl}-phenoxy)-2-methyl-propionic acid.

[0073] **Step A:** 3-Bromoanisole (2.0 mL, 15.8 mmol) is dissolved in dry THF (20 mL) and cooled to –78°C. *n*-Butyllithium (1.6 M solution in hexane; 10.5 mL, 16.8 mmol) is added dropwise, with stirring, over 5 min. Stirring is continued at –78°C for another 45 min to yield a suspension. In a separate, dry flask 1,4-dioxa-spiro[4.5]decan-8-one **80** (2.67 g, 17.1 mmol) is dissolved in dry THF (15 mL) and cooled to –78°C. The suspension prepared above is added cold via a cannula to the ketone solution; the resulting mixture is stirred at –78°C for 15 min, then at rt for 30 min. Treatment with 5 mL saturated aqueous NH_4Cl solution, followed by concentration, treatment with 1N HCl and extraction with ethyl acetate, then washing with water and brine, drying over $MgSO_4$, concentration and silica gel chromatography (10-90% EtOAc/Hex) yields 8-(3-methoxy-phenyl)-1,4-dioxa-spiro[4.5]decan-8-ol **81** as a clear, thick oil: ^{1}H-NMR (400 MHz, $CDCl_3$) $\delta = 7.27$ (t, $J = 7.9$

Hz, 1H), 7.10 (m, 2H), 6.80 (dd, J = 2.4, 8.2 Hz, 1H), 3.99 (m, 4H), 3.82 (s, 3H), 2.13 (m, 4H), 1.81 (d, J = 12.1 Hz, 2H), 1.69 (d, J = 12.0, 2H).

[0074] **Step B:** 8-(3-Methoxy-phenyl)-1,4-dioxa-spiro[4.5]decan-8-ol **81** (1.57 g, 5.9 mmol) is dissolved in benzene (40 mL). *p*-Toluenesulfonic acid monohydrate (0.14 g, 0.74 mmol) is added; the flask is fitted with a Dean-Stark trap and heated to 105°C (bath temperature). After 3 h, the mixture is cooled, diluted with ethyl acetate and washed with sat. aqueous $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated to yield 8-(3-methoxy-phenyl)-1,4-dioxa-spiro[4.5]dec-7-ene **82** as an oil (quant.): MS calcd. for $C_{15}H_{19}O_3$ ($M+H^+$) 247.1, found 247.1; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.22 (t, J = 7.9 Hz, 1H), 6.98 (d, J = 7.8 Hz, 1H), 6.93 (t, J = 2.2 Hz, 1H), 6.78 (dd, J = 2.2, 7.9 Hz, 1H), 5.99 (m, 1H), 4.03 (s, 4H), 3.81 (s, 3H), 2.65 (m, 2H), 2.47 (m, 2H), 1.92 (m, 2H).

[0075] **Step C:** 8-(3-Methoxy-phenyl)-1,4-dioxa-spiro[4.5]dec-7-ene **82** (from Step B above) is dissolved in ethyl acetate (60 mL). Palladium black (5% on C; 0.22 g, 21 mol%) is added, the mixture is degassed and shaken under 50 psi of hydrogen for 3 h. Filtration and concentration yields 8-(3-methoxy-phenyl)-1,4-dioxa-spiro[4.5]decane **83** as an oil (1.31 g, quant.): MS calcd. for $C_{15}H_{21}O_3$ ($M+H^+$) 249.1, found 249.1; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.21 (t, J = 7.9 Hz, 1H), 6.83 (d, J = 7.9 Hz, 1H), 6.79 (t, J = 2.2 Hz, 1H), 6.74 (dd, J = 2.2, 7.9 Hz, 1H), 3.98 (s, 4H), 3.80 (s, 3H), 2.53 (m, 1H), 1.85 (m, 4H), 1.69 (m, 4H).

[0076] **Step D:** 8-(3-Methoxy-phenyl)-1,4-dioxa-spiro[4.5]decane **83** (1.3 g, 5 mmol) is dissolved in acetone (30 mL) and 4 N aqueous HCl (10.0 mL, 40 mmol). The mixture is heated to reflux for 2.5 h. Cooling and concentration, followed by extraction with ethyl acetate, washing the extracts with sat. aqueous $NaHCO_3$, water, and brine, drying over Na_2SO_4 and concentration yielded an oil. Silica gel purification yields 4-(3-methoxy-phenyl)-cyclohexanone **84** as a clear oil that eventually turned into a white solid: MS calcd. for $C_{13}H_{17}O_2$ ($M+H^+$) 205.1, found 205.1; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.25 (t, J = 7.9 Hz, 1H), 6.84 (d, J = 7.9 Hz, 1H), 6.79 (s, 1H), 6.78 (dd, J = 2.2, 7.9 Hz, 1H), 3.81 (s, 3H), 3.01 (tt, J = 3.4, 12.1 Hz, 1H), 2.51 (m, 4H), 2.23 (m, 2H), 1.93 (m, 2H).

[0077] **Step E:** 4-(3-Methoxy-phenyl)-cyclohexanone **84** (0.55 g, 2.7 mmol) is dissolved in AcOH (10 mL) and cooled to 10°C. 2,4-Dichlorophenethylamine (0.50 mL, 3.3 mmol) is added followed by trimethylsilylcyanide (0.50 mL, 3.7 mmol). The ice-bath is removed and the mixture is stirred at rt for 20 h. The mixture is poured on ice-water, adjusted to pH 9 using aqueous ammonia and extracted with EtOAc twice. The organic extracts are combined, then washed with sat. $NaHCO_3$, water and brine, dried over $MgSO_4$ and concentrated to yield an oil. Silica gel chromatography (10-50% EtOAc/Hex) yielded **85** as an oil (0.67 g, 1.66 mmol): MS calcd. for $C_{22}H_{25}Cl_2N_2O$ ($M+H^+$) 403.1, found 403.0; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.39 (s, 1H), 7.23 (t, J = 7.9 Hz, 1H), 7.20 (s, 2H), 6.82 (d, J = 7.9 Hz, 1H), 6.77 (s, 1H), 6.76 (dd, J = 2.2, 7.9 Hz, 1H), 3.80 (s, 3H), 3.06 (t, J = 7.2 Hz, 2H), 2.93 (t, J = 7.2 Hz, 2H), 1.96 (m, 2H), 1.83 (m, 2H), 1.57 (m, 2H).

[0078] **Step F:** Chlorosulfonylisocyanate (0.2 mL, 2.3 mmol)was dissolved in dry DCM (10 mL) and cooled to 0°C. 1-[2-(2,4-Dichloro-phenyl)-ethylamino]-4-(3-methoxy-phenyl)-cyclohexanecarbonitrile **85** (0.67 g, 1.66 mmol) is added dropwise, with stirring, as a solution in DCM (10 mL), the ice-bath is removed and the mixture is stirred at rt for 1 h. The solvent is removed, 1 M HCl (40 mL) is added and the mixture is heated to reflux for 3.5 h. Cooling to rt, followed by vacuum filtration, washing of the white solid with water, and air-drying yielded 1-[2-(2,4-dichloro-phenyl)-ethyl]-8-(3-methoxy-phenyl)-1,3-diaza-spiro[4.5]decane-2,4-dione **86** (0.52 g, 1.16 mmol): MS calcd. for $C_{23}H_{25}Cl_2N_2O_3$ ($M+H^+$) 447.1, found 447.1; ^{1}H-NMR (400 MHz, dmso-d_6) δ = 10.82 (s, 1H), 7.61 (s, 1H), 7.41 (s, 2H), 7.22 (t, J = 7.9 Hz, 1H), 6.81 (d, J = 7.8 Hz, 1H), 6.72 (m, 2H), 3.73 (s, 3H), 3.36 (t, J = 7.2 Hz, 2H), 2.99 (t, J = 7.2 Hz, 2H), 2.15 (m, 2H), 1.85 (m, 2H), 1.68 (m, 4H).

[0079] **Step G:** 1-[2-(2,4-Dichloro-phenyl)-ethyl]-8-(3-methoxy-phenyl)-1,3-diaza-spiro[4.5]decane-2,4-dione **86** (0.52 g, 1.16 mmol), bromomethylcyclobutane (0.175 mL, 1.56 mmol) and potassium carbonate (0.32 g, 2.32 mmol) in dry DMSO (5.0 mL) are stirred for 3 h at 50°C. The mixture is cooled to rt, diluted with water and extracted with DCM (3x). The combined extracts are washed with 1 N HCl, H_2O (3x) and brine, dried over $MgSO_4$, and concentrated to afford 3-cyclobutylmethyl-1-[2-(2,4-dichloro-phenyl)-ethyl]-8-(3-methoxy-phenyl)-1,3-diaza-spiro[4.5]decane-2,4-dione **87** (0.65 g, quant.) as a clear, thick oil: MS calcd. for $C_{28}H_{33}Cl_2N_2O_3$ ($M+H^+$) 515.1, found 515.1; ^{1}H-NMR (400 MHz,

$CDCl_3$) δ = 7.40 (d, *J* = 1.7 Hz, 1H), 7.21 (m, 3H), 6.88 (d, *J* = 7.9 Hz, 1H), 6.83 (t, *J* = 2.2 Hz, 1H), 6.75 (dd, *J* = 2.2, 7.9 Hz, 1H), 3.80 (s, 3H), 3.54 (d, *J* = 7.4 Hz, 2H), 3.41 (t, *J* = 7.2 Hz, 2H), 3.13 (t, *J* = 7.2 Hz, 2H), 2.71 (septet, *J* = 7.7 Hz, 1H), 2.38 (m, 3H), 2.02 (m, 2H), 1.88 (m, 2H), 1.77 (m, 6H), 1.62 (m, 2H).

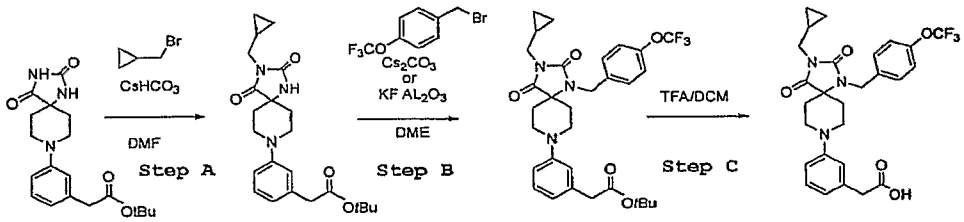
[0080] **Step H:** 3-Cyclobutylmethyl-1-[2-(2,4-dichloro-phenyl)-ethyl]-8-(3-methoxy-phenyl)-1,3-diaza-spiro[4.5]decane-2,4-dione **87** (0.65 g, 1.2 mmol) is dissolved in dry dichloromethane. Neat boron tribromide (0.50 mL, 5.2 mmol) is added and the mixture is stirred at rt for 1.5 h. The reaction mixture is poured over ice and extracted with DCM (3x). The combined extracts are washed with aqueous sat. $NaHCO_3$, dried over $MgSO_4$, and concentrated to yield a glass. Treatment with acetonitrile and concentration yielded 3-cyclobutylmethyl-1-[2-(2,4-dichloro-phenyl)-ethyl]-8-(3-hydroxy-phenyl)-1,3-diaza-spiro[4.5]decane-2,4-dione **88** as a white solid (0.56 g, quant.): MS calcd. for $C_{27}H_{31}Cl_2N_2O_3$ ($M+H^+$) 501.1, found 501.1; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.40 (d, J = 1.7 Hz, 1H), 7.20 (m, 2H), 7.17 (t, *J* = 7.9 Hz, 1H), 6.85 (d, *J* = 7.9 Hz, 1H), 6.77 (t, *J* = 2.2 Hz, 1H), 6.68 (dd, *J* = 2.2, 7.9 Hz, 1H), 3.55 (d, *J* = 7.4 Hz, 2H), 3.41 (t, *J* = 7.2 Hz, 2H), 3.12 (t, *J* = 7.2 Hz, 2H), 2.71 (septet, *J* = 7.7 Hz, 1H), 2.38 (m, 3H), 2.02 (m, 2H), 1.87 (m, 2H), 1.77 (m, 6H), 1.60 (m, 2H).

[0081] **Step I:** 3-Cyclobutylmethyl-1-[2-(2,4-dichloro-phenyl)-ethyl]-8-(3-hydroxy-phenyl)-1,3-diaza-spiro[4.5]decane-2,4-dione **88** (0.28 g, 0.56 mmol) is dissolved in DCM (3 mL) and ACN (6 mL). 2-Bromo-2-methyl-propionic acid methyl ester (0.09 mL, 0.7 mmol) and Cs_2CO_3 (0.38 g, 1.17 mmol) are added and the suspension is vigorously stirred at 60°C for 4 h. Cooling, addition of a small amt. of silica gel, and filtration, followed by concentration yielded the ester **89** as a thick oil: MS calcd. for $C_{32}H_{39}Cl_2N_2O_5$ ($M+H^+$) 601.1, found 601.0; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.40 (d, *J* = 1.7 Hz, 1H), 7.21 (m, 2H), 7.15 (t, *J* = 7.9 Hz, 1H), 6.91 (d, *J* = 7.9 Hz, 1H), 6.80 (t, *J* = 2.2 Hz, 1H), 6.62 (dd, *J* = 2.2, 7.9 Hz, 1H), 3.79 (s, 3H), 3.54 (d, *J* = 7.4 Hz, 2H), 3.41 (t, *J* = 7.2 Hz, 2H), 3.12 (t, *J* = 7.2 Hz, 2H), 2.70 (septet, *J* = 7.7 Hz, 1H), 2.36 (m, 3H), 2.02 (m, 2H), 1.86 (m, 2H), 1.76 (m, 6H), 1.69 (m, 2H), 1.69 (s, 6H).

[0082] **Step J:** 2-(3-{3-Cyclobutylmethyl-1-[2-(2,4-dichloro-phenyl)-ethyl]-2,4-

dioxo-1,3-diaza-spiro[4.5]dec-8-yl}-phenoxy)-2-methyl-propionic acid methyl ester 89 (from Step I above) is dissolved in DME (2 mL). Solid lithium hydroxide monohydrate (0.10 g, excess) is added, followed by water (0.50 mL). The mixture is stirred at 60°C overnight. Cooling, adjusting the pH to 2 using 1 N HCl, and extraction with DCM (3x), followed by drying over $MgSO_4$ and concentration yielded a resin. Treatment with diethyl ether and hexane followed by concentration under high vacuum yielded 2-(3-{3-cyclobutylmethyl-1-[2-(2,4-dichloro-phenyl)-ethyl]-2,4-dioxo-1,3-diaza-spiro[4.5]dec-8-yl}-phenoxy)-2-methyl-propionic acid **Example H1** a solid: MS calcd. for $C_{31}H_{37}Cl_2N_2O_5$ ($M+H^+$) 587.1, found 587.1; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.41 (d, J = 1.7 Hz, 1H), 7.21 (m, 2H), 7.18 (t, J = 7.9 Hz, 1H), 6.90 (d, J = 7.9 Hz, 1H), 6.82 (t, J = 2.2 Hz, 1H), 6.65 (dd, J = 2.2, 7.9 Hz, 1H), 3.54 (d, J = 7.4 Hz, 2H), 3.41 (t, J = 7.2 Hz, 2H), 3.13 (t, J = 7.2 Hz, 2H), 2.70 (septet, J = 7.7 Hz, 1H), 2.36 (m, 3H), 2.02 (m, 2H), 1.88 (m, 2H), 1.77 (m, 6H), 1.70 (m, 2H), 1.69 (s, 6H).

