(19) DANMARK

(10) DK/EP 3074008 T3

(12) Oversættelse af europæisk patentskrift

Patent- og Varemærkestyrelsen

(51) Int.Cl.: *A 61 K 31/401 (2006.01)* *A 61 P 29/00 (2006.01)*

(45) Oversættelsen bekendtgjort den: **2019-10-21**

(80) Dato for Den Europæiske Patentmyndigheds bekendtgørelse om meddelelse af patentet: **2019-09-04**

(86) Europæisk ansøgning nr.: **14805564.3**

(86) Europæisk indleveringsdag: **2014-11-27**

(87) Den europæiske ansøgnings publiceringsdag: **2016-10-05**

(86) International ansøgning nr.: **EP2014075768**

(87) Internationalt publikationsnr.: **WO2015078949**

(30) Prioritet: **2013-11-27 EP 13194730**

(84) Designerede stater: **AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT RO RS SE SI SK SM TR**

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(54) Benævnelse: **FORBINDELSER, FARMACEUTISK SAMMENSÆTNING OG FREMGANGSMÅDER TIL ANVENDELSE I BEHANDLING AF INFLAMMATION**

(56) Fremdragne publikationer:
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WO-A2-2011/151436
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DESCRIPTION

FIELD OF THE INVENTION

[0001] The present invention concerns methods and compounds useful in treating and/or preventing inflammation, especially in inflammatory diseases. More specifically, the invention relates to the use of selective GPR43 agonists or partial agonist and their pharmacologically acceptable salts and solvates thereof, previously described in international patent application WO 2011/073376 in the name of the present Applicant, for the preparation of a medicament for the treatment and/or prevention of inflammatory diseases.

BACKGROUND OF INVENTION

[0002] The present invention comprises compounds useful in treating and/or preventing diseases, such as Tumor Necrosis Factor α (TNF-α), IL-1β, IL-6 and/or IL-8 mediated diseases and other resulting diseases. In particular, the compounds of the invention are useful for the treatment and/or prevention of diseases or conditions involving inflammation.

[0003] TNF-α is upstream in the cytokine cascade of inflammation. As a result, elevated levels of TNF-α may lead to elevated levels of other inflammatory and proinflammatory cytokines, such as IL-1, IL-6 and IL-8.

[0004] TNF-α and Interleukin-1 (IL-1) are pro-inflammatory cytokines secreted by a variety of cells, including monocytes and macrophages, in response to many inflammatory stimuli (e.g. lipopolysaccharide-LPS) or external cellular stress (e.g., osmotic shock and peroxide).

[0005] Elevated levels of TNF-α and/or IL-1 over basal levels have been implicated in mediating or exacerbating a number of disease states including rheumatoid arthritis; inflammatory bowel disease (IBD) including but not limited to Crohn's disease, ulcerative colitis and colitis; Pagets disease; osteoporosis; multiple myeloma; uveitis; acute and chronic myelogenous leukemia; pancreatic β cell destruction; rheumatoid spondylitis; osteoarthritis; gouty arthritis and other arthritis conditions; gout; adult respiratory distress syndrome (ARDS); chronic pulmonary inflammatory diseases; silicosis; pulmonary sarcoidosis; psoriasis; rhinitis; anaphylaxis; contact dermatitis; pancreatitis; asthma; muscle degeneration; cachexia such as cachexia secondary to infection or malignancy, cachexia secondary to acquired immune deficiency syndrome; Reiter's syndrome; type I diabetes; bone resorption disease; graft vs. host reaction; ischemia reperfusion injury; brain trauma; multiple sclerosis; cerebral malaria; sepsis; septic shock; toxic shock syndrome; endotoxic shock; gram negative sepsis; fever and myalgias due to infection such as influenza; pyrosis.

[0006] TNF-α and IL-1 appear to play a role in pancreatic β cell destruction and diabetes.

Pancreatic β cells produce insulin which helps mediate blood glucose homeostasis. Deterioration of pancreatic β cell functional abnormalities may occur in patients with type II diabetes.

[0007] Administration of TNF-α into the rat cortex has been reported to result in significant neutrophil accumulation in capillaries and adherence in small blood vessels. TNF-α promotes the release of other cytokines (IL-1β, IL-6) and also chemokines, which promote neutrophil infiltration into the infarct area (Fleurstein, Stroke 25, 1481 (1994).

[0008] In rheumatoid arthritis models in animals, multiple intra-articular injections of IL-1 have led to an acute and destructive form of arthritis (Chandrasekhar et al., Clinical Immunol Immunopathol. 55, 382 (1990)). In studies using cultured rheumatoid synovial cells, IL-1 is a more potent inducer of stromelysin than TNF-α (Firestein, Am. J. Pathol. 140, 1309 (1992)). At sites of local injection, neutrophil, lymphocyte, and monocyte emigration has been observed. The emigration is attributed to the induction of chemokines (e.g., IL-8), and the up-regulation of adhesion molecules (Dinarello, Eur. Cytokines Netw. 5, 517-531 (1994)).

[0009] IL-8 has been implicated in exacerbating and/or causing many disease states in which massive neutrophil infiltration into sites of inflammation or injury (e.g., ischemia) is mediated by the chemotactic nature of IL-8, including, but not limited to, the following: asthma, inflammatory bowel disease (IBD), psoriasis, adult respiratory distress syndrome, cardiac and renal reperfusion injury, thrombosis and glomerulonephritis. In addition to the chemotaxis effect on neutrophils, IL-8 also has the ability to active neutrophils. Thus, reduction in IL-8 levels may lead to diminished neutrophil infiltration.

[0010] TNF-α and IL-1 affect a wide variety of cell and tissues and these cytokines as well as other leukocytes derived cytokine, such as IL-6 and IL-8, are important and critical inflammatory mediators of a wide variety of diseases states and conditions. The inhibition of these cytokines is of benefit in controlling, reducing and alleviating many of these disease states mediated by these cytokines.

[0011] Several approaches have been taken to block the effect of TNF-α. One approach involves using soluble receptors for TNF-α (e.g. TNFR-55 or TNFR-75), which have demonstrated efficacy in animal models of TNF-α-mediated disease states. A second approach to neutralizing TNF-α using a monoclonal antibody specific to TNF-α, cA2, has demonstrated improvement in swollen joint count in a Phase II human trial of rheumatoid arthritis (Feldmann et al.; Immunological Reviews, pp. 195-223 (1995)). These approaches block the effects of TNF-α and IL-1 by either protein sequestration or receptor antagonism.

[0012] In certain cases, these approaches do not provide effective relief for some sufferers of inflammatory disease and cause adverse effects. Thus, there is currently a need for new anti-inflammatory pharmaceuticals.

[0013] GPR43 (also named FFA2R) belongs to a subfamily of G-Protein-Coupled Receptors

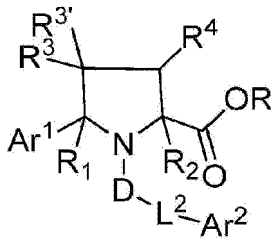
(GPCRs), including GPR40 and GPR41 that have been identified as receptors for free fatty acids (Le Poul et al., J. Biol Chem. 278, 25481-489, 2003; Covington et al., Biochemical Society transaction 34, 770-773, 2006). The 3 family members share 30 to 40% sequences identity with specificity toward different fatty acids carbon chain length, with short chain fatty acids ((SCFAs): six carbons molecules or shorter) activating GPR41 and GPR43 and medium and long chain fatty acids activating GPR40 (Rayasam et al., Expert Opinion on therapeutic targets, 11 661-671, 2007). C2 acetate and C3 propionate are the most potent activators of GPR43.