[0083]



72 I1

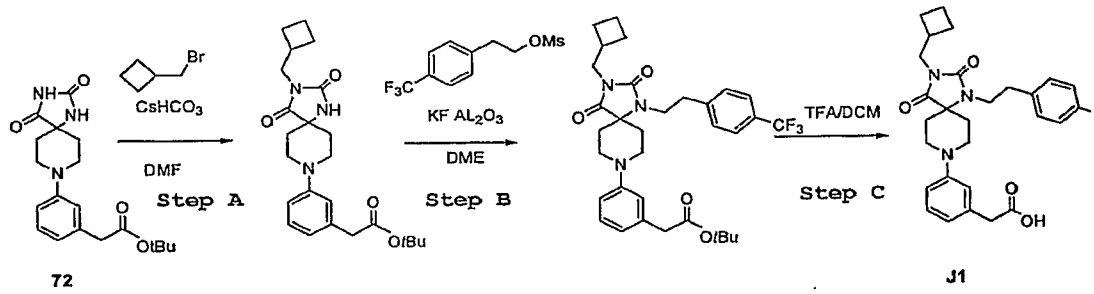
Example I1: {3-[3-Cyclopropylmethyl-2,4-dioxo-1-(4-trifluoromethoxy-benzyl)-1,3,8-triaza-spiro[4.5]dec-8-yl]-phenyl}-acetic acid.

[0084] **Step A:** To a well stirred solution of intermediate **72** (0.17 g, 0.47 mmol) in anhydrous DMF (5 mL)were added $CsHCO_3$ (0.14 g, 0.7 mmol) and bromomethyl-cyclopropane (0.095 g, 0.7 mmol). The reaction mixture is evacuated three times and irradiated in a microwave oven at 130 °C for 20 minutes. The reaction mix is cooled down, diluted with water and extracted with EtOAc twice. The organic layers are combined, washed with 5% Na_2CO_3 solution, brine and concentrated to afford [3-(3-cyclopropylmethyl-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl)-phenyl]-acetic acid tert-butyl ester as a white solid which is used without further purification. MS (m/z) $(M+1)^+$ 414.3.

[0085] **Step B:** To a well stirred solution of crude [3-(3-cyclopropylmethyl-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl)-phenyl]-acetic acid tert-butyl ester (20mg, 0.048 mmol) in anhydrous MeCN (1 mL) are added Cs_2CO_3 (19 mg 0.058 mmol) and 1-bromomethyl-4-trifluoromethoxy-benzene (12.5 uL, 0.77 mmol). The reaction mixture is evacuated three times and irradiated in a microwave oven at 130 °C for 30 minutes. The reaction mix directly purified by preparative LC/MS using a MeCN/H_2O gradient 90-10%. The solvent is removed under vacuum to afford {3-[3-cyclopropylmethyl-2,4-dioxo-1-(4-trifluoromethoxy-benzyl)-1,3,8-triaza-spiro[4.5]dec-8-yl]-phenyl}-acetic acid tert-butyl ester. MS (m/z) $(M+1)^+$ 602.3.

[0086] NB: KF-Al_2O_3 can be used instead of Cs_2CO_3.

[0087] **Step C:** A solution of {3-[3-cyclopropylmethyl-2,4-dioxo-1-(4-trifluoromethoxy-benzyl)-1,3,8-triaza-spiro[4.5]dec-8-yl]-phenyl}-acetic acid tert-butyl ester in DCM (1mL) is treated with a 50% solution of TFA in DCM (2 mL). The reaction mixture is stirred at room temperature for 1 hour. The solvent is removed under vacuum and the crude is purified by preparative LC/MS using a MeCN/H_2O gradient 90-10%. Removal of the solvent affords the title compound **I1** as TFA salt. ^{1}HNMR (400MHz, CD_3OD) δ 7.41 (d, J = 8.0Hz, 2H), 7.29 (t, J = 8.0Hz, 1H), 7.23 (d, J = 8.0Hz, 2H), 7.07-7.04 (m, 2H), 6.95-6.94 (m, 2H), 4.61(s, 2H), 3.73-3.63 (m, 4H), 3.54 (s, 2H), 3.41 (d, J = 4.0Hz, 2H), 2.24-2.17 (m, 2H), 1.82-1.79 (m, 2H), 1.43 (s, 9H), 1.22-1.18 (m, 2H), 0.55-0.51 (m, 1H), 0.38-0.34 (m, 2H). MS (m/z) $(M+1)^+$ 532.0.

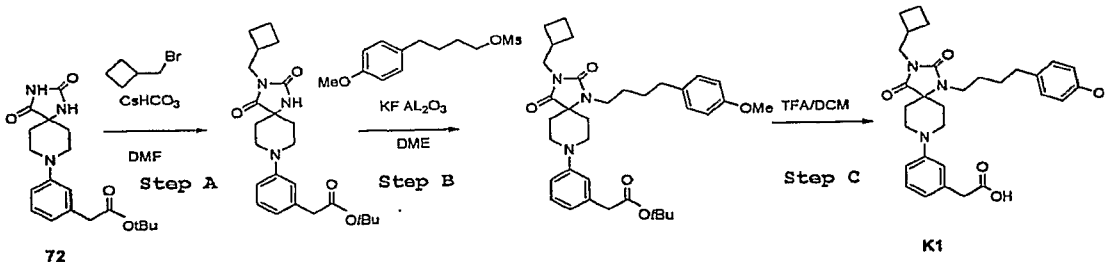


Example J1: (3-{3-Cyclobutylmethyl-2,4-dioxo-1-[2-(4-trifluoromethyl-phenyl)-ethyl]-1,3,8-triaza-spiro[4.5]dec-8-yl}-phenyl)-acetic acid.

[0088] **Step A:** To a well stirred solution of **72** (0.4 g, 1.1 mmol) in anhydrous DMF (5 mL)were added $CsHCO_3$ (0.32 g 1.6 mmol) and bromomethyl-cyclobutane (0.23 g, 1.6 mmol). The reaction mixture is evacuated three times and irradiated in a MW oven at 130 °C for 20 minutes. The reaction mix is cooled down, diluted with water and extracted with EtOAc twice. The organic layers are combined, washed with 5% Na_2CO_3 solution, brine and concentrated to afford [3-(3-cyclobutylmethyl-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl)-phenyl]-acetic acid *tert*-butyl ester as a white solid which is used without further purification. ^{1}HNMR (400MHz, $CDCl_3$) δ 7.17-7.13 (m, 1H), 6.79-6.73 (m, 3H), 5.89 (bs, 1H), 3.65-3.61 (m, 2H), 3.47 (d, J = 4.0Hz, 2H), 3.42 (s, 2H), 2.94-2.88 (m, 2H), 2.63 (quint. J = 8.0Hz, 1H), 2.19-2.12 (m, 2H), 1.97-1.90 (m, 2H), 1.81-1.65 (m, 6H), 1.37 (s, 9H). MS (m/z) $(M+1)^+$ 428.3.

[0089] **Step B:** To a solution of [3-(3-cyclobutylmethyl-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl)-phenyl]-acetic acid *tert*-butyl ester (22mg, 0.05 mmol) in anhydrous DME (2mL) are added methanesulfonic acid 2-(4-trifluoromethyl-phenyl)-ethyl ester (30 mg 0.1mmol) and KF-Al_2O_3 (0.2g). The reaction mixture is stirred in an oil bath at 80 °C for 8 hours. After this time, the reaction mix is filtered and directly purified by preparative LC/MS using a MeCN/H_2O gradient 90-10% to afford (3-{3-cyclobutylmethyl-2,4-dioxo-1-[2-(4-trifluoromethyl-phenyl)-ethyl]-1,3,8-triaza-spiro[4.5]dec-8-yl}-phenyl)-acetic acid *tert*-butyl ester. MS (m/z) $(M+1)^+$ 600.2.

[0090] **Step C:** (3-{3-cyclobutylmethyl-2,4-dioxo-1-[2-(4-trifluoromethyl-phenyl)-ethyl]-1,3,8-triaza-spiro[4.5]dec-8-yl}-phenyl)-acetic acid *tert*-butyl ester **is** converted in the title compound (3-{3-cyclobutylmethyl-2,4-dioxo-1-[2-(4-trifluoromethyl-phenyl)-ethyl]-1,3,8-triaza-spiro[4.5]dec-8-yl}-phenyl)-acetic acid as a TFA salt following the same procedure as described in Step C for the preparation of Example **I1**. ^{1}HNMR (400MHz, CD_3OD) δ 7.59 (d, J = 8.0Hz, 2H), 7.43 (d, J = 8.0H, 1H), 7.22 (t, J = 8.0Hz, 1H), 6.96-6.81 (m, 3H), 3.63-3.57 (m, 2H), 3.52-3.45 (m, 6H), 3.08-3.04 (m, 2H), 2.71-2.63 (m, 1H), 2.05-2.00 (m, 4H), 1.89-1.87 (m, 2H), 1.80-1.77 (m, 2H), 0.91-0.98 (m, 2H). MS (m/z) $(M+1)^+$ 544.3.



Example K1: (3-{3-Cyclobutylmethyl-1-[4-(4-methoxy-phenyl)-butyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl}-phenyl)-acetic acid.

[0091] **Step A:** To a well stirred solution of **72** (0.4 g, 1.1 mmol) in anhydrous DMF (5 mL)were added $CsHCO_3$ (0.32 g 1.6 mmol) and bromomethyl-cyclobutane (0.23 g, 1.6 mmol). The reaction mixture is evacuated three times and irradiated in a MW oven at 130 °C for 20 minutes. The reaction mix is cooled down, diluted with water and extracted with EtOAc twice. The organic layers are combined, washed with 5% Na_2CO_3 solution, brine and concentrated to afford [3-(3-cyclobutylmethyl-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl)-phenyl]-acetic acid *tert*-butyl ester as a white solid which is used without further purification. ^{1}HNMR (400MHz, $CDCl_3$) δ 7.17-7.13 (m, 1H), 6.79-6.73 (m, 3H), 5.89 (bs, 1H), 3.65-3.61 (m, 2H), 3.47 (d, J = 4.0Hz, 2H), 3.42 (s, 2H), 2.94-2.88 (m, 2H), 2.63 (quint. J = 8.0Hz, 1H), 2.19-2.12 (m, 2H), 1.97-1.90 (m, 2H), 1.81-1.65 (m, 6H), 1.37 (s, 9H). MS (m/z) $(M+1)^+$ 428.3.

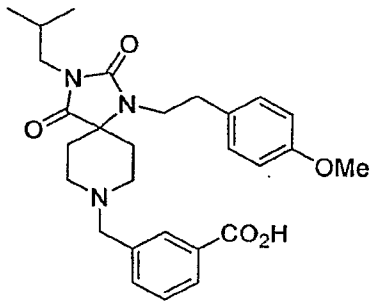
[0092] **Step B:** (3-{3-Cyclobutylmethyl-1-[4-(4-methoxy-phenyl)-butyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl}-phenyl)-acetic acid *tert*-butyl ester is prepared from [3-(3-cyclobutylmethyl-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl)-phenyl]-acetic acid *tert*-butyl ester using the same procedure described in Step B for the preparation of **J1**. The reaction mixture is purified by preparative LC/MS using a MeCN/H_2O gradient 90-10%. The solvent is removed under vacuum to afford the title compound. MS (m/z) $(M+1)^+$ 590.2.

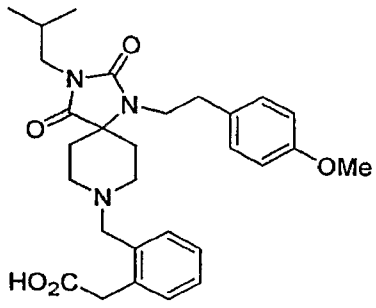
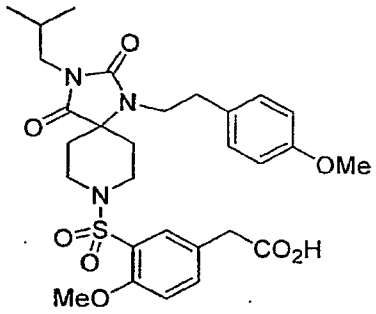
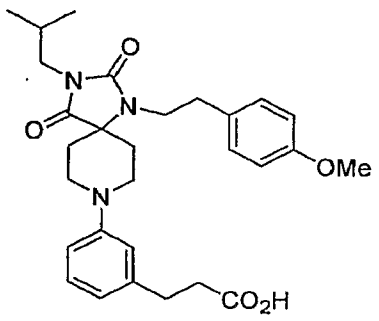
[0093] **Step C:** (3-{3-Cyclobutylmethyl-1-[4-(4-methoxy-phenyl)-butyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl}-phenyl)-acetic acid *tert*-butyl ester is converted in the title compound(3-{3-cyclobutylmethyl-1-[4-(4-methoxy-phenyl)-butyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl}-phenyl)-acetic acid as a TFA salt following the same procedure as

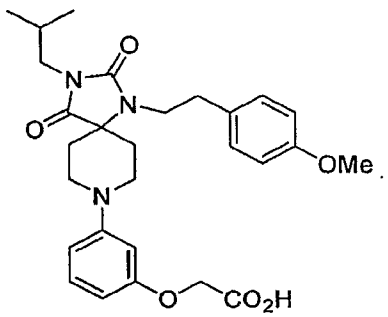
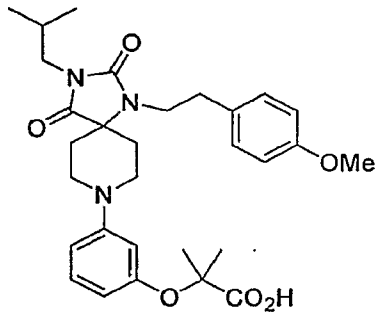
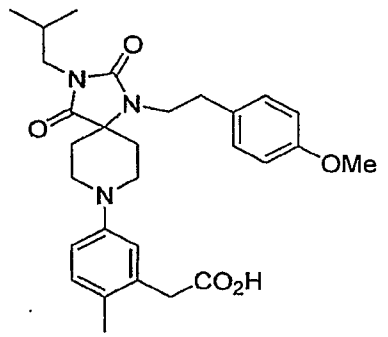
described in Step C for the preparation of Example **I1**. ^{1}HNMR (400MHz, $CDCl_3$) δ 7.59 (s, 1H), 7.53-7.50 (m, 1H), 7.45 (t, J = 8.0Hz, 1H), 7..36 (d, J = 8.0Hz, 1H), 7.09 (d, J = 8.0Hz, 2H), 6.82 (d, J = 8.0Hz, 2H), 4.20 (t, J = 12.0Hz, 2H), 3.78 (s, 3H), 3.68-3.66 (m, 3H), 3.55 (d, J = 8.0Hz, 2H), 3.29 (t, J = 8.0Hz, 2H), 2.83 (dt, J = 4.0 and 12.0Hz, 2H), 2.67 (quint. J = 12.0Hz, 1H), 2.58 (t, J = 8.0Hz, 2H), 2.05-1.98 (m, 2H), 1.89-1.73 (m, 6H), 1.66-1.60 (m, 4H). MS (m/z) $(M+1)^+$ 534.2.

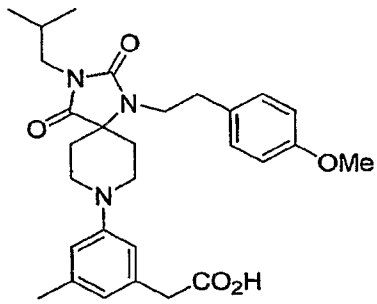
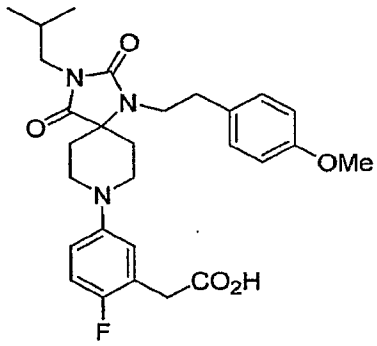
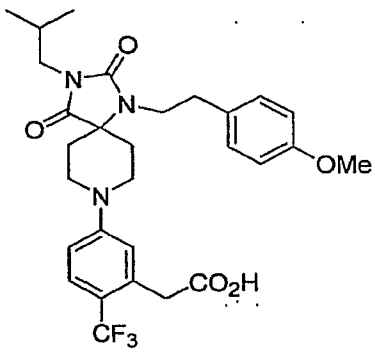
[0094] By repeating the procedures described in the above examples, using appropriate starting materials, the following compounds of Formula I, as identified in Table 1, are obtained.

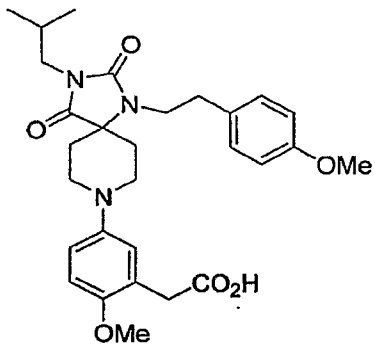
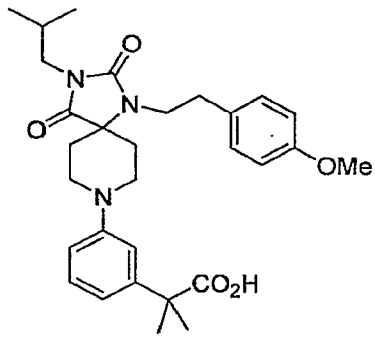
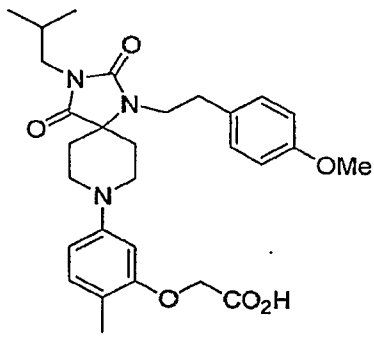
Table 1

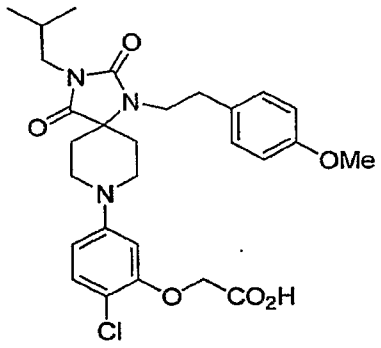
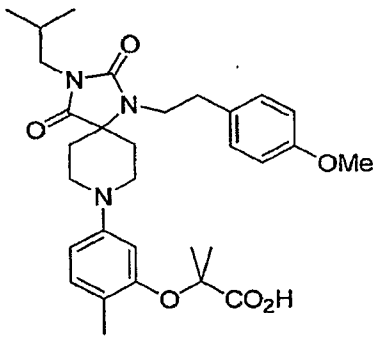
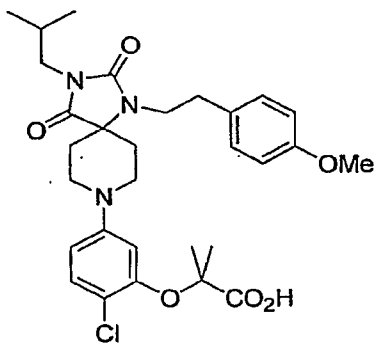
Compound Number	**Compound Structure**	**Physical Data** ^{1}**H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)**
A2		^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.18 (s, 1H), 8.04 (d, J = 7.7 Hz, 1H), 7.67 (d, J = 7.7 Hz, 1H), 7.52 (t, J = 7.7 Hz, 1H), 7.08 (d, J = 8.6 Hz, 2H), 6.78 (d, J = 8.6 Hz, 2H), 4.28 (s, 2H), 3.73 (s, 3H), 3.56 (m, 4H), 3.38 (t, J = 7.1 Hz, 2H), 3.30 (d, J = 7.4 Hz, 2H), 2.92 (t, J = 7.1 Hz, 2H), 2.39 (m, 2H), 2.07 (m, 1H), 1.45 (m, 2H), 0.90 (d, J = 6.7 Hz, 6H). MS calcd. for $C_{28}H_{36}N_3O_5$ $(M+H^+)$ 494.3, found 494.3.

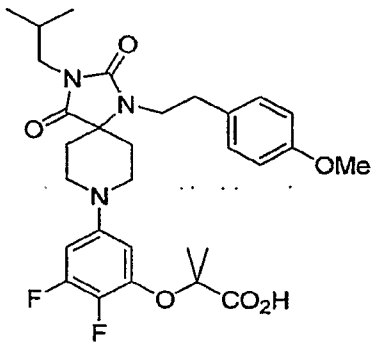
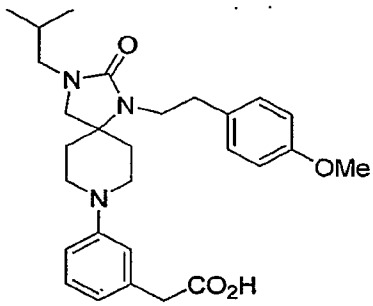
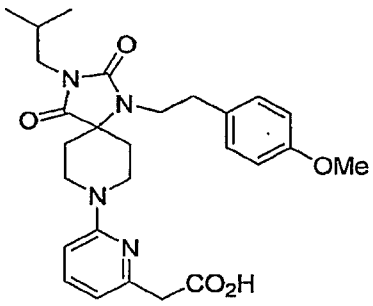
Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
A3		^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.34-7.26 (m, 4H), 7.17 (d, J = 8.6 Hz, 2H), 6.84 (d, J = 8.6 Hz, 2H), 3.86 (t, J = 10.8 Hz, 2H), 3.76 (s, 3H), 3.48 (t, J = 7.1 Hz, 2H), 3.35 (d, J = 7.4 Hz, 2H), 3.18 (d, J = 11.5 Hz, 2H), 2.98 (m, 4H), 2.82 (t, J = 6.6 Hz, 2H), 2.32 (m, 2H), 2.11 (m, 1H), 1.55 (d, J = 14.0 Hz, 2H), 0.93 (d, J = 6.7 Hz, 6H). MS calcd. for $C_{29}H_{38}N_3O_5$ ($M+H^+$) 508.3, found 508.2.
B2		^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.78 (d, J = 2.3 Hz, 1H), 7.44 (dd, J = 2.3 Hz, J = 8.5 Hz, 1H), 7.11 (d, J = 8.6 Hz, 2H), 6.98 (d, J = 7.8 Hz, 1H), 6.83 (d, J = 8.6 Hz, 2H), 3.92 (s, 3H), 3.79 (s, 3H), 3.77 (m, 2H), 3.62 (s, 2H), 3.36 (m, 4H), 3.27 (d, J = 7.4 Hz, 2H), 2.93 (t, J = 7.4 Hz, 2H), 2.03 (m, 1H), 1.86 (m, 2H), 1.44 (d, J = 13.7 Hz, 2H), 0.87 (d, J = 6.7 Hz, 6H). MS calcd. for $C_{29}H_{38}N_3O_8S$ ($M+H^+$) 588.2, found 588.2.
C2		MS calcd. for $C_{29}H_{38}N_3O_5$ ($M+H^+$) 508.3, found 508.2.

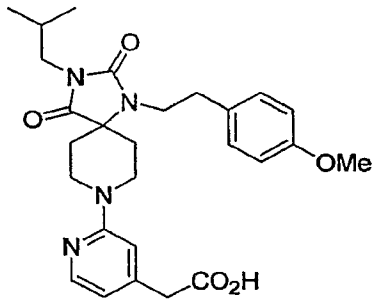
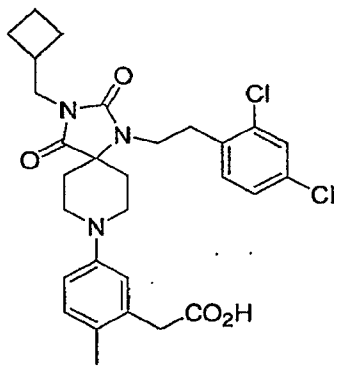
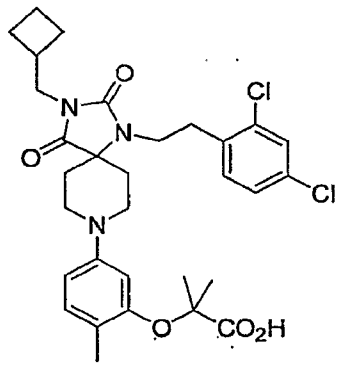
Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
C3		^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.27 (m, 1H), 7.11 (d, J = 8.5 Hz, 2H), 6.93 (s, 1H), 6.85 (m, 1H), 6.82 (d, J = 8.5 Hz, 2H), 6.70 (m, 1H), 4.65 (s, 2H), 3.78 (m, 2H), 3.77 (s, 3H), 3.53 (m, 2H), 3.39 (t, J = 7.1 Hz, 2H), 3.34 (d, J = 7.4 Hz, 2H), 2.95 (t, J = 7.4 Hz, 2H), 2.22 (m, 2H), 2.09 (m, 1H), 1.51 (d, J = 13.8 Hz, 2H), 0.92 (d, J = 6.7 Hz, 6H). MS calcd. for $C_{28}H_{36}N_3O_6$ ($M+H^+$) 510.3, found 510.2.
C4		^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.31 (m, 2H), 7.13 (d, J = 8.5 Hz, 2H), 7.01 (s, 1H), 6.82 (m, 1H), 6.82 (d, J = 8.5 Hz, 2H), 3.90 (m, 2H), 3.77 (s, 3H), 3.50 (m, 2H), 3.40 (t, J = 7.1 Hz, 2H), 3.34 (d, J = 7.4 Hz, 2H), 2.96 (t, J = 7.4 Hz, 2H), 2.31 (m, 2H), 2.09 (m, 1H), 1.51 (d, J = 13.8 Hz, 2H), 1.60 (s, 6H), 0.92 (d, J = 6.7 Hz, 6H). MS calcd. for $C_{30}H_{40}N_3O_6$ ($M+H^+$) 538.3, found 538.3.
C5		^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.45 (s, 1H), 7.34 (d, J = 8.2 Hz, 1H), 7.26 (m, 1H), 7.13 (d, J = 8.5 Hz, 2H), 6.82 (d, J = 8.5 Hz, 2H), 4.05 (t, J = 12.7 Hz, 2H), 3.76 (s, 3H), 3.64 (s, 2H), 3.53 (m, 2H), 3.44 (t, J = 5.0 Hz, 2H), 3.34 (m, 2H), 2.96 (t, J = 5.0 Hz, 2H), 2.58 (t, 12.7 Hz, 2H), 2.30 (s, 3H), 2.10 (m, 1H), 1.50 (d, J = 14.2 Hz, 2H), 0.93 (d, J = 6.7 Hz, 6H). MS calcd. for $C_{29}H_{38}N_3O_5$ ($M+H^+$) 508.3, found 508.3.

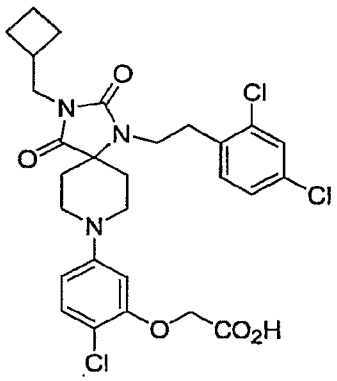
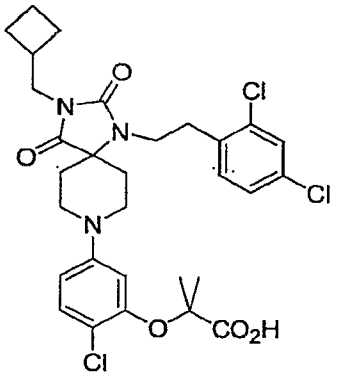
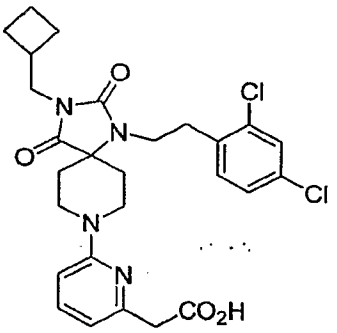
Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
C6		^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.20 (s, 1H), 7.14 (s, 1H), 7.12 (d, J = 8.6 Hz, 2H), 7.04 (s, 1H), 6.82 (d, J = 8.6 Hz, 2H), 3.96 (m, 2H), 3.76 (s, 3H), 3.59 (s, 2H), 3.53 (m, 2H), 3.43 (t, J = 7.2 Hz, 2H), 3.35 (d, J = 7.5 Hz, 2H), 2.96 (t, J = 7.2 Hz, 2H), 2.47 (m, 2H), 2.35 (s, 3H), 2.10 (m, 1H), 1.50 (d, J = 14.0 Hz, 2H), 0.93 (d, J = 6.7 Hz, 6H). MS calcd. for $C_{29}H_{38}N_3O_5$ ($M+H^+$) 508.3, found 508.3.
C7		^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.39 (m, 1H), 7.31 (m, 1H), 7.13 (d, J = 8.5 Hz, 2H), 7.12 (m, 1H), 6.83 (d, J = 8.5 Hz, 2H), 3.88 (m, 2H), 3.77 (s, 3H), 3.71 (s, 2H), 3.48 (m, 2H), 3.43 (t, J = 7.2 Hz, 2H), 3.34 (d, J = 7.5 Hz, 2H), 2.97 (t, J = 7.2 Hz, 2H), 2.38 (m, 2H), 2.10 (m, 1H), 1.50 (d, J = 14.1 Hz, 2H), 0.93 (d, J = 6.7 Hz, 6H). MS calcd. for $C_{28}H_{35}FN_3O_5$ ($M+H^+$) 512.3, found 512.3.
C8		^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.58 (d, J = 8.7 Hz, 1H), 7.20-7.10 (m, 2H), 7.10 (d, J = 8.3 Hz, 2H), 7.12 (m, 1H), 6.81 (d, J = 8.3 Hz, 2H), 3.83 (s, 2H), 3.80-3.60 (m, 4H), 3.78 (s, 3H), 3.34 (m, 4H), 2.94 (t, J = 7.2 Hz, 2H), 2.10 (m, 1H), 2.02 (m, 2H), 1.51 (d, J = 13.5 Hz, 2H), 0.93 (d, J = 6.7 Hz, 6H). MS calcd. for $C_{29}H_{35}F_3N_3O_5$ ($M+H^+$) 562.3, found 562.3.