[0014] GPR43 is strongly expressed in peripheral blood mononuclear cell (PBMC), bone marrow, and polymorphonuclear cells such as neutrophils. The involvement of GPR43 in leukocyte function is supported by the induction of its mRNA during the differentiation and activation of monocytes and neutrophils cells (Le Poul et al., J. Biol. Chem., 2003, 278: 25481-25489; Senga et al., Blood, 2003, 101: 1185-1187). Recent studies have shown that both acetate and propionate decreased LPS-stimulated TNF-α release from neutrophils. In addition propionate dose-dependently suppressed IL-6 mRNA and protein release from colitis mouse colon organ cultures. TNF-α and members of the interleukin family are known to play a key role in the pathogenesis of IBD (Fuss, Curr Drug Targets Inflamm allergy 2003, 2: 101-112; Tedelind et al., World J Gastroenterol 2007, 13(20): 2826-2832). Further, GPR43 has been described to regulate the anti-inflammatory responses by SCFA in various in vivo model such as colitis, rheumatoid arthritis and asthma through a regulation of the neutrophil physiolology. SCFA-mediated GPR43 activation decreased TNF-α and MIP-1α, levels in mouse DSS colitis model, as well as neutrophil chemotactic responsiveness (Maslowski et al, Nature, 2009, 461(7268): 1282-1286). Taken together these results suggest that therapeutic strategies based on GPR43, the major receptor for acetate and propionate for which anti-inflammatory properties have been clearly demonstrated, could be useful in treatment of inflammatory diseases.

[0015] On this basis, GPR43 agonists or partial agonists may be of therapeutic value for the treatment and/or prevention of inflammatory diseases.

SUMMARY

[0016] The invention relates to compounds of general Formula Ia-1b',



or a pharmaceutically acceptable salt or solvate thereof, wherein

R1 and **R2** are H,

D is C=O;

L^2 is single bond;

R is H or linear or branched alkyl, aryl, acyloxyalkyl, dioxolene;

Ar^1 is a 5- to 6-membered aryl or heteroaryl group, 3- to 6-membered cycloalkyl group, or a linear or branched C_3-C_6 alkyl group, each of which being optionally substituted by one or more group(s) selected from halo, cyano, alkyl, haloalkyl, cycloalkyl, aryl, heteroaryl, hydroxyl, alkoxy, haloalkoxy, amino, alkylamino, carboxy, alkoxycarbonyl, alkylcarbonyloxy, alkylcarbonylamino, haloalkylcarbonylamino, carbamoyl, hydroxycarbamoyl, alkylcarbamoyl, carbamoylamino, alkylcarbamoylamino, alkylsulfonyl, haloalkylsulfonyl, sulfamoyl, alkylsulfamoyl, alkylsulfonylamino, haloalkylsulfonylamino, or two substituents form an alkylenedioxy group or a haloalkylenedioxy group, each of said aryl or heteroaryl substituents being optionally substituted by one or more further substituents selected from halo, cyano, alkyl, haloalkyl, hydroxyl, alkoxy, haloalkoxy;

Ar^2 is an aryl or heteroaryl, cycloalkyl, monocyclic heterocyclyl or C_2-C_6 alkyl group, each of which being optionally substituted by one or more group(s) selected from halo, cyano, nitro, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, heteroalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, benzoxazol-2-yl, heteroarylalkyl, hydroxyl, hydroxyalkyl, alkoxy, haloalkoxy, alkoxyalkoxy, cycloalkyloxy, cycloalkylalkyloxy, heterocyclyloxy, aryloxy, heteroaryloxy, alkoxyalkyl, haloalkoxyalkyl, arylalkyloxy, heteroarylalkyloxy, aryloxyalkyl, heteroaryloxyalkyl, amino, alkylamino, arylcarbonyl, carboxy, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, alkylcarbonyloxy, arylcarbonyloxy, heteroarylcarbonyloxy, alkylcarbonylamino, carbamoyl, hydroxycarbamoyl, alkylcarbamoyl, arylcarbamoyl, heteroarylcarbamoyl, carbamoylamino, alkylcarbamoylamino, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, heteroarylsulfamoyl, alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, oxo, or two substituents form an alkylenedioxy group or a haloalkylenedioxy group, or fused to the aryl, heteroaryl or cycloalkyl group may be one or more aryl or heteroaryl moiety, each of said substituents being optionally substituted by one or more further substituents selected from halo, cyano, nitro, alkyl, hydroxyalkyl, haloalkyl, cyanomethyl, cycloalkyl, heterocyclyl, aryl optionally substituted by a chloro or methyl group, heteroaryl, heteroalkyl, hydroxyl, alkoxy, alkoxyalkyl, alkoxyalkoxy, haloalkoxy, cycloalkyloxy, cycloalkylalkyloxy, aryloxy, aralkyloxy optionally substituted by a fluoro group, carboxy, alkoxycarbonyl, alkylcarbonyloxy, amino, alkylamino, alkylcarbonylamino, haloalkylcarbonylamino, carbamoyl, hydroxycarbamoyl, alkylcarbamoyl, carbamoylalkyloxy, carbamoylamino, alkylcarbamoylamino, carbamimidoyl, hydroxycarbamimidoyl, alkylsulfonyl, haloalkylsulfonyl, cycloalkylsulfonyl, heterocyclylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, alkylsulfonylamino, haloalkylsulfonylamino, oxo, and haloalkoxyalkyl;

R^3 is H, cyano, alkyl, hydroxyalkyl, aralkyl, alkoxyalkyl, acetyl, arylsulfonyl;

$R^{3'}$ is H or C_1-C_4 alkyl;

R^4 is H, cyano, C_1-C_4 alkyl;

wherein, unless indicated otherwise:

alkyl group, by itself or as part of another substituent, comprises 1 to 6 carbon atoms,

aryl group has 1 or 2 rings and contains 5 to 12 atoms in the ring,

heterocyclyl group, by itself or as part of another substituent, has 1 or 2 rings and contains 3 to 10 atoms in the ring comprising 1 to 4 heteroatoms selected from N, O and/or S atoms,

heteroaryl, by itself or as part of another substituent, has 1 or 2 rings and

contains 5 to 6 atoms in the ring comprising one or more heteroatoms selected from N, O and/or S atoms,

cycloalkyl group has 1 or 2 cyclic structures and contains from 3 to 10 carbon atoms in the ring;

under the condition that the compound of formula (Ia-1b') is not (2S)-methyl 1-benzoyl-5-mesitylpyrrolidine-2-carboxylate, (2S)-methyl 1-benzoyl-5-(2,4,6-triethylphenyl)pyrrolidine-2-carboxylate, (2S,5S)-1-benzoyl-5-mesitylpyrrolidine-2-carboxylic acid, (2S)-methyl 1-benzoyl-5-propylpyrrolidine-2-carboxylate, (2S,5S)-methyl 1-benzoyl-5-propylpyrrolidine-2-carboxylate, (2S,5R)-methyl 1-benzoyl-5-propylpyrrolidine-2-carboxylate, (2S,5R)-5-(*tert*-butyl)-1-(4-phenylbutanoyl)pyrrolidine-2-carboxylic acid, (2S,5R)-methyl 5-(tert-butyl)-1-(4-phenylbutanoyl)pyrrolidine-2-carboxylate, (2R,5R)-1-(4-bromothiophene-2-carbonyl)-5-phenylpyrrolidine-2-carboxylic acid, (2R,5S)-1-(3-bromo-2,6-dimethoxybenzoyl)-5-phenylpyrrolidine-2-carboxylic acid, 1-[7-(4-tert-butyl-phenoxy)-1-cyclopentylmethyl-isoquinoline-3-carbonyl]-(5R)-phenyl-pyrrolidine-(2S)-carboxylic acid,
and under the condition that:

Ar^2 is not phthalazin-6-yl, pyrido[2,3-d]pyridazin-2-yl, pyrido[2,3-d]pyridazin-3-yl, or pyrazino[2,3-d]pyridazin-2-yl; and/or

R^3 is not a mono substituted hydroxymethyl;

for use in the treatment and/or prevention of inflammation, especially in inflammatory diseases, including, but not limited to, rheumatoid arthritis; inflammatory bowel disease (IBD) including but not limited to Crohn's disease, ulcerative colitis and colitis; Pagets disease; osteoporosis; multiple myeloma; uveitis; acute and chronic myelogenous leukemia; pancreatic β cell destruction; rheumatoid spondylitis; osteoarthritis; gouty arthritis and other arthritis conditions; gout; adult respiratory distress syndrome (ARDS); chronic pulmonary inflammatory diseases; silicosis; pulmonary sarcoidosis; psoriasis; rhinitis; anaphylaxis; contact dermatitis; pancreatitis; asthma; muscle degeneration; cachexia such as cachexia secondary to infection or malignancy, cachexia secondary to acquired immune deficiency syndrome; Reiter's syndrome;

type I diabetes; bone resorption disease; graft vs. host reaction; ischemia reperfusion injury; brain trauma; multiple sclerosis; cerebral malaria; sepsis; septic shock; toxic shock syndrome; endotoxic shock; gram negative sepsis; fever and myalgias due to infection such as influenza; pyrosis.

[0017] In other terms, the invention provides compounds for use in methods for treating and/or preventing in a patient the development of an inflammatory disease, including, but not limited to, rheumatoid arthritis; inflammatory bowel disease (IBD) including but not limited to Crohn's disease, ulcerative colitis and colitis; Pagets disease; osteoporosis; multiple myeloma; uveitis; acute and chronic myelogenous leukemia; pancreatic β cell destruction; rheumatoid spondylitis; osteoarthritis; gouty arthritis and other arthritis conditions; gout; adult respiratory distress syndrome (ARDS); chronic pulmonary inflammatory diseases; silicosis; pulmonary sarcoidosis; psoriasis; rhinitis; anaphylaxis; contact dermatitis; pancreatitis; asthma; muscle degeneration; cachexia such as cachexia secondary to infection or malignancy, cachexia secondary to acquired immune deficiency syndrome; Reiter's syndrome; type I diabetes; bone resorption disease; graft vs. host reaction; ischemia reperfusion injury; brain trauma; multiple sclerosis; cerebral malaria; sepsis; septic shock; toxic shock syndrome; endotoxic shock; gram negative sepsis; fever and myalgias due to infection such as influenza; pyrosis, comprising the administration of a pharmaceutically effective amount of a compound of formula (I) or pharmaceutically acceptable salt and solvate thereof to a patient in need thereof.

[0018] According to one embodiment, the invention relates to the compound of the invention and to pharmaceutically acceptable salts and solvates thereof for use in the treatment and /or prevention of inflammatory diseases. According to one embodiment, the invention relates to the compound of the invention and to pharmaceutically acceptable salts thereof for use in the treatment and /or prevention of inflammatory diseases. According to one embodiment, the invention relates to the compound of the invention and to solvates thereof for use in the treatment and /or prevention of inflammatory diseases.

DETAILED DESCRIPTION

[0019] As noted above, the invention relates to compounds of formula (Ia-1b') as well as pharmaceutically acceptable salts and solvates thereof for use in the treatment and/or prevention of inflammation, especially in inflammatory diseases or in other terms to methods for treating and/or preventing in a patient the development of an inflammatory disease, comprising the administration of a pharmaceutically effective amount of a compound of formula (Ia-1b') or pharmaceutically acceptable salt and solvates thereof to a patient in need thereof.

[0020] Preferred compounds of formula Ia-1b' and pharmaceutically acceptable salts and solvates thereof are those wherein all the following descriptions are independently

R^3 is H, cyano, alkyl, preferably methyl, aralkyl, preferably benzyl, acetyl linked to the ring by bond drawn as a dotted wedge, alkoxyalkyl preferably methoxymethyl, even more preferably

R^3 is H; and/or

R^4 is H, methyl or cyano, more preferably **R^4** is H; and/or

$R^{3'}$ is H or methyl; and/or

Ar^1 is a phenyl, pyridin-2-yl, pyridin-3-yl, cyclohexyl, cyclopentyl, isopropyl, isobutyl or isopentyl group, each of said phenyl, pyridin-2-yl, pyridin-3-yl, cyclohexyl or cyclopentyl group being optionally substituted by one or more group(s) selected from halo preferably bromo, chloro or fluoro, cyano, C_1-C_4 alkyl preferably methyl, C_1-C_4 haloalkyl preferably CF_3 or CHF_2, cycloalkyl, aryl preferably phenyl, heteroaryl, hydroxyl, C_1-C_4 alkoxy preferably methoxy, C_1-C_4 haloalkoxy preferably OCF_3 or $OCHF_2$, C_1-C_4 alkylamino, alkylcarbonylamino, carbamoyl, C_1-C_4 alkylcarbamoyl, carbamoylamino, C_1-C_4 alkylcarbamoylamino, alkylsulfonyl, sulfamoyl, alkylsulfamoyl, alkylsulfonylamino, or two substituents form an alkylenedioxy group or a haloalkylenedioxy group, more preferably **Ar^1** is a phenyl, cyclohexyl, isobutyl or isopentyl group, said phenyl or cyclohexyl, group being optionally substituted by one or more group(s) selected from halo preferably bromo, chloro or fluoro, cyano, C_1-C_4 alkyl preferably methyl, C_1-C_4 haloalkyl preferably CF_3 or CHF_2, cycloalkyl, aryl preferably phenyl, heteroaryl preferably hydroxyl, C_1-C_4 alkoxy preferably methoxy, C_1-C_4 haloalkoxy preferably OCF_3 or $OCHF_2$, C_1-C_4 alkylamino, alkylcarbonylamino, alkylsulfonyl, or two substituents form an alkylenedioxy group or a haloalkylenedioxy group, more preferably **Ar^1** is a phenyl or isobutyl group, said phenyl group being optionally substituted by one or more group(s) selected from halo preferably bromo, chloro or fluoro, cyano or C_1-C_4 alkyl preferably methyl, alkoxy preferably methoxy; and/or

Ar^2 is an aryl or heteroaryl preferably pyridyl, pyrazinyl, cycloalkyl, monocyclic heterocyclyl or C_2-C_6 alkyl group, each of said aryl, heteroaryl, cycloalkyl and heterocyclyl groups being optionally substituted by one or more group(s) selected from halo preferably chloro and fluoro, cyano, nitro, alkyl, haloalkyl preferably CF_3 or CHF_2, heterocyclyl, aryl, aralkyl, heteroaryl, benzoxazol-2-yl, heteroarylalkyl, hydroxyl, alkoxy, haloalkoxy preferably OCF_3 or $OCHF_2$, alkoxyalkoxy, aryloxy, alkoxyalkyl, cycloalkylalkyloxy, arylalkyloxy, heteroarylalkyloxy, aryloxyalkyl, heteroaryloxyalkyl, arylcarbonyl, or two substituents form an alkylenedioxy group or a haloalkylenedioxy group, or fused to the cycloalkyl or heterocycloalkyl group may be one aryl moiety, each of said substituents being optionally substituted by one or more further substituents selected from halo preferably chloro or fluoro, cyano, nitro, alkyl preferably methyl, ethyl, propyl, isopropyl, *tert*-butyl, haloalkyl preferably CF_3, cyanomethyl, alkoxy preferably methoxy, ethoxy, isopropoxy, cycloalkyl, cycloalkylalkyloxy, alkoxyalkoxy, aryloxy, aralkyloxy optionally substituted with one fluoro, amino, alkylcarbonylamino, carbamoyl, hydroxycarbamimidoyl, alkylsulfonyl, alkylsulfonylamino, preferably **Ar^2** is an aryl preferably phenyl, heteroaryl preferably pyridyl, monocyclic heterocyclyl preferably piperidinyl, C_2-C_6 alkyl group preferably isobutyl, each of said aryl, heteroaryl and heterocyclyl groups being optionally substituted by one or more group(s) selected from halo preferably chloro and fluoro, cyano, nitro, alkyl preferably methyl, heterocyclyl preferably pyrrolidin-1-yl, 4-methylpiperidin-1-yl, aryl, heteroaryl preferably pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, benzoxazol-2-yl, alkoxy