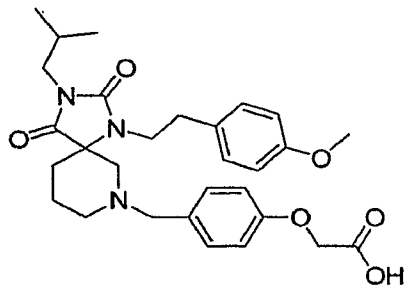
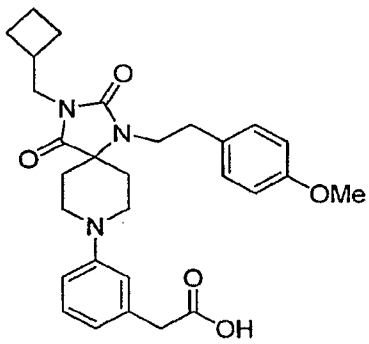
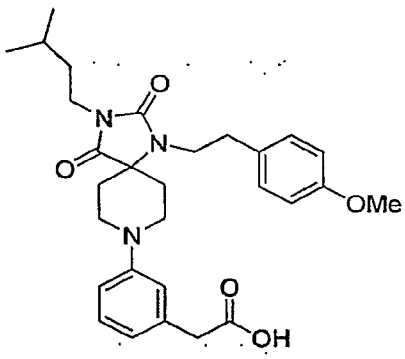
Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
C9		^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.59 (d, J = 8.9 Hz, 1H), 7.52 (s, 1H), 7.16 (d, J = 8.4 Hz, 2H), 6.92 (d, J = 8.9 Hz, 1H), 6.82 (d, J = 8.4 Hz, 2H), 4.11 (m, 2H), 3.84 (s, 3H), 3.76 (s, 3H), 3.65 (s, 2H), 3.51 (m, 4H), 3.35 (d, J = 7.4 Hz, 2H), 2.99 (t, J = 7.0 Hz, 2H), 2.76 (m, 2H), 2.10 (m, 1H), 1.48 (d, J = 14.3 Hz, 2H), 0.93 (d, J = 6.7 Hz, 6H). MS calcd. for $C_{29}H_{38}N_3O_6$ ($M+H^+$) 524.3, found 524.3.
C10		^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.34 (m, 2H), 7.18 (d, J = 7.8 Hz, 1H), 7.12 (d, J = 8.4 Hz, 2H), 6.82 (d, J = 8.4 Hz, 2H), 3.77 (m, 2H), 3.77 (s, 3H), 3.52 (m, 2H), 3.41 (t, J = 7.3 Hz, 2H), 3.34 (d, J = 7.4 Hz, 2H), 2.95 (t, J = 7.3 Hz, 2H), 2.29 (m, 2H), 2.10 (m, 1H), 1.58 (s, 6H), 1.52 (d, J = 13.7 Hz, 2H), 0.92 (d, J = 6.7 Hz, 6H). MS calcd. for $C_{30}H_{40}N_3O_5$ ($M+H^+$) 522.3, found 522.3.
C11		^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.20 (m, 2H), 7.12 (d, J = 8.3 Hz, 2H), 7.18 (d, J = 8.1 Hz, 1H), 6.82 (d, J = 8.3 Hz, 2H), 4.71 (s, 2H), 4.01 (m, 2H), 3.76 (s, 3H), 3.49 (m, 2H), 3.42 (t, J = 7.1 Hz, 2H), 3.34 (d, J = 7.4 Hz, 2H), 2.96 (t, J = 7.1 Hz, 2H), 2.49 (m, 2H), 2.25 (s, 3H), 2.10 (m, 1H), 1.49 (d, J = 14.2 Hz, 2H), 0.93 (d, J = 6.7 Hz, 6H). MS calcd. for $C_{29}H_{38}N_3O_6$ ($M+H^+$) 524.3, found 524.3.

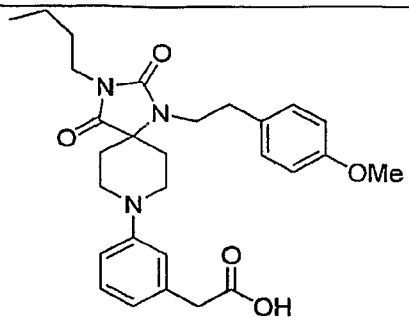
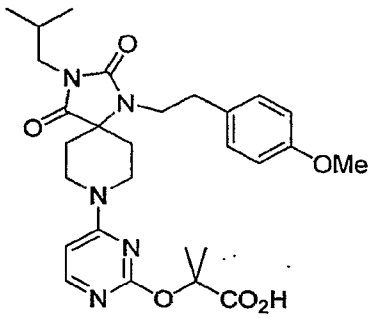
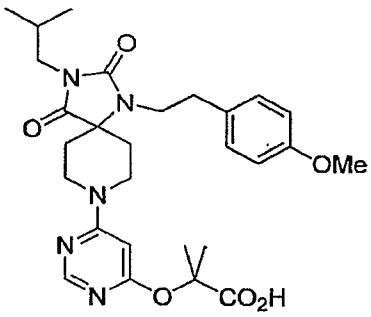
Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
C12		^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.43-6.82 (m, 7H), 4.78 (s, 2H), 3.99 (m, 2H), 3.76 (s, 3H), 3.52 (m, 2H), 3.40 (t, J = 7.2 Hz, 2H), 3.34 (d, J = 7.4 Hz, 2H), 2.96 (t, J = 7.2 Hz, 2H), 2.38 (m, 2H), 2.10 (m, 1H), 1.49 (d, J = 14.3 Hz, 2H), 0.92 (d, J = 6.7 Hz, 6H). MS calcd. for $C_{28}H_{35}ClN_3O_6$ ($M+H^+$) 544.2, found 544.2.
C13		^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.19 (d, J = 8.3 Hz, 1H), 7.11 (d, J = 8.2 Hz, 2H), 7.05 (m, 1H), 6.90 (m, 1H), 6.82 (d, J = 8.2 Hz, 2H), 3.93 (m, 2H), 3.76 (s, 3H), 3.47 (m, 2H), 3.39 (t, J = 7.2 Hz, 2H), 3.34 (d, J = 7.4 Hz, 2H), 2.94 (t, J = 7.2 Hz, 2H), 2.38 (m, 2H), 2.21 (s, 3H), 2.09 (m, 1H), 1.61 (s, 6H), 1.49 (d, J = 14.2 Hz, 2H), 0.92 (d, J = 6.7 Hz, 6H). MS calcd. for $C_{31}H_{42}N_3O_6$ ($M+H^+$) 552.3, found 552.3.
C14		^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.43 (d, J = 8.7 Hz, 1H), 7.26 (s, 1H), 7.10 (d, J = 8.3 Hz, 2H), 6.97 (d, J = 8.7 Hz, 1H), 6.82 (d, J = 8.3 Hz, 2H), 3.95 (m, 2H), 3.77 (s, 3H), 3.50 (m, 2H), 3.39 (t, J = 7.2 Hz, 2H), 3.35 (d, J = 7.4 Hz, 2H), 2.96 (t, J = 7.2 Hz, 2H), 2.34 (m, 2H), 2.10 (m, 1H), 1.64 (s, 6H), 1.49 (d, J = 13.7 Hz, 2H), 0.92 (d, J = 6.7 Hz, 6H). MS calcd. for $C_{30}H_{39}ClN_3O_6$ ($M+H^+$) 572.2, found 572.3.

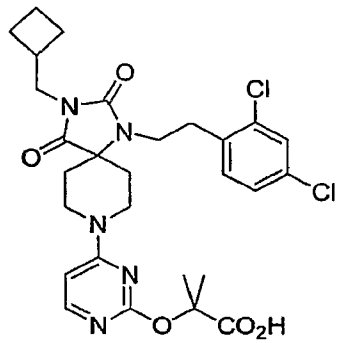
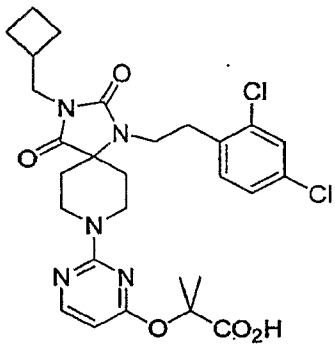
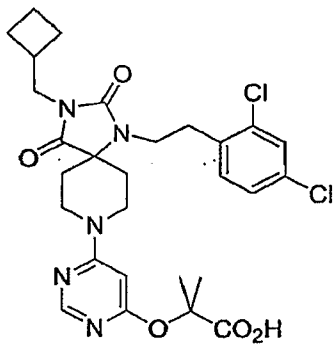
Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
C15		^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.10 (d, J = 8.3 Hz, 2H), 6.91 (m, 1H), 6.82 (d, J = 8.3 Hz, 2H), 6.81 (m,1H), 3.75 (m, 2H), 3.77 (s, 3H), 3.45 (m, 2H), 3.38 (t, J = 7.2 Hz, 2H), 3.34 (d, J = 7.4 Hz, 2H), 2.95 (t, J = 7.2 Hz, 2H), 2.19 (m, 2H), 2.10 (m, 1H), 1.62 (s, 6H), 1.49 (d, J = 14.4 Hz, 2H), 0.92 (d, J = 6.7 Hz, 6H). MS calcd. for $C_{30}H_{38}F_2N_3O_6$ ($M+H^+$) 574.3, found 574.3.
C16		^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.25-6.98 (m, 4H), 7.05 (d, J = 8.4 Hz, 2H), 6.82 (d, J = 8.4 Hz, 2H), 3.70 (s, 3H), 3.54 (m, 4H), 3.15 (m, 4H), 2.96 (d, J = 7.3 Hz, 2H), 2.87 (t, J = 11.6 Hz, 2H), 2.75 (t, J = 7.0 Hz, 2H), 2.09 (t, J = 11.6 Hz, 2H), 1.78 (m, 1H), 1.42 (d, J = 13.1 Hz, 2H), 0.83 (d, J = 6.6 Hz, 6H). MS calcd. for $C_{28}H_{38}N_3O_4$ ($M+H^+$) 480.3, found 480.2.
C17		^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.69 (t, J = 8.0 Hz, 1H), 7.03 (d, J = 8.5 Hz, 2H), 6.76 (d, J = 9.2 Hz, 1H), 6.73 (d, J = 8.5 Hz, 2H), 6.65 (d, J = 7.2 Hz, 1H), 4.00 (m, 2H), 3.85 (m, 4H), 3.69 (s, 3H), 3.27 (m, 4H), 2.85 (t, J = 7.4 Hz, 2H), 2.03 (m, 1H), 1.88 (m, 2H), 1.55 (d, J = 13.5 Hz, 2H), 0.85 (d, J = 6.7 Hz, 6H). MS calcd. for $C_{27}H_{35}N_4O_5$ ($M+H^+$) 495.3, found 495.2.

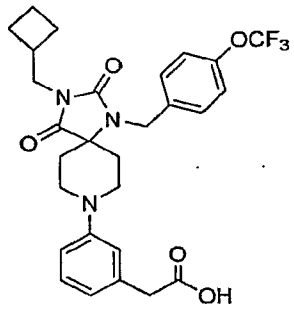
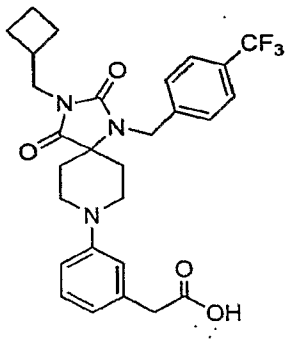
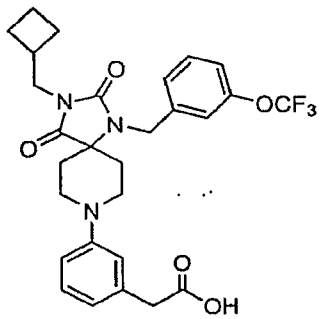
Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
C18		^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.90 (d, J = 6.4 Hz, 1H), 7.08 (d, J = 8.5 Hz, 2H), 6.88 (s, 1H), 6.79 (d, J = 8.5 Hz, 2H), 6.73 (d, J = 6.4 Hz, 2H), 4.07 (m, 2H), 3.93 (m, 2H), 3.76 (s, 3H), 3.61 (s, 2H), 3.33 (m, 4H), 2.92 (t, J = 7.4 Hz, 2H), 2.08 (m, 1H), 1.92 (m, 2H), 1.64 (d, J = 14.0 Hz, 2H), 0.91 (d, J = 6.7 Hz, 6H). MS calcd. for $C_{27}H_{35}N_4O_5$ ($M+H^+$) 495.3, found 495.2.
C19		^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.48 (d, J = 2.2 Hz, 1H), 7.37 (m, 2H), 7.29 (d, J = 8.4 Hz, 2H), 7.18 (m, 2H), 4.16 (m, 2H), 3.66 (s, 2H), 3.60 (m, 2H), 3.56 (d, J = 7.5 Hz, 2H), 3.49 (t, J = 7.1 Hz, 2H), 3.13 (t, J = 7.1 Hz, 2H), 2.70 (m, 3H), 2.32 (s, 3H), 2.02 (m, 2H), 1.89 (m, 2H), 1.76 (m, 2H), 1.61 (d, J = 14.4 Hz, 2H). MS calcd. for $C_{29}H_{34}Cl_2N_3O_4$ ($M+H^+$) 558.2, found 558.2.
C20		MS calcd. for $C_{31}H_{38}Cl_2N_3O_5$ ($M+H^+$) 602.2, found 602.2.

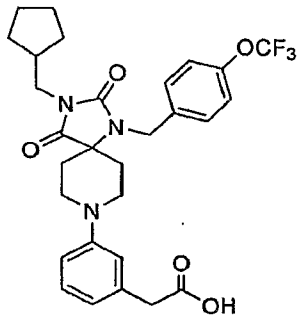
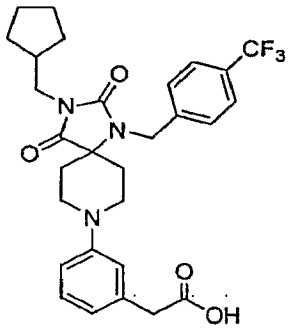
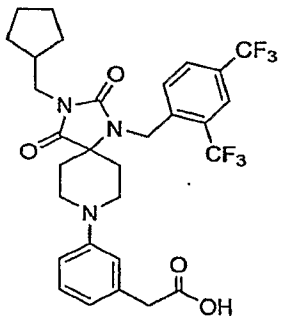
Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
C21		^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.46 (d, J = 8.7 Hz, 1H), 7.39 (s, 1H), 7.33 (d, J = 2.2 Hz, 1H), 7.18 (m, 2H), 6.99 (dd, J = 2.2 Hz, J = 8.7 Hz, 1H), 4.79 (s, 2H), 4.07 (m, 2H), 3.59 (m, 2H), 3.56 (d, J = 7.5 Hz, 2H), 3.46 (t, J = 7.2 Hz, 2H), 3.13 (t, J = 7.2 Hz, 2H), 2.69 (m, 1H), 2.49 (m, 2H), 2.02 (m, 2H), 1.90 (m, 2H), 1.76 (m, 2H), 1.60 (d, J = 14.3 Hz, 2H). MS calcd. for $C_{28}H_{31}Cl_3N_3O_5$ ($M+H^+$) 594.1, found 594.1.
C22		^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.48 (d, J = 8.7 Hz, 1H), 7.38 (s, 1H), 7.31 (d, J = 2.1 Hz, 1H), 7.18 (m, 2H), 7.04 (dd, J = 2.2 Hz, J = 8.7 Hz, 1H), 4.79 (s, 2H), 4.05 (m, 2H), 3.58 (m, 2H), 3.56 (d, J = 7.5 Hz, 2H), 3.45 (t, J = 7.2 Hz, 2H), 3.12 (t, J = 7.2 Hz, 2H), 2.69 (m, 1H), 2.47 (m, 2H), 2.03 (m, 2H), 1.90 (m, 2H), 1.76 (m, 2H), 1.65 (s, 6H), 1.60 (d, J = 13.5 Hz, 2H). MS calcd. for $C_{30}H_{35}Cl_3N_3O_5$ ($M+H^+$) 622.2, found 622.1.
C23		MS calcd. for $C_{27}H_{31}Cl_2N_4O_4$ ($M+H^+$) 545.2, found 545.2.