preferably methoxy, ethoxy and isopropyloxy, alkoxyalkyl, cycloalkylalkyloxy, arylalkyloxy preferably benzyloxy, phenethyloxy and 3,3-diphenylpropan-1-oxy heteroarylalkyloxy preferably pyridylmethyloxy or pyridylethyloxy, aryloxyalkyl preferably phenoxymethyl, heteroaryloxyalkyl preferably pyridyloxymethyl, arylcarbonyl, or two substituents form an haloalkylenedioxy group each of said substituents being optionally substituted by one or more further substituents selected from halo preferably chloro or fluoro, more preferably fluoro, cyano, alkyl preferably methyl, cycloalkyl, alkoxy preferably methoxy, isopropyloxy, isobutyloxy, alkoxyalkyl preferably methoxymethyl, alkoxyalkoxy preferably 2-methoxyethoxy, cycloalkylalkyloxy preferably cyclopropylmethyloxy, aryloxy preferably phenoxy, aralkyloxy optionally substituted with one fluoro, preferably benzyloxy, 4-fluorobenzyloxy, amino, alkylcarbonylamino preferably acetylamino, alkylsulfonyl preferably methylsulfonyl, alkylsulfonylamino preferably methylsulfonylamino, (N-methyl-N-methylsulfonyl)amino.

[0021] Preferred compound of formula Ia-1b' and pharmaceutically acceptable salts and solvates thereof, are those wherein

R^1 and **R^2** are H,
D is C=O;

L^2 is single bond;
R is H or linear or branched alkyl, aryl, acyloxyalkyl, dioxolene;

Ar^1 is a 5- to 6-membered aryl or heteroaryl group, 3- to 6-membered cycloalkyl group, or a linear or branched C_3-C_6 alkyl group, each of which being optionally substituted by one or more group(s) selected from halo, cyano, alkyl, haloalkyl, cycloalkyl, aryl, heteroaryl, hydroxyl, alkoxy, haloalkoxy, amino, alkylamino, carboxy, alkoxycarbonyl, alkylcarbonyloxy, alkylcarbonylamino, haloalkylcarbonylamino, carbamoyl, hydroxycarbamoyl, alkylcarbamoyl, carbamoylamino, alkylcarbamoylamino, alkylsulfonyl, haloalkylsulfonyl, sulfamoyl, alkylsulfamoyl, alkylsulfonylamino, haloalkylsulfonylamino, or two substituents form an alkylenedioxy group or a haloalkylenedioxy group, each of said aryl or heteroaryl substituents being optionally substituted by one or more further substituents selected from halo, cyano, alkyl, haloalkyl, hydroxyl, alkoxy, haloalkoxy;

Ar^2 is an aryl or heteroaryl, cycloalkyl or monocyclic heterocyclyl group, each of which being optionally substituted by one or more group(s) selected from halo, cyano, nitro, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, heteroalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, benzoxazol-2-yl, heteroarylalkyl, hydroxyl, hydroxyalkyl, alkoxy, haloalkoxy, alkoxyalkoxy, cycloalkyloxy, cycloalkylalkyloxy, heterocyclyloxy, aryloxy, heteroaryloxy, alkoxyalkyl, haloalkoxyalkyl, arylalkyloxy, heteroarylalkyloxy, aryloxyalkyl, heteroaryloxyalkyl, amino, alkylamino, arylcarbonyl, carboxy, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, alkylcarbonyloxy, arylcarbonyloxy, heteroarylcarbonyloxy, alkylcarbonylamino, carbamoyl, hydroxycarbamoyl, alkylcarbamoyl, arylcarbamoyl, heteroarylcarbamoyl, carbamoylamino, alkylcarbamoylamino, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, heteroarylsulfamoyl, alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, oxo, or two substituents form an alkylenedioxy group or a haloalkylenedioxy group, or fused to the aryl, heteroaryl or cycloalkyl group may be one or more aryl or heteroaryl moiety, each of said substituents being optionally substituted by one or

more further substituents selected from halo, cyano, nitro, alkyl, hydroxyalkyl, haloalkyl, cyanomethyl, cycloalkyl, heterocyclyl, aryl optionally substituted by a chloro or methyl group, heteroaryl, heteroalkyl, hydroxyl, alkoxy, alkoxyalkyl, alkoxyalkoxy, haloalkoxy, cycloalkyloxy, cycloalkylalkyloxy, aryloxy, aralkyloxy optionally substituted by a fluoro group, carboxy, alkoxycarbonyl, alkylcarbonyloxy, amino, alkylamino, alkylcarbonylamino, haloalkylcarbonylamino, carbamoyl, hydroxycarbamoyl, alkylcarbamoyl, carbamoylalkyloxy, carbamoylamino, alkylcarbamoylamino, carbamimidoyl, hydroxycarbamimidoyl, alkylsulfonyl, haloalkylsulfonyl, cycloalkylsulfonyl, heterocyclylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, alkylsulfonylamino, haloalkylsulfonylamino, oxo, and haloalkoxyalkyl;

R^3 is H, cyano, alkyl, hydroxyalkyl, aralkyl, alkoxyalkyl, acetyl, arylsulfonyl;

$R^{3'}$ is H or C_1-C_4 alkyl;

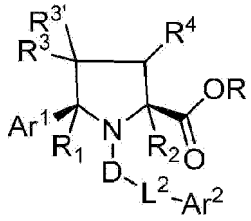
R^4 is H, cyano, C_1-C_4 alkyl;

under the condition that the compound of formula (Ia-1b') is not (2S)-methyl 1-benzoyl-5-mesitylpyrrolidine-2-carboxylate, (2S)-methyl 1-benzoyl-5-(2,4,6-triethylphenyl)pyrrolidine-2-carboxylate, (2S,5S)-1-benzoyl-5-mesitylpyrrolidine-2-carboxylic acid, (2S)-methyl 1-benzoyl-5-propylpyrrolidine-2-carboxylate, (2S,5S)-methyl 1-benzoyl-5-propylpyrrolidine-2-carboxylate, (2S,5R)-methyl 1-benzoyl-5-propylpyrrolidine-2-carboxylate, (2S,5R)-5-(*tert*-butyl)-1-(4-phenylbutanoyl)pyrrolidine-2-carboxylic acid, (2S,5R)-methyl 5-(tert-butyl)-1-(4-phenylbutanoyl)pyrrolidine-2-carboxylate, (2R,5R)-1-(4-bromothiophene-2-carbonyl)-5-phenylpyrrolidine-2-carboxylic acid, (2R,5S)-1-(3-bromo-2,6-dimethoxybenzoyl)-5-phenylpyrrolidine-2-carboxylic acid,
and under the condition that:

Ar^2 is not phthalazin-6-yl, pyrido[2,3-d]pyridazin-2-yl, pyrido[2,3-d]pyridazin-3-yl, or pyrazino[2,3-d]pyridazin-2-yl; and/or

R^3 is not a mono substituted hydroxymethyl.