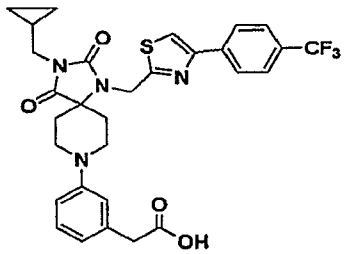
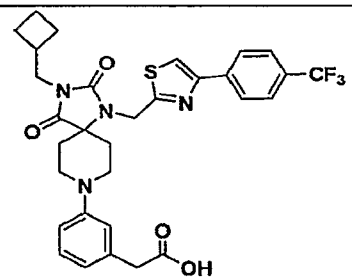
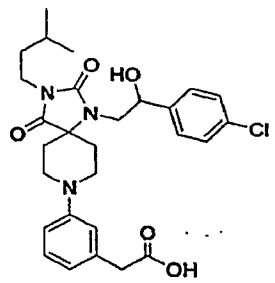
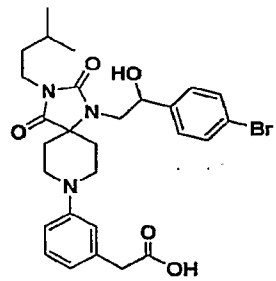
Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
D2		^{1}H-NMR (400 MHz, CDCl3) δ = 7.24 (d, J = 7.6 Hz, 2H), 7.20 (d, J = 8.0 Hz, 2H), 6.93 (s, 4H), 4.79 (s, 2H), 3.92 (s, 3H), 3.62 (m, 1H), 3.45 (m, 3H), 3.17 (m, 1H), 3.04 (m, 2H), 2.53 (m, 1H), 2.16 (m, 1H), 2.02 (m, 2H), 1.72 (m, 1H), 0.99 (d, J = 6.7 Hz, 6H). MS calcd. for $C_{29}H_{38}N_3O_6$ (M+H+) 523.3, found 523.3.
E2		^{1}H NMR (400 MHz, CDCl3) δ 7.62 (s, 1H), 7.54 (d, J = 7.6 Hz, 1H), 7.48 (t, J = 8.2 Hz, 1H), 7.38 (d, J = 7.6 Hz, 1H), 7.14 (d, J = 8.8 Hz, 2H), 6.83 (d, J = 8.6 Hz, 2H), 4.13 (t, J = 11.7 Hz, 2H), 3.76 (s, 3H), 3.72 (s, 2H), 3.53-3.58 (m, 4H), 3.47 (t, , J = 7.2 Hz, 2H), 3.41 (d, J = 7.3 Hz, 2H), 2.99 (t, J = 7.2 Hz, 2H), 2.61-2.75 (m, 3H), 1.73-1.83 (m, 6H), 1.47 (d, J = 14.5 Hz, 2H). LC/MS ($M+H^+$): 506.2.
E3		^{1}H NMR (400 MHz, CDCl3) δ 7.62 (s, 1H), 7.5 (m, 1H), 7.46 (t, J = 8.2 Hz, 1H), 7.35 (d, J = 8.3 Hz, 1H), 7.16 (d, J = 8.3 Hz, 2H), 6.83 (d, J = 8.2 Hz, 2H), 4.11 (t, J = 11.7 Hz, 2H), 3.77 (s, 3H), 3.72 (s, 2H), 3.48-3.57 (m, 6H), 2.98(t, J = 6.1 Hz, 2H), 2.68(m, 2), 1.55 (m, 4H), 1.22 (m, 1H), 0.98 (d, J = 6.2, 6H). LC/MS ($M+H^+$): 508.2

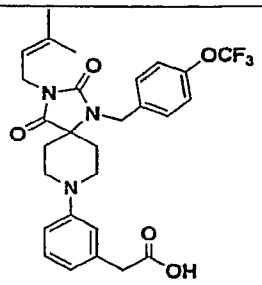
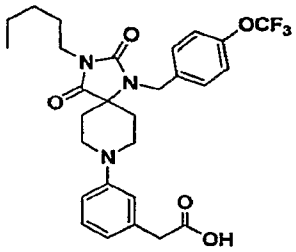
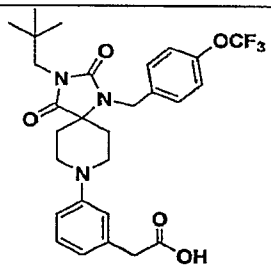
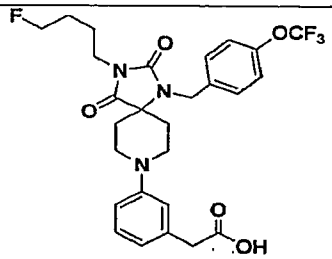
Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
E4		LC/MS ($M+H^+$): 494.2.
G2		^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.87 (s, 1H), 7.00 (d, J = 8.5 Hz, 2H), 6.75 (d, J = 8.5 Hz, 2H), 6.32 (s, 1H), 4.53-4.34 (m, 1H), 3.89 (m, 1H), 3.76 (m, 1H), 3.71 (s, 3H), 3.59-3.44 (m, 1H), 3.26 (m, 4H), 2.86 (m, 2H), 2.02 (m, 1H), 1.95-1.62 (m, 2H), 1.64-1.61 (s, 6H), 1.45 (m, 2H), 0.84 (d, J = 6.7 Hz, 6H). MS calculated for $C_{28}H_{38}N_5O_6$ ($M+H^+$) 540.3, found 540.3.
G3		^{1}H-NMR (400MHz, $CDCl_3$) δ = 8.33 (s, 1H), 7.02 (d, J = 8.5 Hz, 2H), 6.75 (d, J = 8.5 Hz, 2H), 5.92 (s, 1H), 4.04 (m, 2H), 3.77 (m, 2H), 3.71 (s, 3H), 3.27 (m, 4H), 2.86 (t, J = 7.2 Hz, 2H), 2.03 (m, 1H), 1.74 (m, 2H), 1.64 (s, 6H), 1.50 (m, 2H), 0.85 (d, J = 6.7 Hz, 6H). MS calculated for $C_{28}H_{38}N_5O_6$ ($M+H^+$) 540.3, found 540.3.

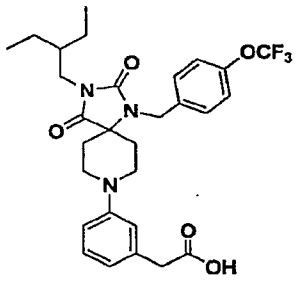
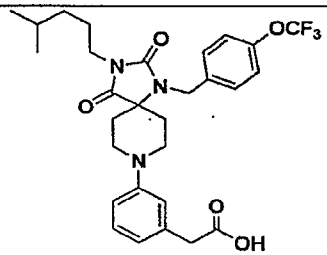
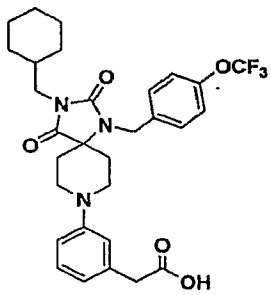
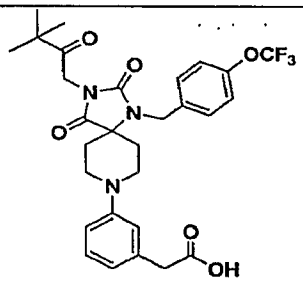
Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
G4		^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.94 (d, J = 7.4 Hz, 1H), 7.34 (s, 1H), 7.15 (s, 2H), 6.43 (d, J = 7.4 Hz, 1H), 4.64 (m, 1H), 4.00 (m, 1H), 3.89 (m, 1H), 3.69 (m, 1H), 3.54 (d, J = 7.2 Hz, 2H), 3.36 (m, 2H), 3.08 (t, J = 7.2 Hz, 2H), 2.67 (m, 1H), 2.00-1.62 (m, 16H). MS calcd. for $C_{28}H_{34}Cl_2N_5O_5$ ($M+H^+$) 590.2, found 590.2.
G5		^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.13 (d, J = 6.9 Hz, 1H), 7.34 (s, 1H), 7.16 (s, 2H), 6.24 (d, J = 6.9 Hz, 1H), 4.41 (m, 2H), 3.76 (m, 2H), 3.52 (d, J = 7.4 Hz, 2H), 3.31 (m, 2H), 3.05 (m, 2H), 2.66 (m, 1H), 2.02-1.57 (m, 16H). MS calcd. for $C_{28}H_{34}Cl_2N_5O_5$ ($M+H^+$) 590.2, found 590.2.
G6		^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.42 (s, 1H), 7.37 (s, 1H), 7.17 (s, 2H), 6.03 (s, 1H), 4.16 (m, 2H), 3.88 (m, 2H), 3.54 (d, J = 7.2 Hz, 2H), 3.37 (t, J = 7.2 Hz, 2H), 3.08 (t, J = 7.2 Hz, 2H), 2.68 (m, 1H), 2.00-1.62 (m, 16H). MS calcd. for $C_{28}H_{34}Cl_2N_5O_5$ ($M+H^+$) 590.2, found 590.2.

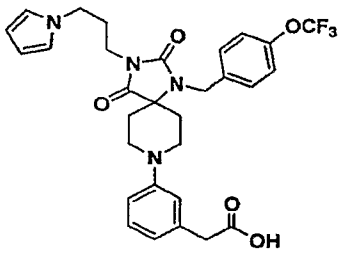
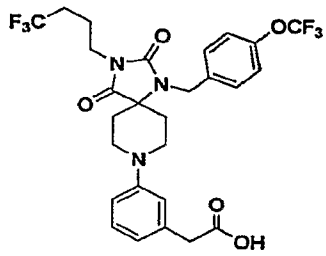
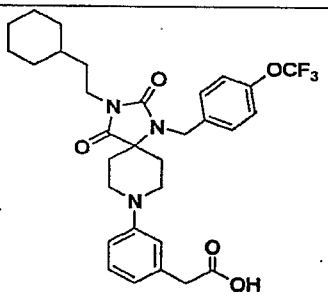
Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
I2		^{1}HNMR (400MHz, CD_3OD) δ 7.48-7.41 (m, 4H), 7.37-7.35 (m, 1H), 7.30-7.24(m, 3H), 4.63 (s, 2H), 4.11-4.05 (m, 2H), 3.69-3.65(m, 2H), 3.61 (d, J = 8.0Hz, 2H), 2.75(quint, J = 8.0Hz, 1H), 2.4. (dt, J = 4.0 and 12.0Hz, 2H), 2.09-2.03 (m, 2H), 1.95-1.80 (m, 6H). MS (m/z) $(M+1)^+$ 546.2.
I3		^{1}HNMR (400MHz, CD_3OD) δ 7.60 (d, J = 8.0Hz, 2H), 7.45- (d, J = 8.0Hz, 2H), 7.17(t, J = 8.0Hz, 1H), 6.89 (s, 1H), 6.85 (d, J = 8.0Hz, 1H), 6.77 (d, J = 8.0Hz, 1H), 4.62 (s, 2H), 3.64-3.57 (m, 4H), 3.54 (bs, 2H), 3.51-3.44 (m, 2H), 2.72 (quint, J = 8.0Hz, 1H), 2.11. (m, 4H), 1.93-1.79 (m, 4H), 1.66-1.63 (m, 2H). MS (m/z) $(M+1)^+$ 530.2.
I4		^{1}HNMR (400MHz, CD_3OD) δ 7.48 (t, J = 8.0Hz, 1H), 7.32-7.29 (m, 2H), 7.24 (s, 1H), 7.20-7.18 (m, 1H), 7.11-6.99 (m, 3H), 4.62 (s, 2H), 3.78-3.71 (m, 2H), 3.66-3.59 (m, 6H), 2.75-2.71 (m, 1H), 2.23-2.16 (M, 2H), 2.08-2.01 (m, 2H), 1.93-1.75 (m, 6). MS (m/z) $(M+1)^+$ 546.3.

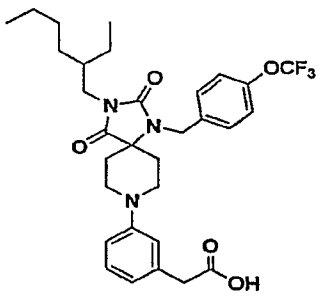
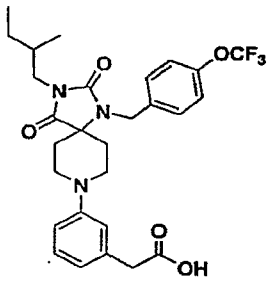
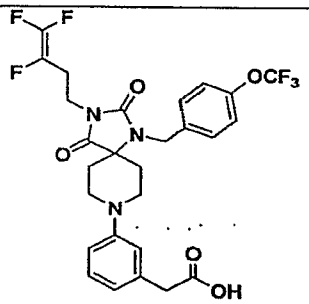
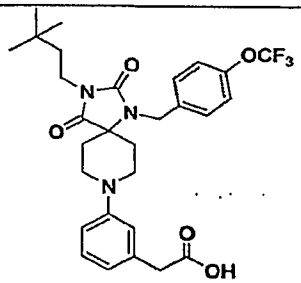
Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
I5		^{1}HNMR (400MHz, CD_3OD) δ 7.41 (d, J = 8.0Hz, 2H), 7.34 (t, J = 8.0Hz, 1H), 7.24 (d, J = 8.0Hz, 2H), 7.18 (s, 1H), 7.14-7.05 (m, 2H), 4.60 (s, 2H), 3.68-3.57 (m, 6H), 2.23 (dt, J = 8.0 and 12.0Hz, 2H), 1.84-1.81 (m, 2H), 1.64-1.52 (m, 3H), 099 (d, J = 8.0 Hz, 6H). MS (m/z) $(M+1)^+$ 548.3.
I6		^{1}HNMR (400MHz, CD_3OD) δ 7.64 (d, J = 8.0Hz, 2H), 7.51 (d, J = 8.0Hz, 2H), 7.35 (t, J = 8.0Hz, 1H), 7.21 (s, 1H), 7.15-7.08(m, 2H), 4.67 (s, 2H), 3.89-3.83 (m, 2H), 3.68-3.59 (m, 6H), 2.22 (dt, J = 8.0 and 16Hz, 2H), 1.88-1.84 (m, 2H), 1.63-1.53 (m, 3H), 0.98 (d, J = 8.0Hz, 6H). MS (m/z) $(M+1)^+$ 532.3.
I7		^{1}HNMR (400MHz, CD_3OD) δ 7.99 (s, 1H), 7.93 (d, J = 8.0H, 1H), 7.69 (d, J = 8.0Hz, 1H), 7.33 (t, J = 8.0Hz, 1H), 7.19 (s, 1H), 7.15-7.06 (m, 2H), 4.18 (s, 2H), 3.87-3.84 (m, 2H), 3.68.3.60 (m, 7H), 2.13 (dt J = 8.0 and 16 Hz, 2H), 2.02-1.99 (m, 2H), 1.65-1.55 (m, 3H), 1.00 (d, J = 8.0Hz, 6H). MS (m/z) $(M+1)^+$ 600.2.