[0022] Other preferred compounds are those of formula Ib-1b'



Ib-1b'

and pharmaceutically acceptable salts and solvates thereof, wherein

R^2 and **R** is as defined above in respect of formula Ia-1b';

R^1 is H;

D is C=O;

L^2 is single bond;

Ar^1 is a 5- to 6-membered aryl or heteroaryl group, 3- to 6-membered cycloalkyl group, or a linear or branched C_3-C_6 alkyl group, each of which being optionally substituted by one or more group(s) selected from halo, cyano, alkyl, haloalkyl, cycloalkyl, aryl, heteroaryl, hydroxyl, alkoxy, haloalkoxy, amino, alkylamino, carboxy, alkoxycarbonyl, alkylcarbonyloxy, alkylcarbonylamino, haloalkylcarbonylamino, carbamoyl, hydroxycarbamoyl, alkylcarbamoyl, carbamoylamino, alkylcarbamoylamino, alkylsulfonyl, haloalkylsulfonyl, sulfamoyl, alkylsulfamoyl, alkylsulfonylamino, or two substituents form an alkylenedioxy group or a haloalkylenedioxy group, each of said aryl or heteroaryl substituents being optionally substituted by one or more further substituents selected from halo, cyano, alkyl, haloalkyl, hydroxyl, alkoxy, haloalkoxy, preferably **Ar^1** is a 5- to 6-membered aryl preferably phenyl, 5- to 6-membered heteroaryl group preferably pyridin-2-yl, pyridin-3-yl, cyclohexyl, cyclopentyl, isopropyl, isobutyl or isopentyl each of said phenyl, pyridin-2-yl, pyridin-3-yl, cyclohexyl or cyclopentyl group being optionally substituted by one or more group(s) selected from halo preferably bromo, chloro or fluoro, cyano, C_1-C_4 alkyl preferably methyl, C_1-C_4 alkoxy preferably methoxy, aryl preferably phenyl, still more preferably **Ar^1** is aryl preferably phenyl, cyclohexyl, isobutyl or isopentyl, said phenyl group being optionally substituted by one or more halo group preferably bromo, chloro or fluoro, cyano, methyl, phenyl or methoxy, further more preferably **Ar^1** is phenyl, cyclohexyl, isobutyl, 2-chlorophenyl, 2-tolyl, 2-methoxyphenyl, 3-chlorophenyl, 4-chlorophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2,6-difluorophenyl, 2,4-difluorophenyl, 2,4-dichlorophenyl, 2-bromophenyl, 2-cyanophenyl, 3,5-difluorophenyl, 3,4-difluorophenyl, 2,3-difluorophenyl, 2,5-difluorophenyl, 1,1'-biphenyl-2-yl, 4-cyanophenyl, even more preferably **Ar^1** is isobutyl, cyclohexyl, phenyl , 2-chlorophenyl, 2-tolyl, 2-methoxyphenyl, 3-chlorophenyl, 4-chlorophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2,4-difluorophenyl, 2,4-dichlorophenyl, 2-bromophenyl, 2,3-difluorophenyl, 2,5-difluorophenyl, still even more preferably **Ar^1** is isobutyl, 2-chlorophenyl, 2-tolyl, 2-methoxyphenyl, 2-fluorophenyl, 2,4-difluorophenyl, 2-bromophenyl, 2,3-difluorophenyl, 2,5-difluorophenyl;

Ar^2 is an aryl or heteroaryl, cycloalkyl, monocyclic heterocyclyl or C_2-C_6 alkyl group, each of which being optionally substituted by one or more group(s) selected from halo, cyano, nitro, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, heteroalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, benzoxazol-2-yl heteroarylalkyl, hydroxyl, hydroxyalkyl, alkoxy, haloalkoxy, alkoxyalkoxy, cycloalkyloxy, cycloalkylalkyloxy, heterocyclyloxy, aryloxy, heteroaryloxy, alkoxyalkyl, haloalkoxyalkyl, arylalkyloxy, heteroarylalkyloxy, aryloxyalkyl, heteroaryloxyalkyl, amino, alkylamino, arylcarbonyl, carboxy, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, alkylcarbonyloxy, arylcarbonyloxy, heteroarylcarbonyloxy, alkylcarbonylamino, carbamoyl, hydroxycarbamoyl, alkylcarbamoyl, arylcarbamoyl, heteroarylcarbamoyl, carbamoylamino, alkylcarbamoylamino, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, heteroarylsulfamoyl,

alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, oxo, or two substituents form an alkylenedioxy group or a haloalkylenedioxy group, or fused to the aryl, heteroaryl, cycloalkyl or heterocyclyl group may be one or more aryl or heteroaryl moiety, each of said substituents being optionally substituted by one or more further substituents selected from halo, cyano, nitro, alkyl, hydroxyalkyl, haloalkyl, cyanomethyl, cycloalkyl, heterocyclyl, aryl optionally substituted by a chloro or methyl group, heteroaryl, heteroalkyl, hydroxyl, alkoxy, alkoxyalkyl, alkoxyalkoxy, haloalkoxy, cycloalkyloxy, cycloalkylalkyloxy, aryloxy, aralkyloxy optionally substituted by a fluoro group, carboxy, alkoxycarbonyl, alkylcarbonyloxy, amino, alkylamino, alkylcarbonylamino, haloalkylcarbonylamino, carbamoyl, hydroxycarbamoyl, alkylcarbamoyl, carbamoylalkyloxy, carbamoylamino, alkylcarbamoylamino, carbamimidoyl, hydroxycarbamimidoyl, alkylsulfonyl, haloalkylsulfonyl, cycloalkylsulfonyl, heterocyclylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, alkylsulfonylamino, haloalkylsulfonylamino, oxo, and haloalkoxyalkyl; preferably **Ar^2** is an aryl or heteroaryl preferably pyridyl, pyrazinyl, cycloalkyl, monocyclic heterocyclyl or C_2-C_6 alkyl group, each of each of said aryl, heteroaryl, cycloalkyl and heterocyclyl groups being optionally substituted by one or more group(s) selected from halo preferably chloro and fluoro, cyano, nitro, alkyl, haloalkyl preferably CF_3 or CHF_2, heterocyclyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, hydroxyl, alkoxy, haloalkoxy preferably OCF_3 or $OCHF_2$, alkoxyalkoxy, aryloxy, alkoxyalkyl, arylalkyloxy, heteroarylalkyloxy, cycloalkylalkyloxy, aryloxyalkyl, heteroaryloxyalkyl, arylcarbonyl, or two substituents form an alkylenedioxy group or a haloalkylenedioxy group, or fused to the cycloalkyl or heterocycloalkyl group may be one aryl moiety, each of said substituents being optionally substituted by one or more further substituents selected from halo preferably chloro or fluoro, cyano, nitro, alkyl preferably methyl, ethyl, propyl, isopropyl, *tert*-butyl, haloalkyl preferably CF_3, cyanomethyl, alkoxy preferably methoxy, ethoxy, isopropoxy, alkoxyalkyl, alkoxyalkoxy, cycloalkylalkyloxy, aryloxy, aralkyloxy optionally substituted by one fluoro, amino, alkylcarbonylamino, carbamoyl, hydroxycarbamimidoyl, alkylsulfonyl, alkylsulfonylamino, still more preferably **Ar^2** is an aryl preferably phenyl, heteroaryl preferably pyridyl, monocyclic heterocyclyl preferably piperidinyl, C_2-C_6 alkyl group preferably isobutyl, each of said aryl, heteroaryl and heterocyclyl groups being optionally substituted by one or more group(s) selected from halo preferably chloro and fluoro, cyano, nitro, alkyl, preferably methyl, heterocyclyl preferably pyrrolidin-1-yl, 4-methylpiperidin-1-yl, aryl preferably phenyl, heteroaryl preferably pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, alkoxy preferably methoxy, ethoxy or isopropyloxy, alkoxyalkyl, cycloalkylalkyloxy, arylalkyloxy preferably benzyloxy, phenethyloxy or 3,3-diphenylpropan-1-oxy, heteroarylalkyloxy preferably pyridylmethyloxy or pyridylethyloxy, aryloxyalkyl preferably phenoxymethyl, heteroaryloxyalkyl preferably pyridinyloxymethyl, arylcarbonyl preferably phenylacetyl, or two substituents form an haloalkylenedioxy group each of said substituents being optionally substituted by one or more further substituents selected from halo preferably chloro or fluoro, more preferably fluoro, cyano, nitro, alkyl preferably methyl, cycloalkyl, alkoxy preferably methoxy, isopropyloxy, isobutyloxy, cycloalkylalkyloxy preferably cyclopropylmethyloxy, alkoxyalkyl preferably methoxymethyl, alkoxyalkoxy preferably 2-methoxyethoxy, aryloxy preferably phenoxy, aralkyloxy optionally substituted by one fluoro, preferably benzyloxy or 4-fluorobenzyloxy, amino, alkylcarbonylamino preferably acetylamino, alkylsulfonyl preferably methylsulfonyl, alkylsulfonylamino preferably methylsulfonylamino, (N-

methyl-N-methylsulfonyl)amino, further more preferably **Ar^2** is a biaryl consisting of two 6-membered aryl moieties preferably biphenyl, more preferably a biphenyl linked to **L^2** at position 4' and monosubstituted at position 2, or **Ar^2** is a heterobiaryl consisting of one 6-membered aryl moiety and one 6-membered heteroaryl moiety or two 6-membered heteroaryl moieties, said heterobiaryl being linked to **L^2** either on the aryl or on the heteroaryl moiety and being preferably phenylpyridyl, pyrimidinylphenyl, pyridazinylphenyl, pyrazinylphenyl, or **Ar^2** is an aryl or heteroaryl optionally substituted by one group selected from arylalkyloxy, aryloxyalkyl, arylcarbonyl, each of said biaryl, heterobiaryl, aryl and heteroaryl groups being optionally substituted by one or more group(s) selected from halo preferably chloro or fluoro, cyano, nitro, alkyl preferably methyl, ethyl, propyl, isopropyl, *tert*-butyl, alkoxy preferably methoxy, isopropyloxy, isobutyloxy, cycloalkylalkyloxy, aryloxy preferably phenoxy, aralkyloxy optionally substituted by one fluoro preferably benzyloxy or 4-fluorobenzyloxy, amino, alkylcarbonylamino preferably acetylamino, alkylsulfonylamino preferably methylsulfonylamino, (N-methyl-N-methylsulfonyl)amino, or **Ar^2** is a piperidinyl ring linked to **L^2** at position 4 and N substituted with a phenyl, 4-(4-chlorophenyl)thiazol-2-yl or benzoxazol-2-yl moiety, said phenyl moiety being further substituted by one or more substituents selected from halo preferably chloro and fluoro, cyano, nitro, alkyl preferably methyl, haloalkyl preferably CF_3, alkoxy preferably methoxy, heterocyclylsulfonyl preferably (piperidin-1-yl)sulfonyl, (morpholin-4-yl)sulfonyl, alkylsulfamoyl preferably methylsulfonylamino, diethylaminosulfonyl, even more preferably **Ar^2** is 4'-(2-methoxy-1,1'-biphenyl), 4'-(2-methyl-1,1'-biphenyl), 4'-(2-fluoro-1,1'-biphenyl), 4'-(4-chloro-1,1'-biphenyl), 4'-(2-chloro-1,1'-biphenyl), 4'-(2-chloro-2'-methoxy-1,1'-biphenyl), 4'-(2-(2-methoxyethoxy)-1,1'-biphenyl), 4'-(2-(methoxymethyl)-1,1'-biphenyl), 4'-(4-methoxy-1,1'-biphenyl), 4'-(4-cyano-1,1'-biphenyl), 4'-(3-chloro-1,1'-biphenyl), 4'-(2-chloro-1,1'-biphenyl), 4'-(4-methylsulfonylamino-1,1'-biphenyl), 4'-(2-trifluoromethoxy-1,1'-biphenyl), 4' -(2-isopropoxy-1,1'-biphenyl), 4'-(2-cyclopropylmethyloxy-1,1'-biphenyl), 4'-(2-cyano-1,1'-biphenyl), 4'-(2,6-dimethoxy-1,1'-biphenyl), 4'-(2,4-dichloro-1,1'-biphenyl), 4'-(2-trifluoromethyl-1,1'-biphenyl), 4'-(2-methoxy-4-chloro-1,1'-biphenyl), 4'-(2,4-dimethoxy-1,1'-biphenyl), 4-(2,2'-dimethoxy-1,1'-biphenyl), 4-(naphtalen-2-yl)phenyl, 5-(2-phenyl)pyridyl, 4-cyclohexylphenyl, 4-benzylphenyl, 4-(3-thienyl)phenyl, 4-(pyridin-3-yl)phenyl, 4-(2-methoxypyridin-3-yl)phenyl, 4-(2,6-dimethoxy-pyridin-3-yl)phenyl, 4-(2-(2-methoxyethoxy)-pyridin-3-yl)phenyl, 4-(pyrimidin-2-yl)phenyl, 4-(pyrimidin-5-yl)phenyl, 4-(2-methoxypyrimidin-5-yl)-3-methoxyphenyl, 4-(2,4-dimethoxypyrimidin-6-yl)phenyl, 4-(2,4-dimethoxypyrimidin-5-yl)phenyl, (4-benzyloxy)phenyl, 4-phenoxyphenyl, (3-phenethyloxy)phenyl, (4-phenethyloxy)phenyl, (4-phenoxymethyl)phenyl, optionally substituted by one or more group(s) selected from halo preferably chloro or fluoro, more preferably fluoro, alkyl preferably methyl, alkoxy preferably methoxy, or **Ar^2** is 4'-(2,4-difluoro-1,1'-biphenyl), 4'-(3'-methyl-1,1'-biphenyl), 4'-(3'-fluoro-1,1'-biphenyl), 4'-(2-fluoro-4-methoxy-1,1'-biphenyl), 4'-(4-fluoro-2-methoxy-1,1'-biphenyl), 4'-(2,3-dimethoxy-1,1'-biphenyl), 4'-(3,4-dimethoxy-1,1'-biphenyl), 4'-(2,3,4-trimethoxy-1,1'-biphenyl), 4'-(2,3,6-trimethoxy-1,1'-biphenyl), 4'-(3,5-dimethoxy-1,1'-biphenyl), 4'-(2,5-dimethoxy-1,1'-biphenyl), 4'-(2-isopropyl-1,1'-biphenyl), 4'-(2,2'-dimethoxy-1,1'-biphenyl), 4'-(2'-fluoro,2-dimethoxy-1,1'-biphenyl), 4'-(2-ethyl-1,1'-biphenyl), 4'-(4-propyl-1,1'-biphenyl), 4'-(4-*tert*-butyl-1,1'-biphenyl), 4'-(2-methoxy-4-methylsulfonylamino-1,1'-biphenyl), 4'-(2-methoxy-4-acetylamino-1,1'-biphenyl), 4'-(3-