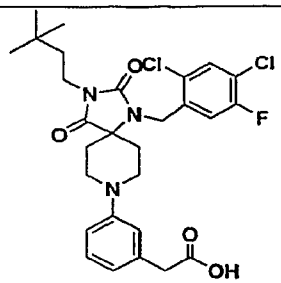
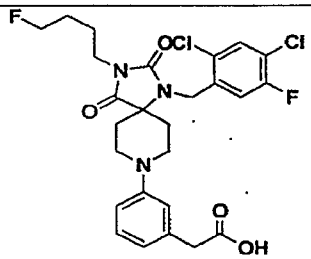
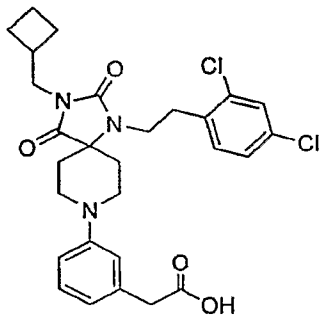
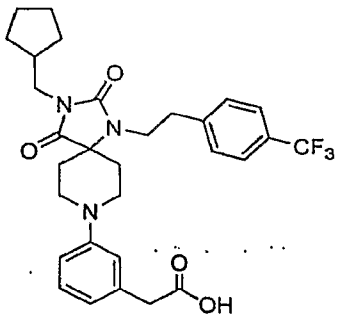
Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
I8		^{1}HNMR (400MHz, $CDCl_3$) δ 7.98 (d, J = 7.9Hz, 2H), 7.56-7.68 (m, 5H), 7.48 (t, J = 8.1Hz, 1H), 7.38 (d, J = 7.6Hz, 1H), 4.97 (s, 2H), 4.24 (t, J= 11.5Hz, 2H), 3.68 (d, J= 12.1Hz, 2H), 3.47 (d, J= 7Hz, 2H), 3.17 (t, J= 13.1Hz, 2H), 2.33 (m, 1H), 2.0 (d, J= 14.5Hz, 2H), 1.22 (m, 2H), 0.56 (dd, J = 13.5, 5.4Hz, 2H), 0.4 (dd, J = 9.9, 5.0Hz, 2H). MS (m/z) $(M+1)^+$ 655.2.
I9		MS (m/z) $(M+1)^+$ 669.2.
I10		^{1}HNMR (400MHz, $CDCl_3$) δ 7.73 (s, 1H), 7.65 (d, J = 7.8Hz, 1H), 7.5 (t, J= 7.6Hz, 1H), 7.43 (m, 3H), 7.35 (s, 2H), 7.34 (d, J= 7.9Hz, 1H), 5.1 (m, 1H), 4.2 (m, 2H), 3.74 (s, 2H), 3.6 (m, 6H), 3.2 (m, 2H), 1.81 (d, J= 12.4Hz, 1H), 1.56 (m, 4H), 0.97 (d, J = 5.2Hz, 6H). MS (m/z) $(M+1)^+$ 528.2, 530.2.
I11		^{1}HNMR (400MHz, $CDCl_3$) δ 7.68 (s, 1H), 7.59 (d, J = 8.2Hz, 1H), 7.49 (m, 3H), 7.41 (d, J = 7.6Hz, 1H), 7.34 (d, J = 8.1Hz, 2H), 5.06 (m, 1H), 4.2 (t, J= 12.4Hz, 2H), 3.72 (s, 2H), 3.61 (m, 6H), 3.08 (m, 2H), 1.81 (d, J= 13.9Hz, 1H), 1.56 (m, 4H), 0.97 (d, J = 6Hz, 6H). MS (m/z) $(M+1)^+$ 572.2, 574.2.

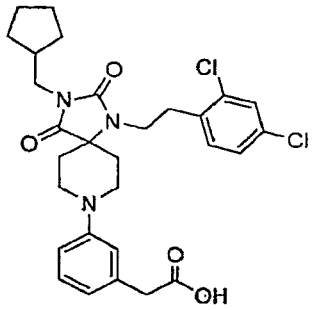
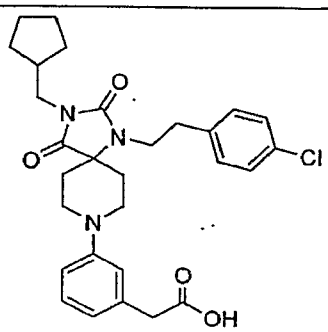
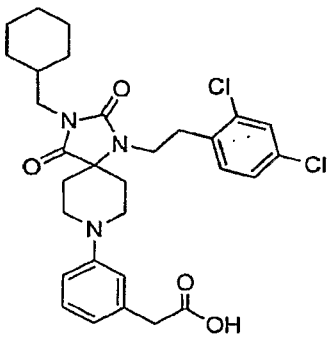
Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
I12		MS (m/z) $(M+1)^+$ 546.2.
I13		^{1}HNMR (400MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.69 (d, J = 7.3Hz, 1H), 7.62 (d, J = 8.1Hz, 2H), 7.5 (t, J = 7.8Hz, 1H), 7.42 (d, J = 7.5Hz, 1H), 7.18 (d, J = 7.9Hz, 2H), 4.67 (s, 2H), 4.23 (t, J= 12.2Hz, 2H), 3.73 (s, 2H), 3.61 (m, 4H), 3.32 (m, 2H), 1.71 (m, 4H), 1.34 (m, 4H), 0.92 (t, J= 7.2Hz, 3H). MS (m/z) $(M+1)^+$ 548.2.
I14		MS (m/z) $(M+1)^+$ 548.2.
I15		MS (m/z) $(M+1)^+$ 552.2.

Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
I16		^{1}HNMR (400MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.7 (d, J = 8.1Hz, 1H), 7.62 (d, J = 8.1Hz, 2H), 7.5 (t, J = 7.7Hz, 1H), 7.42 (d, J = 7.6Hz, 1H), 7.18 (d, J = 7.8Hz, 2H), 4.67 (s, 2H), 4.24 (t, J= 11.5Hz, 2H), 3.73 (s, 2H), 3.61 (d, J= 12.5Hz, 2H), 3.49 (d, J= 7.4Hz, 2H), 3.33 (m, 2H), 1.8 (quint, J= 6.7Hz, 1H), 1.72 (d, J= 14Hz, 2H), 1.34 (t, J = 6.5Hz, 4H), 0.94 (m, 6H). MS (m/z) $(M+1)^+$ 562.2.
I17		MS (m/z) $(M+1)^+$ 562.2.
I18		^{1}HNMR (400MHz, $CDCl_3$) δ 7.69 (s, 1H), 7.61 (d, J = 8.3Hz, 1H), 7.52 (d, J = 8.3Hz, 2H), 7.48 (t, J = 8.1Hz, 1H), 7.4 (d, J = 7.5Hz, 1H), 7.18 (d, J = 8.1Hz, 2H), 4.63 (s, 2H), 4.23 (t, J= 11.9Hz, 2H), 3.7 (s, 2H), 3.62 (d, J= 13.2Hz, 2H), 3.42 (d, J= 7.3Hz, 2H), 3.1(m, 2H), 1.74 (m, 8H), 1.25 (m, 3H), 1.01 (q, J = 12Hz, 2H). MS (m/z) $(M+1)^+$ 574.2.
I19		MS (m/z) $(M+1)^+$ 576.2.

Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
I20		^{1}HNMR (400MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.72 (d, J = 8.6H, 1H),7.66 (d, J = 8.5Hz, 2H), 7.5 (t, J = 8.0Hz, 1H), 7.43 (d, J = 7.3Hz, 1H), 7.19 (d, J = 8.7Hz, 2H), 6.67(s, 2H), 6.06(s, 2H), 4.64 (s, 2H), 4.5 (t, J = 12.4Hz, 2H), 3.99 (t, J = 6.6Hz, 2H), 3.74 (s, 2H), 3.65 (t, J = 6.6Hz, 2H), 3.56 (d, J = 11.5Hz, 2H), 3.35 (t, J = 11.2Hz, 2H), 2.22 (t, J = 6.6Hz, 2H), 1.6 (d, J= 13.3, 2H). MS (m/z) $(M+1)^+$ 585.2.
I21		^{1}HNMR (400MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.73 (d, J = 7.4H, 1H),7.66 (d, J = 8Hz, 2H), 7.51 (t, J = 7.4Hz, 1H), 7.43 (d, J = 8Hz, 1H), 7.19 (d, J = 7.5Hz, 2H), 4.69 (s, 2H), 4.21 (t, J = 11.6Hz, 2H), 3.74 (s, 2H), 3.63 (m, 4H), 3.44 (m, 2H), 1.98 (m, 4H), 1.72 (m, 2H). MS (m/z) $(M+1)^+$ 588.2.
I22		MS (m/z) $(M+1)^+$ 588.2.

Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
I23		^{1}HNMR (400MHz, $CDCl_3$) δ 7.74 (s, 1H), 7.66 (d, J = 7.8H, 1H),7.58 (d, J = 8.3Hz, 2H), 7.49 (t, J = 8.0Hz, 1H), 7.41 (d, J = 7.5Hz, 1H), 7.18 (d, J = 8.1Hz, 2H), 4.66 (s, 2H), 4.22 (t, J = 11.7Hz, 2H), 3.72 (s, 2H), 3.62 (d, J = 8Hz, 2H), 3.49 (d, J = 7.4Hz, 2H), 3.24 (m, 2H), 1.84 (m, 1H), 1.71 (d, J = 14.6Hz, 2H), 1.29 (m, 10H), 0.93 (t, J = 7.3Hz, 3H), 0.89 (t, J = 6.7Hz, 3H). MS (m/z) $(M+1)^+$ 590.2.
I24		^{1}HNMR (400MHz, $CDCl_3$) δ 7.79 (s, 1H), 7.7 (d, J = 7.3Hz, 1H), 7.62 (d, J = 8.2Hz, 2H), 7.5 (t, J = 7.9Hz, 1H), 7.42 (d, J = 7.6Hz, 1H), 7.18 (d, J = 7.4Hz, 2H), 4.66 (s, 2H), 4.23 (m, 2H), 3.73 (s, 2H), 3.6 (m, 2H), 3.32 (m, 2H), 1.72 (d, J = 12.9Hz, 2H), 1.58 (m, 3H), 0.97 (m, 6H). MS (m/z) $(M+1)^+$ 548.2.
I25		MS (m/z) $(M+1)^+$ 586.2.
I26		MS (m/z) $(M+1)^+$ 562.2.

Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
I27		MS (m/z) $(M+1)^+$ 564.2, 565.2, 566.2, 567.2, 568.2.
I28		MS (m/z) $(M+1)^+$ 554.2, 555.2, 556.2, 557.2, 558.2.
J2		^{1}HNMR (400MHz, $CDCl_3$) δ 7.42-7.32 (m, 4H), 7.22-7.17 (m, 3H), 3.99 (t, J = 8.0Hz, 2H), 3.66 (s, 2H), 3.63-3.55 (m, 4H), 3.49-3.46 (m, 2H), 3.14-3.11 (m, 2H), 2.68 (quint, J = 8.0Hz, 1H), 2.55-2.48 (m, 2H), 2.05—2.01 (m, 2H), 1.91-1.87 (m, 2H), 1.81-1.74 (m, 2H), 1.59-1.56 (m, 2H). MS (m/z) $(M+1)^+$ 545.3.
J3		^{1}HNMR (400MHz, CD_3OD) δ 7.60 (d, J = 8.0Hz, 2H), 7.45 (d, J = 8.0H, 1H), 7.34 (t, J = 8.0Hz, 1H), 7.18 (s, 1H), 7.12 (d, J = 8.0Hz, 1H), 7.03 (d, J = 8.0Hz, 1H), 3.82 (t, J = 8.0Hz 2H), 3.68-3.64 (m, 4H), 3.55-3.47 (m, 4H), 3.10-3.04 (m, 2H), 2.18 (dt, J = 4.0 and 12.0 Hz, 2H), 1.72 (m, 2H), 1.58-1.48 (m, 3H), 0.96 (t, J = 4.0Hz, 6H). MS (m/z) $(M+1)^+$ 546.3.

Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
J4		^{1}HNMR (400MHz, CD_3OD) δ 7.45 (s, 1H), 7.31-7.26 (m, 3H), 7.06 (s, 1H), 7.02 (d, J = 8.0H, 1H), 6.92 (d, J = 8.0Hz, 1H),3.68 (m, 4H), 3.60 (s, 2H), 3.52 (t, J = 8.0Hz 2H),3.42 (t, J = 8.0Hz, 2H), 3.12-3.08 (m, 2H), 2.12-2.04 (m, 2H), 1.65-1.47 (m, 6H), 1.31 (t, J = 8.0Hz, 2H), 0.97 (d, J = 4.0Hz, 6H). MS (m/z) $(M+1)^+$ 547.2.
J5		^{1}HNMR (400MHz, CD_3OD) δ 7.42 (t, J = 8.0Hz, 1H), 7.33-7.28 (m, 4H), 7.26-7.18 (m, 3H), 3.94 (dt, J = 4.0 and 12.0Hz, 2H), 3.70-3.64 (m, 4H) 3.54 (t, J = 8.0Hz, 2H), 3.45 (t, J = 8.0Hz, 2H), 2.26 (dt, J = 4.0 and 16.0 Hz, 2H), 1.77-1.74 (m, 2H), 1.58-1.45 (m, 3H), 0.97 (d, J = 4.0Hz, 6H). MS (m/z) $(M+1)^+$ 513.2.
J6		^{1}HNMR (400MHz, $CDCl_3$) δ 7.49 (s, 1H), 7.44-7.43 (m, 2H), 7.38 (s, 1H), 7.31-7.29 (m, 1H), 7.23-7.16 (m, 2H), 4.13-4.09 (M, 2H), 3.69 (s, 2H), 3.64-3.60 (m, 2H), 3.51(t, J = 8.0Hz, 2H), 3.35 (m, 2H), 3.16 (t, J = 8.0Hz, 2H), 2.68-2.63 (m, 4H), 1.76-160 (m, 4H), 1.28-1.18 (m, 4H), 0.9-0.87 (m,3H). . MS (m/z) $(M+1)^+$ 573.2.

Transcriptional Assay

[0049] Transfection assays are used to assess the ability of compounds of the invention to modulate the transcriptional activity of the PPARs. Briefly, expression

vectors for chimeric proteins containing the DNA binding domain of yeast GAL4 fused to the ligand-binding domain (LBD) of either PPARδ, PPARα or PPARγ are introduced via transient transfection into mammalian cells, together with a reporter plasmid where the luciferase gene is under the control of a GAL4 binding site. Upon exposure to a PPAR modulator, PPAR transcriptional activity varies, and this can be monitored by changes in luciferase levels. If transfected cells are exposed to a PPAR agonist, PPAR-dependent transcriptional activity increases and luciferase levels rise.

[0050] 293T human embryonic kidney cells ($8x10^6$) are seeded in a $175cm^2$ flask a day prior to the start of the experiment in 10% FBS, 1% Penicillin/Streptomycin/Fungizome, DMEM Media. The cells are harvested by washing with PBS (30ml) and then dissociating using trypsin (0.05%; 3ml). The trypsin is inactivated by the addition of assay media (DMEM, CA-dextran fetal bovine serum (5%). The cells are spun down and resuspended to 170,000cells/ml. A Transfection mixture of GAL4-PPAR LBD expression plasmid (1μg), UAS-luciferase reporter plasmid (1μg), Fugene (3:1 ratio; 6μL) and serum-free media (200μL) was prepared and incubated for 15-40 minutes at room temperature. Transfection mixtures are added to the cells to give 0.16M cells/mL, and cells (50μl/well) are then plated into 384 white, solid-bottom, TC-treated plates. The cells are further incubated at 37°C, 5.0% CO_2 for 5-7 hours. A 12-point series of dilutions (3 fold serial dilutions) are prepared for each test compound in DMSO with a starting compound concentration of 10μM. Test compound (500nl) is added to each well of cells in the assay plate and the cells are incubated at 37°C, 5.0% CO_2 for 18-24 hours. The cell lysis/luciferase assay buffer, Bright-Glo™ (25%; 25μl; Promega), is added to each well. After a further incubation for 5 minutes at room temperature, the luciferase activity is measured.

[0051] Raw luminescence values are normalized by dividing them by the value of the DMSO control present on each plate. Normalized data is analyzed and dose-response curves are fitted using Prizm graph fitting program. EC50 is defined as the concentration at which the compound elicits a response that is half way between the maximum and minimum values. Relative efficacy (or percent efficacy) is calculated by comparison of

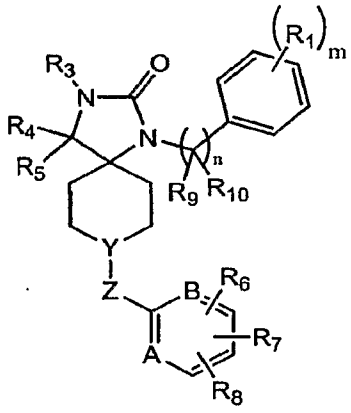
the response elicited by the compound with the maximum value obtained for a reference PPAR modulator.

[0052] Compounds of Formula I, in free form or in pharmaceutically acceptable salt form, exhibit valuable pharmacological properties, for example, as indicated by the *in vitro* tests described in this application. Compounds of the invention preferably have an EC50 for PPARδ and/or PPARα and/or PPARγ, of less than 5μM, more preferably less than 1μM, more preferably less than 500nm, more preferably less than 100nM. Compounds of the invention preferably have an EC50 for PPARδ that is less than or equal to PPARα which in turn has an EC50 that is at least 10-fold less than PPARγ.

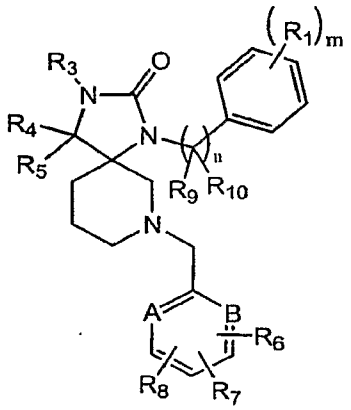
[0053] It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the appended claims. All publications, patents, and patent applications cited herein are hereby incorporated by reference for all purposes.

WE CLAIM:

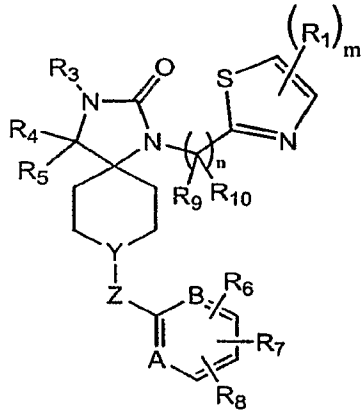
1. A compound selected from Ia, Ib and Ic:



Ia



Ib



Ic

in which:

n is selected from 1, 2, 3, 4 and 5;

m is selected from 1, 2, 3, 4 and 5; each

R_1 is independently selected from hydrogen, halo, C_{1-6}alkyl, halo-substituted C_{1-6}alkyl, C_{1-6}alkoxy and halo-substituted-C_{1-6}alkoxy;

R_3 is selected from C_{1-8}alkyl, C_{2-8}alkenyl, halo-substituted-C_{1-6}alkyl, halo-substituted-C_{2-6}alkenyl, $-X_1C(O)R_2$, C_{5-10}heteroaryl-C_{0-4}alkyl and C_{3-12}cycloalkyl-C_{0-4}alkyl; wherein R_2 is selected from hydrogen and C_{1-6}alkyl;

R_4 is selected from hydrogen and C_{1-6}alkyl;

R_5 is selected from hydrogen and C_{1-6}alkyl; or R_4 and R_5 together with the carbon atom to which R_4 and R_5 are both attached form carbonyl;

Y is selected from N and CH;

Z is selected from a bond, $-S(O)_{0-2}-$ and $-CR_{11}R_{12}-$; wherein R_{11} and R_{12} are independently selected from hydrogen and C_{1-6}alkyl;

A and B are independently selected from CH and N;

R_6 and R_7 are independently selected from hydrogen, halo, C_{1-6}alkyl, halo-substituted C_{1-6}alkyl, C_{1-6}alkoxy and halo-substituted-C_{1-6}alkoxy;

R_8 is selected from $-X_2CO_2R_{13}$, $-X_2CR_{14}R_{15}X_3CO_2R_{13}$, $-X_2SCR_{14}R_{15}X_3CO_2R_{13}$ and $-X_2OCR_{14}R_{15}X_3CO_2R_{13}$; wherein X_2 and X_3 are independently selected from a bond and C_{1-4}alkylene; and R_{14} and R_{15} are independently selected from hydrogen, C_{1-4}alkyl and C_{1-4}alkoxy; or R_{14} and R_{15} together with the carbon atom to which R_{14} and R_{15} are attached form C_{3-12}cycloalkyl; and R_{13} is selected from hydrogen and C_{1-6}alkyl;

R_9 and R_{10} are independently selected from hydrogen, C_{1-6}alkyl and $-OR_{16}$; wherein R_{16} is selected from hydrogen and C_{1-6}alkyl; and the pharmaceutically acceptable salts, hydrates, solvates, isomers and prodrugs thereof.

2. The compound of claim 1 in which:

n is selected from 1, 2, 3 and 4;

m is selected from 1, 2 and 3; each

R_1 is independently selected from hydrogen, halo, C_{1-6}alkyl, halo-substituted C_{1-6}alkyl, C_{1-6}alkoxy and halo-substituted-C_{1-6}alkoxy;

R_3 is selected from C_{1-8}alkyl, C_{2-8}alkenyl, halo-substituted-C_{1-6}alkyl, halo-substituted-C_{2-6}alkenyl, $-X_1C(O)R_2$, C_{5-10}heteroaryl-C_{0-4}alkyl and C_{3-12}cycloalkyl-C_{0-4}alkyl; wherein R_2 is selected from hydrogen and C_{1-6}alkyl;

R_4 is selected from hydrogen and C_{1-6}alkyl;

R_5 is selected from hydrogen and C_{1-6}alkyl; or R_4 and R_5 together with the carbon atom to which R_4 and R_5 are both attached form carbonyl;

Y is selected from N and CH;

Z is selected from a bond, $-S(O)_{0-2}-$ and $-CR_{11}R_{12}-$; wherein R_{11} and R_{12} are independently selected from hydrogen and C_{1-6}alkyl;

A and B are independently selected from CH and N;

R_6 and R_7 are independently selected from hydrogen, halo, C_{1-6}alkyl, halo-substituted C_{1-6}alkyl and C_{1-6}alkoxy;

R_8 is selected from $-X_2CO_2R_{13}$, $-X_2CR_{14}R_{15}X_3CO_2R_{13}$ and $-X_2OCR_{14}R_{15}X_3CO_2R_{13}$; wherein X_2 and X_3 are independently selected from a bond and C_{1-}

$_4$alkylene; and R_{14} and R_{15} are independently selected from hydrogen and C_{1-4}alkyl; R_{13} is selected from hydrogen and C_{1-6}alkyl; and

R_9 and R_{10} are independently selected from hydrogen, C_{1-6}alkyl and $-OR_{16}$; wherein R_{16} is selected from hydrogen and C_{1-6}alkyl.

3. The compound of claim 2 in which: R_1 is independently selected from hydrogen, halo, methoxy, trifluormethoxy and trifluoromethyl; R_3 is selected from isobutyl, cyclopropyl-methyl, cyclobutyl-methyl, isopentyl, butyl, cyclopentyl-methyl, 3-methyl-but-2-enyl, pentyl, 2,2-dimethyl-propyl, 4-fluoro-butyl, 2-ethyl-butyl, 2-methyl-pentyl, cyclohexyl-methyl, 3,3-dimethyl-2-oxo-butyl, pyrrolyl-propyl, 3-trifluoromethyl-propyl, cyclohexyl-ethyl, 2-ethyl-hexyl, 2-methyl-butyl, 3,4,4-trifluoro-but-3-enyl and 3,3-dimethyl-butyl; R_4 and R_5 are each hydrogen or R_4 and R_5 together with the carbon atom to which R_4 and R_5 are both attached form carbonyl; and Z is selected from a bond, $-S(O)_2-$ and $-CH_2-$.

4. The compound of claim 3 in which: R_8 is selected from $-CH_2C(O)OH$, $-CH(CH_2)C(O)OH$, $-OC(CH_2)_2C(O)OH$, $-(CH_2)_2C(O)OH$ and $-OCH_2C(O)OH$; and R_9 and R_{10} are independently selected from hydrogen, halo, methyl, methoxy and trifluoromethyl.

5. The compound of claim 1 selected from: (3-{3-Isobutyl-1-[2-(4-methoxy-phenyl)-ethyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-ylmethyl}-phenyl)-acetic acid; (3-{3-Isobutyl-1-[2-(4-methoxy-phenyl)-ethyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]decane-8-sulfonyl}-4-methyl-phenyl)-acetic acid; (3-{3-Isobutyl-1-[2-(4-methoxy-phenyl)-ethyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl}-phenyl)-acetic acid; 2-(4-{3-Isobutyl-1-[2-(4-methoxy-phenyl)-ethyl]-2,4-dioxo-1,3-diaza-spiro[4.5]dec-7-ylmethyl}-phenyl)-propionic acid; (3-{3-Cyclopropylmethyl-1-[2-(4-methoxy-phenyl)-ethyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl}-phenyl)-acetic acid; {3-[3-Isobutyl-2,4-dioxo-1-(4-trifluoromethoxy-benzyl)-1,3,8-triaza-spiro[4.5]dec-8-yl]-phenyl}-acetic acid; 2-(2-{3-Isobutyl-1-[2-(4-methoxy-phenyl)-ethyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl}-pyrimidin-4-yloxy)-2-methyl-propionic acid; 2-(3-{3-Cyclobutylmethyl-1-[2-(2,4-dichloro-phenyl)-ethyl]-2,4-dioxo-1,3-diaza-spiro[4.5]dec-8-yl}-phenoxy)-2-methyl-propionic acid; {3-[3-Cyclopropylmethyl-2,4-dioxo-1-(4-trifluoromethoxy-benzyl)-1,3,8-triaza-spiro[4.5]dec-8-

yl]-phenyl}-acetic acid; (3-{3-Cyclobutylmethyl-2,4-dioxo-1-[2-(4-trifluoromethyl-phenyl)-ethyl]-1,3,8-triaza-spiro[4.5]dec-8-yl}-phenyl)-acetic acid; (3-{3-Cyclobutylmethyl-1-[4-(4-methoxy-phenyl)-butyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl}-phenyl)-acetic acid; 3-{3-Isobutyl-1-[2-(4-methoxy-phenyl)-ethyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-ylmethyl}-benzoic acid; (2-{3-Isobutyl-1-[2-(4-methoxy-phenyl)-ethyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-ylmethyl}-phenyl)-acetic acid; (3-{3-Isobutyl-1-[2-(4-methoxy-phenyl)-ethyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]decane-8-sulfonyl}-4-methoxy-phenyl)-acetic acid; 3-(3-{3-Isobutyl-1-[2-(4-methoxy-phenyl)-ethyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl}-phenyl)-propionic acid; (3-{3-Isobutyl-1-[2-(4-methoxy-phenyl)-ethyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl}-phenoxy)-acetic acid; 2-(3-{3-Isobutyl-1-[2-(4-methoxy-phenyl)-ethyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl}-phenoxy)-2-methyl-propionic acid; (5-{3-Isobutyl-1-[2-(4-methoxy-phenyl)-ethyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl}-2-methyl-phenyl)-acetic acid; (3-{3-Isobutyl-1-[2-(4-methoxy-phenyl)-ethyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl}-5-methyl-phenyl)-acetic acid; (2-Fluoro-5-{3-isobutyl-1-[2-(4-methoxy-phenyl)-ethyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl}-phenyl)-acetic acid; (5-{3-Isobutyl-1-[2-(4-methoxy-phenyl)-ethyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl}-2-trifluoromethyl-phenyl)-acetic acid; (5-{3-Isobutyl-1-[2-(4-methoxy-phenyl)-ethyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl}-2-methoxy-phenyl)-acetic acid; 2-(3-{3-Isobutyl-1-[2-(4-methoxy-phenyl)-ethyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl}-phenyl)-2-methyl-propionic acid; (5-{3-Isobutyl-1-[2-(4-methoxy-phenyl)-ethyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl}-2-methyl-phenoxy)-acetic acid; (2-Chloro-5-{3-isobutyl-1-[2-(4-methoxy-phenyl)-ethyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl}-phenoxy)-acetic acid; 2-(5-{3-Isobutyl-1-[2-(4-methoxy-phenyl)-ethyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl}-2-methyl-phenoxy)-2-methyl-propionic acid; 2-(2-Chloro-5-{3-isobutyl-1-[2-(4-methoxy-phenyl)-ethyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl}-phenoxy)-2-methyl-propionic acid; 2-(2,3-Difluoro-5-{3-isobutyl-1-[2-(4-methoxy-phenyl)-ethyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl}-phenoxy)-2-methyl-propionic acid; (3-{3-Isobutyl-1-[2-(4-methoxy-phenyl)-ethyl]-2-oxo-1,3,8-triaza-spiro[4.5]dec-8-yl}-phenyl)-acetic acid; (6-{3-Isobutyl-1-[2-(4-methoxy-phenyl)-ethyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl}-pyridin-2-yl)-acetic acid; (2-{3-Isobutyl-1-[2-(4-methoxy-phenyl)-ethyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl}-pyridin-4-yl)-acetic acid; (5-{3-Cyclobutylmethyl-1-[2-(2,4-dichloro-

phenyl)-ethyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl}-2-methyl-phenyl)-acetic acid; 2-(5-{3-Cyclobutylmethyl-1-[2-(2,4-dichloro-phenyl)-ethyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl}-2-methyl-phenoxy)-2-methyl-propionic acid; (2-Chloro-5-{3-cyclobutylmethyl-1-[2-(2,4-dichloro-phenyl)-ethyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl}-phenoxy)-acetic acid; 2-(2-Chloro-5-{3-cyclobutylmethyl-1-[2-(2,4-dichloro-phenyl)-ethyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl}-phenoxy)-2-methyl-propionic acid; (6-{3-Cyclobutylmethyl-1-[2-(2,4-dichloro-phenyl)-ethyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl}-pyridin-2-yl)-acetic acid; (4-{3-Isobutyl-1-[2-(4-methoxy-phenyl)-ethyl]-2,4-dioxo-1,3,7-triaza-spiro[4.5]dec-7-ylmethyl}-phenoxy)-acetic acid; (3-{3-Cyclobutylmethyl-1-[2-(4-methoxy-phenyl)-ethyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl}-phenyl)-acetic acid; {3-[1-[2-(4-Methoxy-phenyl)-ethyl]-3-(3-methyl-butyl)-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl]-phenyl}-acetic acid; (3-{3-Butyl-1-[2-(4-methoxy-phenyl)-ethyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl}-phenyl)-acetic acid; 2-(4-{3-Isobutyl-1-[2-(4-methoxy-phenyl)-ethyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl}-pyrimidin-2-yloxy)-2-methyl-propionic acid; 2-(6-{3-Isobutyl-1-[2-(4-methoxy-phenyl)-ethyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl}-pyrimidin-4-yloxy)-2-methyl-propionic acid; 2-(4-{3-Cyclobutylmethyl-1-[2-(2,4-dichloro-phenyl)-ethyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl}-pyrimidin-2-yloxy)-2-methyl-propionic acid; 2-(2-{3-Cyclobutylmethyl-1-[2-(2,4-dichloro-phenyl)-ethyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl}-pyrimidin-4-yloxy)-2-methyl-propionic acid; 2-(6-{3-Cyclobutylmethyl-1-[2-(2,4-dichloro-phenyl)-ethyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl}-pyrimidin-4-yloxy)-2-methyl-propionic acid; {3-[3-Cyclobutylmethyl-2,4-dioxo-1-(4-trifluoromethoxy-benzyl)-1,3,8-triaza-spiro[4.5]dec-8-yl]-phenyl}-acetic acid; {3-[3-Cyclobutylmethyl-2,4-dioxo-1-(4-trifluoromethyl-benzyl)-1,3,8-triaza-spiro[4.5]dec-8-yl]-phenyl}-acetic acid; {3-[3-Cyclopentylmethyl-2,4-dioxo-1-(4-trifluoromethyl-benzyl)-1,3,8-triaza-spiro[4.5]dec-8-yl]-phenyl}-acetic acid; {3-[3-Cyclopentylmethyl-2,4-dioxo-1-(4-trifluoromethoxy-benzyl)-1,3,8-triaza-spiro[4.5]dec-8-yl]-phenyl}-acetic acid; {3-[1-(2,4-Bis-trifluoromethyl-benzyl)-3-cyclopentylmethyl-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl]-phenyl}-acetic acid; {3-[3-Cyclobutylmethyl-2,4-dioxo-1-(3-trifluoromethoxy-benzyl)-1,3,8-triaza-spiro[4.5]dec-8-yl]-phenyl}-acetic acid; (3-{3-Cyclobutylmethyl-2,4-dioxo-1-[4-(4-trifluoromethyl-phenyl)-thiazol-2-ylmethyl]-1,3,8-triaza-spiro[4.5]dec-8-yl}-phenyl)-acetic acid; (3-{3-Cyclopropylmethyl-2,4-dioxo-1-[4-(4-trifluoromethyl-phenyl)-thiazol-2-ylmethyl]-1,3,8-