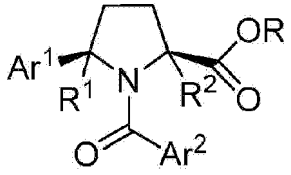
hydroxycarbamimidoyl-1,1'-biphenyl), 4'-(4-amino-2-methoxy-1,1'-biphenyl), 4'-(3-carbamoyl-1,1'-biphenyl), 4'-(5-cyano-2,3-dimethoxy-1,1'-biphenyl), 4'-(2-cyano-4,5-dimethoxy-1,1'-biphenyl), 4'-(3,4,5-trimethoxy-1,1'-biphenyl), 4'-(2-cyanomethyl-4,5-dimethoxy-1,1'-biphenyl), 4'-(2-fluoro-5-cyano-1,1'-biphenyl), 4'-(2'-fluoro-3,4-dimethoxy-1,1'-biphenyl), 4'-(3-carbamoyl-4-cyano-1,1'-biphenyl), 4'-(2-cyano-4-methoxy-1,1'-biphenyl), 4'-(2'-fluoro-4-methylsulfonylamino-1,1'-biphenyl), 4'-(2'-fluoro-3-methylsulfonylamino-1,1'-biphenyl), 4'-(2-cyano-2'-fluoro-1,1'-biphenyl), 4'-(2-chloro-5-cyano-1,1'-biphenyl), 4'-(2-cyano-4-trifluoromethyl-1,1'-biphenyl), 4'-(2-methyl-3-(N-methyl-N-methylsulfonyl)amino-1,1'-biphenyl), 4'-(2-methyl-4-(N-methyl-N-methylsulfonyl)amino-1,1'-biphenyl), 4'-(4-methylsulfonyl-1,1'-biphenyl), 4'-(3-methylsulfonylamino-1,1'-biphenyl), 4'-(4-amino-2-methyl-1,1'-biphenyl), 4'-(5-cyano-2-methyl-1,1'-biphenyl), 4'-(5-cyano-2-methoxy-1,1'-biphenyl), 4'-(3-cyano-1,1'-biphenyl), 4'-(2-cyano-3-methoxy-1,1'-biphenyl), 4'-(2-methyl-3-methylsulfonylamino-1,1'-biphenyl), 4'-(2-methyl-3-acetylamino-1,1'-biphenyl), 4-(2-chloro-6-methoxypyrimidin-5-yl)phenyl, 4-(2-ethoxypyridin-5-yl)phenyl, 4-(2-isopropoxypyridin-5-yl)phenyl, 4-(2-methoxy-6-methylpyridin-5-yl)phenyl, 4-(2-methoxy-pyrimidin-4-yl)-3-chlorophenyl, 4-(2,6-dimethylpyridin-5-yl)phenyl, 4-(2,6-dimethoxy-pyrimidin-5-yl)-3-chlorophenyl, 4-(4-methoxy-pyridin-3-yl)-3-methoxyphenyl, 4-(6-methoxy-pyridin-3-yl)-3-methoxyphenyl, 4-(6-methoxy-pyridin-3-yl)-3-chlorophenyl, 4-(4,6-dimethoxy-pyridin-3-yl)phenyl, 4-(3,6-dimethoxy-pyridazin-5-yl)phenyl, 4-(2,6-dimethoxy-pyridin-3-yl)phenyl, 4-(5-methoxy-pyridin-3-yl)-3-methoxyphenyl, 4-(2,6-dimethoxy-pyridin-3-yl)-3-fluorophenyl, 4-(6-methoxy-pyridin-3-yl)-3-fluorophenyl, 4-(3,6-dimethoxy-pyridazin-5-yl)-3-fluorophenyl, 4-(4,6-dimethoxy-pyrimidin-5-yl)phenyl, 4-(2-methoxy-pyrimidin-5-yl)-3-methoxyphenyl, 4-(3-methoxy-pyridin-4-yl)phenyl, 4-(4-methoxy-pyridin-3-yl)phenyl, 4-(2-methoxy-pyrimidin-3-yl)phenyl, 3-methoxy-2-(2-methoxyphenyl)pyridin-5-yl, 3-methoxy-2-(5-cyano-2-methoxyphenyl)pyridin-5-yl, 3-methoxy-2-(2,4-dimethoxyphenyl)pyridin-5-yl, 2-(2,4-dimethoxyphenyl)pyridin-5-yl, 1-(2-cyano-4-trifluoromethyl)piperidin-4-yl, 1-(2-nitro-4-trifluoromethyl)piperidin-4-yl, 1-(2-methoxy-4-trifluoromethyl)piperidin-4-yl;

R^3 is H, cyano, alkyl, hydroxyalkyl, aralkyl, alkoxyalkyl, acetyl, arylsulfonyl;

$R^{3'}$ is H or C_1-C_4 alkyl;

R^4 is H, cyano, C_1-C_4 alkyl.

[0023] Preferred compounds of formula Ib-1b' are those of formula Ib-1d

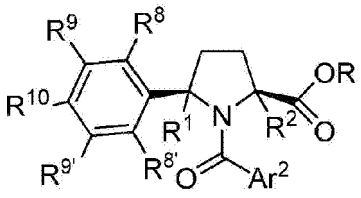


Ib-1d

and pharmaceutically acceptable salts and solvates thereof, wherein **Ar^1, Ar^2, R^1** and **R^2** and **R**

are as defined above.

[0024] Preferred compounds of formula Ib-1d are those of formula Ib-1e



Ib-1e

and pharmaceutically acceptable salts and solvates thereof, wherein

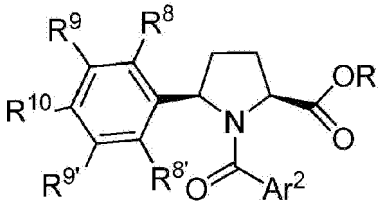
Ar^2, R^1 and **R^2** are as defined above in respect of formula Ib-1b';

R is as defined above in respect of formula Ia-1b';

R^8, $R^{8'}$, R^9, $R^{9'}$ and **R^{10}** are independently selected from H, halo preferably fluoro, chloro, bromo, cyano, alkyl, hydroxyalkyl, haloalkyl preferably CF_3 or CHF_2, cycloalkyl, cycloalkylalkyl, heteroalkyl, heterocyclyl, heterocyclylalkyl, aryl preferably phenyl, aralkyl, heteroaryl, heteroarylalkyl, hydroxyl, haloalkoxy preferably OCF_3 or $OCHF_2$, heterocyclyloxy, alkylamino, alkoxycarbonyl, cycloalkyloxycarbonyl, heterocyclyloxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, alkylcarbonyloxy, cycloalkylcarbonyloxy, heterocyclylcarbonyloxy, arylcarbonyloxy, heteroarylcarbonyloxy, arylalkyloxy, alkylcarbonylamino, haloalkylcarbonylamino, cycloalkylcarbonylamino, heterocyclylcarbonylamino arylcarbonylamino, heteroarylcarbonylamino, alkylcarbonylaminoalkyl, carbamoyl, hydroxycarbamoyl, alkylcarbamoyl, arylcarbamoyl, heteroarylcarbamoyl, carbamoylalkyl, carbamoylamino, alkylcarbamoylamino, alkylsulfonyl, haloalkylsulfonyl, cycloalkylsulfonyl, heterocyclylsulfonyl, arylsulfonyl, heteroarylsulfonyl sulfamoyl, alkylsulfamoyl, arylsulfamoyl, heteroarylsulfamoyl, alkylsulfonylamino, cycloalkylsulfonylamino, heterocyclylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, or one or more of **R^8** and **R^9,** or **R^9** and **R^{10},** or **R^{10}** and **$R^{9'}$,** or **$R^{9'}$** and **$R^{8'}$** form an alkylenedioxy group or a haloalkylenedioxy group together with the phenyl group they are attached to, or one or more of **R^8** and **R^9,** or **R^9** and **R^{10},** or **R^{10}** and **$R^{9'}$,** or **$R^{9'}$** and **$R^{8'}$** form together a cycloalkyl, aryl, heterocycloalyl or heteroaryl moiety fused to the phenyl group they are attached to, each of said substituents being optionally substituted by one or more further substituents selected from halo, cyano, alkyl, hydroxyalkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, heteroalkyl, hydroxyl, alkoxy, haloalkoxy, cycloalkyloxy, alkylamino, carboxy, alkoxycarbonyl, alkylcarbonyloxy, cycloalkylcarbonyloxy, alkylcarbonylamino, haloalkylcarbonylamino, cycloalkylcarbonylamino, alkylcarbonylaminoalkyl, carbamoyl, hydroxycarbamoyl, alkylcarbamoyl, carbamoylalkyl, carbamoylamino, alkylcarbamoylamino, alkylsulfonyl, haloalkylsulfonyl, cycloalkylsulfonyl, sulfamoyl, alkylsulfamoyl, alkylsulfonylamino, cycloalkylsulfonylamino, haloalkylsulfonylamino or oxo, preferably **R^8, $R^{8'}$, R^9, $R^{9'}$** and **R^{10}** are independently selected from H, halo preferably fluoro, chloro, bromo, cyano, alkyl, haloalkyl preferably CF_3 or CHF_2, cycloalkyl, aryl preferably phenyl, heteroaryl, hydroxyl, haloalkoxy preferably OCF_3 or $OCHF_2$, alkylamino, alkoxycarbonyl, alkylcarbonyloxy, alkylcarbonylamino,