triaza-spiro[4.5]dec-8-yl}-phenyl)-acetic acid; {3-[3-(3-Methyl-but-2-enyl)-2,4-dioxo-1-(4-trifluoromethoxy-benzyl)-1,3,8-triaza-spiro[4.5]dec-8-yl]-phenyl}-acetic acid; {3-[1-[2-(4-Bromo-phenyl)-2-hydroxy-ethyl]-3-(3-methyl-butyl)-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl]-phenyl}-acetic acid; {3-[1-[2-(4-Chloro-phenyl)-2-hydroxy-ethyl]-3-(3-methyl-butyl)-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl]-phenyl}-acetic acid; {3-[2,4-Dioxo-3-pentyl-1-(4-trifluoromethoxy-benzyl)-1,3,8-triaza-spiro[4.5]dec-8-yl]-phenyl}-acetic acid; {3-[3-(2,2-Dimethyl-propyl)-2,4-dioxo-1-(4-trifluoromethoxy-benzyl)-1,3,8-triaza-spiro[4.5]dec-8-yl]-phenyl}-acetic acid; {3-[3-(2-Ethyl-butyl)-2,4-dioxo-1-(4-trifluoromethoxy-benzyl)-1,3,8-triaza-spiro[4.5]dec-8-yl]-phenyl}-acetic acid; {3-[3-(4-Fluoro-butyl)-2,4-dioxo-1-(4-trifluoromethoxy-benzyl)-1,3,8-triaza-spiro[4.5]dec-8-yl]-phenyl}-acetic acid; {3-[3-(4-Methyl-pentyl)-2,4-dioxo-1-(4-trifluoromethoxy-benzyl)-1,3,8-triaza-spiro[4.5]dec-8-yl]-phenyl}-acetic acid; {3-[3-Cyclohexylmethyl-2,4-dioxo-1-(4-trifluoromethoxy-benzyl)-1,3,8-triaza-spiro[4.5]dec-8-yl]-phenyl}-acetic acid; {3-[2,4-Dioxo-3-(3-pyrrol-1-yl-propyl)-1-(4-trifluoromethoxy-benzyl)-1,3,8-triaza-spiro[4.5]dec-8-yl]-phenyl}-acetic acid; {3-[3-(3,3-Dimethyl-2-oxo-butyl)-2,4-dioxo-1-(4-trifluoromethoxy-benzyl)-1,3,8-triaza-spiro[4.5]dec-8-yl]-phenyl}-acetic acid; {3-[2,4-Dioxo-3-(4,4,4-trifluoro-butyl)-1-(4-trifluoromethoxy-benzyl)-1,3,8-triaza-spiro[4.5]dec-8-yl]-phenyl}-acetic acid; {3-[3-(2-Cyclohexyl-ethyl)-2,4-dioxo-1-(4-trifluoromethoxy-benzyl)-1,3,8-triaza-spiro[4.5]dec-8-yl]-phenyl}-acetic acid; {3-[3-(2-Ethyl-hexyl)-2,4-dioxo-1-(4-trifluoromethoxy-benzyl)-1,3,8-triaza-spiro[4.5]dec-8-yl]-phenyl}-acetic acid; {3-[3-(2-Methyl-butyl)-2,4-dioxo-1-(4-trifluoromethoxy-benzyl)-1,3,8-triaza-spiro[4.5]dec-8-yl]-phenyl}-acetic acid; {3-[2,4-Dioxo-3-(3,4,4-trifluoro-but-3-enyl)-1-(4-trifluoromethoxy-benzyl)-1,3,8-triaza-spiro[4.5]dec-8-yl]-phenyl}-acetic acid; {3-[3-(3,3-Dimethyl-butyl)-2,4-dioxo-1-(4-trifluoromethoxy-benzyl)-1,3,8-triaza-spiro[4.5]dec-8-yl]-phenyl}-acetic acid; {3-[1-(2,4-Dichloro-5-fluoro-benzyl)-3-(3,3-dimethyl-butyl)-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl]-phenyl}-acetic acid; {3-[1-(2,4-Dichloro-5-fluoro-benzyl)-3-(4-fluoro-butyl)-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl]-phenyl}-acetic acid; (3-{3-Cyclobutylmethyl-1-[2-(2,4-dichloro-phenyl)-ethyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl}-phenyl)-acetic acid; (3-{3-Cyclopentylmethyl-2,4-dioxo-1-[2-(4-trifluoromethyl-phenyl)-ethyl]-1,3,8-triaza-spiro[4.5]dec-8-yl}-phenyl)-acetic acid; (3-{3-Cyclopentylmethyl-1-[2-(2,4-dichloro-phenyl)-ethyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl}-phenyl)-acetic acid; (3-{3-

Cyclohexylmethyl-1-[2-(2,4-dichloro-phenyl)-ethyl]-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl}-phenyl)-acetic acid; and (3-{1-[2-(4-Chloro-phenyl)-ethyl]-3-cyclopentylmethyl-2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl}-phenyl)-acetic acid.

6. A method for treating a disease or disorder in an animal in which modulation of PPAR activity can prevent, inhibit or ameliorate the pathology and/or symptomology of the disease, which method comprises administering to the animal a therapeutically effective amount of a compound of Claim 1.

7. The method of claim 6 in which the PPAR activity is at least one PPAR selected from PPARα, PPARδ and PPARγ.

8. The method of claim 7 in which the PPAR activity is both PPARα and PPARδ.

9. The method of claim 6 in which the disease or disorder is selected from the treatment of prophylaxis, dyslipidemia, hyperlipidemia, hypercholesteremia, atherosclerosis, atherogenesis, hypertriglyceridemia, heart failure, myocardial infarction, vascular diseases, cardiovascular diseases, hypertension, obesity, cachexia, inflammation, arthritis, cancer, anorexia, anorexia nervosa, bulimia, Alzheimer's disease, skin disorders, respiratory diseases, ophthalmic disorders, irritable bowel diseases, ulcerative colitis, Crohn's disease, type-1 diabetes, type-2 diabetes and Syndrome X.

10. The method of claim 6 in which the disease or disorder is selected from HIV wasting syndrome, long term critical illness, decreased muscle mass and/or muscle strength, decreased lean body mass, maintenance of muscle strength and function in the elderly, diminished muscle endurance and muscle function, and frailty in the elderly.

11. The use of a compound according to any of claims 1 to 5 in the manufacture of a medicament for treating a disease in an animal in which PPAR activity contributes to the pathology and/or symptomology of the disease.

12. The use of claim 11 in which the PPAR activity is at least one PPAR selected from PPARα, PPARδ and PPARγ.

13. The use of claim 12 in which the PPAR activity is both PPARα and PPARδ.

14. A pharmaceutical composition comprising a therapeutically effective amount of a compound of any of claim 1 to 5 in combination with one or more pharmaceutically acceptable excipients.

15. A pharmaceutical combination, especially a pharmaceutical composition, comprising: 1) a compound of any of claims 1 to 5 or a pharmaceutical acceptable salt thereof; and 2) at least one active ingredient selected from:
a) anti-diabetic agents such as insulin, insulin derivatives and mimetics; insulin secretagogues such as the sulfonylureas, e.g., Glipizide, glyburide and Amaryl; insulinotropic sulfonylurea receptor ligands such as meglitinides, e.g., nateglinide and repaglinide; insulin sensitizer such as protein tyrosine phosphatase-1B (PTP-1B) inhibitors such as PTP-112; GSK3 (glycogen synthase kinase-3) inhibitors such as SB-517955, SB-4195052, SB-216763, NN-57-05441 and NN-57-05445; RXR ligands such as GW-0791 and AGN-194204; sodium-dependent glucose co-transporter inhibitors such as T-1095; glycogen phosphorylase A inhibitors such as BAY R3401; biguanides such as metformin; alpha-glucosidase inhibitors such as acarbose; GLP-1 (glucagon like peptide-1), GLP-1 analogs such as Exendin-4 and GLP-1 mimetics; dipeptidyl peptidase IV inhibitors such as DPP728, vildagliptin, MK-0431, saxagliptin, GSK23A ; an AGE breaker; a thiazolidone derivative (glitazone) such as pioglitazone, rosiglitazone, or (R)-1-{4-[5-methyl-2-(4-trifluoromethyl-phenyl)-oxazol-4-ylmethoxy]-benzenesulfonyl}-2,3-dihydro-1H-indole-2-carboxylic acid, a non-glitazone type PPARγ agonist e.g. GI-262570;
b) hypolipidemic agents such as 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase inhibitors, e.g., lovastatin, pitavastatin, simvastatin, pravastatin, cerivastatin, mevastatin, velostatin, fluvastatin, dalvastatin, atorvastatin, rosuvastatin and rivastatin; squalene synthase inhibitors; FXR (farnesoid X receptor) and LXR (liver X receptor) ligands; cholestyramine; fibrates; nicotinic acid and aspirin;

c) an anti-obesity agent or appetite regulating agent such as phentermine, leptin, bromocriptine, dexamphetamine, amphetamine, fenfluramine, dexfenfluramine, sibutramine, orlistat, dexfenfluramine, mazindol, phentermine, phendimetrazine, diethylpropion, fluoxetine, bupropion, topiramate, diethylpropion, benzphetamine, phenylpropanolamine or ecopipam, ephedrine, pseudoephedrine or cannabinoid receptor antagonists;
d) anti-hypertensive agents, e.g., loop diuretics such as ethacrynic acid, furosemide and torsemide; diuretics such as thiazide derivatives, chlorithiazide, hydrochlorothiazide, amiloride; angiotensin converting enzyme (ACE) inhibitors such as benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perinodopril, quinapril, ramipril and trandolapril; inhibitors of the Na-K-ATPase membrane pump such as digoxin; neutralendopeptidase (NEP) inhibitors e.g. thiorphan, terteo-thiorphan, SQ29072; ECE inhibitors e.g. SLV306; ACE/NEP inhibitors such as omapatrilat, sampatrilat and fasidotril; angiotensin II antagonists such as candesartan, eprosartan, irbesartan, losartan, telmisartan and valsartan, in particular valsartan; renin inhibitors such as aliskiren, terlakiren, ditekiren, RO 66-1132, RO-66-1168; β-adrenergic receptor blockers such as acebutolol, atenolol, betaxolol, bisoprolol, metoprolol, nadolol, propranolol, sotalol and timolol; inotropic agents such as digoxin, dobutamine and milrinone; calcium channel blockers such as amlodipine, bepridil, diltiazem, felodipine, nicardipine, nimodipine, nifedipine, nisoldipine and verapamil; aldosterone receptor antagonists; and aldosterone synthase inhibitors;
e) a HDL increasing compound;
f) a cholesterol absorption modulator such as Zetia® and KT6-971;
g) Apo-A1 analogues and mimetics;
h) thrombin inhibitors such as Ximelagatran;
i) aldosterone inhibitors such as anastrazole, fadrazole, eplerenone;
j) Inhibitors of platelet aggregation such as aspirin, clopidogrel bisulfate;
k) estrogen, testosterone, a selective estrogen receptor modulator, a selective androgen receptor modulator;
l) a chemotherapeutic agent such as aromatase inhibitors e.g. femara, anti-estrogens, topoisomerase I inhibitors, topoisomerase II inhibitors, microtubule active agents, alkylating agents, antineoplastic antimetabolites, platin compounds, compounds decreasing the protein kinase activity such as a PDGF receptor tyrosine kinase inhibitor preferably Imatinib or 4-

Methyl-N-[3-(4-methyl-imidazol-1-yl)-5-trifluoromethyl-phenyl]-3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-benzamide; and

m) an agent interacting with a 5-HT_3 receptor and/or an agent interacting with 5-HT_4 receptor such as tegaserod, tegaserod hydrogen maleate, cisapride, cilansetron;

or, in each case a pharmaceutically acceptable salt thereof; and optionally a pharmaceutically acceptable carrier.

16. A pharmaceutical composition according to claim 14 or a combination according to claim 15, for the treatment or prevention of dyslipidemia, hyperlipidemia, hypercholesteremia, atherosclerosis, hypertriglyceridemia, heart failure, myocardial infarction, vascular diseases, cardiovascular diseases, hypertension, obesity, inflammation, arthritis, cancer, Alzheimer's disease, skin disorders, respiratory diseases, ophthalmic disorders, inflammatory bowel diseases, IBDs (irritable bowel disease), ulcerative colitis, Crohn's disease, conditions in which impaired glucose tolerance, hyperglycemia and insulin resistance are implicated, such as type-1 and type-2 diabetes, Impaired Glucose Metabolism (IGM), Impaired Glucose Tolerance (IGT), Impaired Fasting Glucose (IFG), and Syndrome-X.

17. A compound according to any of claims 1 to 5, or a pharmaceutical composition according to claim 10 or a combination according to claim 11, for use as a medicament.

18. Use of a compound according to any of claims 1 to 5, or a pharmaceutical composition according to claim 14 or a combination according to claim 15, for the manufacture of a medicament for the treatment or prevention of dyslipidemia, hyperlipidemia, hypercholesteremia, atherosclerosis, hypertriglyceridemia, heart failure, myocardial infarction, vascular diseases, cardiovascular diseases, hypertension, obesity, inflammation, arthritis, cancer, Alzheimer's disease, skin disorders, respiratory diseases, ophthalmic disorders, inflammatory bowel diseases, IBDs (irritable bowel disease), ulcerative colitis, Crohn's disease, conditions in which impaired glucose tolerance, hyperglycemia and insulin resistance are implicated, such as type-1 and type-2 diabetes,

Impaired Glucose Metabolism (IGM), Impaired Glucose Tolerance (IGT), Impaired Fasting Glucose (IFG), and Syndrome-X.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2007/002315

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D471/10 A61K31/435 A61P3/00 A61P9/00 A61P11/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 1 619 193 A (ONO PHARMACEUTICAL CO [JP]) 25 January 2006 (2006-01-25) paragraph [0031] - paragraph [0037]; claims 1,11	1-5
A	WINTERS, GIORGIO ET AL: "Synthesis of spirohydantoins from basic heterocyclic ketones" FARMACO, EDIZIONE SCIENTIFICA , 25(9), 681-93 CODEN: FRPSAX; ISSN: 0430-0920, 1970, XP009083295 page 685; example 37	1-5

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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

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

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

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

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Date of the actual completion of the international search	Date of mailing of the international search report
8 May 2007	16/05/2007

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Gettins, Marc

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2007/002315

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

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

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

Although claims 6-10 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

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

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

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

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

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

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

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

Remark on Protest

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

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2007/002315

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 1619193 A	25-01-2006	WO 2004092169 A1	28-10-2004
		US 2006229301 A1	12-10-2006