haloalkylcarbonylamino, carbamoyl, hydroxycarbamoyl, alkylcarbamoyl, carbamoylamino, alkylcarbamoylamino, alkylsulfonyl, haloalkylsulfonyl, sulfamoyl, alkylsulfamoyl, alkylsulfonylamino, or one or more of **R^8** and **R^9**, or **R^9** and **R^{10}**, or **R^{10}** and **$R^{9'}$**, or **$R^{9'}$** and **$R^{8'}$** form an alkylenedioxy group or a haloalkylenedioxy group together with the phenyl group they are attached to, each of said substituents being optionally substituted by one or more further substituents selected from halo, cyano, alkyl, haloalkyl, hydroxyl, alkoxy, haloalkoxy, more preferably **R^8**, **$R^{8'}$**, **R^9**, **$R^{9'}$** and **R^{10}** are independently selected from H, halo preferably bromo, fluoro or chloro, cyano, C_1-C_4 alkyl preferably methyl, aryl preferably phenyl, alkoxy preferably methoxy, still more preferably **R^8**, **$R^{8'}$**, **R^9**, **$R^{9'}$** and **R^{10}** are independently selected from H, halo preferably bromo, fluoro or chloro, alkyl preferably methyl, still more preferably **R^8** is Br, Cl or F, preferably Cl and **$R^{8'}$**, **R^9**, **$R^{9'}$** and **R^{10}** are independently selected from H or F, or **R^9** is Cl or F and **R^8**, **$R^{8'}$**, **$R^{9'}$** and **R^{10}** are H, or **R^9** and **$R^{9'}$** are F and **R^8**, **$R^{8'}$** and **R^{10}** are H, or **R^{10}** is Cl or F and **R^8**, **$R^{8'}$**, **R^9** and **$R^{9'}$** are H, even more preferably **R^8** is Br, Cl or F and **$R^{8'}$**, **R^9**, **$R^{9'}$** and **R^{10}** are H, or **R^8** and **R^9** are F and **$R^{8'}$**, **$R^{9'}$** and **R^{10}** are H, or **R^8** and **R^{10}** are F and **$R^{8'}$**, **R^9** and **$R^{9'}$** are H.

[0025] Preferred compounds of formula Ib-1e are those of formula Ib-1f



Ib-1f

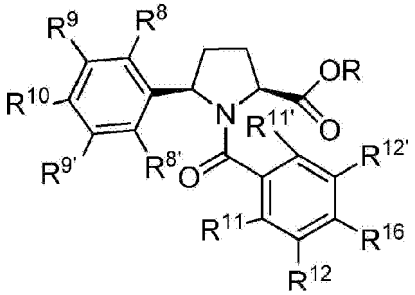
and pharmaceutically acceptable salts and solvates thereof, wherein

Ar^2 is as defined above in respect of formula Ib-1b';

R is as defined above in respect of formula Ia-1b';

R^8, **$R^{8'}$**, **R^9**, **$R^{9'}$** and **R^{10}** are as defined above in respect of formula Ib-1e.

[0026] Preferred compounds of formula Ib-1f are those of formula Ib-1g



Ib-1g

and pharmaceutically acceptable salts and solvates thereof, wherein

R is as defined above in respect of formula Ia-1b';

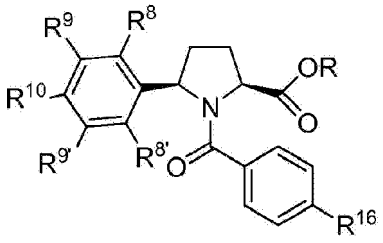
R^8, $R^{8'}$, R^9, $R^{9'}$ and **R^{10}** are as defined above in respect of formula Ib-1e;

R^{11}, $R^{11'}$, R^{12}, $R^{12'}$ and **R^{16}** are independently selected from H, halo preferably chloro and fluoro more preferably chloro, cyano, nitro, alkyl, haloalkyl preferably CF_3 or CHF_2, cycloalkyl, cycloalkylalkyl, heteroalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, hydroxyl, hydroxyalkyl, alkoxy, haloalkoxy preferably $-OCF_3$ or $-OCHF_2$, alkoxyalkoxy, cycloalkyloxy, heterocyclyloxy, aryloxy, heteroaryloxy, alkoxyalkyl, haloalkoxyalkyl, cycloalkylalkyloxy, arylalkyloxy, heteroarylalkyloxy, aryloxyalkyl, heteroaryloxyalkyl, arylcarbonyl, alkyloxycarbonyl, aminoalkylalkoxycarbonyl, cycloalkyloxycarbonyl, heterocyclyloxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, alkylcarbonyloxy, cycloalkylcarbonyloxy, heterocyclylcarbonyloxy, arylcarbonyloxy, heteroarylcarbonyloxy, alkylcarbonylamino, haloalkylcarbonylamino, cycloalkylcarbonylamino, heterocyclylcarbonylamino arylcarbonylamino, heteroarylcarbonylamino, alkylcarbonylaminoalkyl, carbamoyl, hydroxycarbamoyl, alkylcarbamoyl, arylcarbamoyl, heteroarylcarbamoyl, carbamoylalkyl, carbamoylamino, alkylcarbamoylamino, alkylsulfonyl, haloalkylsulfonyl, cycloalkylsulfonyl, heterocyclylsulfonyl, arylsulfonyl, heteroarylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, heteroarylsulfamoyl, alkylsulfonylamino, cycloalkylsulfonylamino, heterocyclylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, haloalkylsulfonylamino, or one or more of **R^{11}** and **R^{12}**, or **R^{12}** and **R^{16}**, or **R^{16}** and **$R^{12'}$**, or **$R^{12'}$** and **$R^{11'}$** form an alkylenedioxy group or a haloalkylenedioxy group together with the phenyl group they are attached to, or one or more of **R^{11}** and **R^{12}**, or **R^{12}** and **R^{16}**, or **R^{16}** and **$R^{12'}$**, or **$R^{12'}$** and **$R^{11'}$** form together a cycloalkyl, aryl, heterocycloalkyl or heteroaryl moiety fused to the phenyl group they are attached to, each of said substituents being optionally substituted by one or more further substituents selected from halo preferably chloro or fluoro, cyano, alkyl, hydroxyalkyl, alkoxyalkyl, haloalkyl, cyanomethyl, cycloalkyl, heterocyclyl, aryl optionally substituted by one a chloro or methyl group, heteroaryl, cycloalkylalkyl, aralkyl, heteroarylalkyl, heteroalkyl, hydroxyl, alkoxy, alkoxyalkoxy, haloalkoxy preferably trifluoromethoxy, 1,1,1-trifluoroethyloxy, haloalkoxyalkyl, cycloalkyloxy, cycloalkylalkyloxy preferably cyclopropylmethyloxy, aryloxy, aralkyloxy optionally substituted by one fluoro, amino, alkylamino, carboxy, alkoxycarbonyl, alkylcarbonyloxy, alkylcarbonylamino, haloalkylcarbonylamino, cycloalkylcarbonylamino, alkylcarbonylaminoalkyl, carbamoyl, hydroxycarbamoyl, alkylcarbamoyl, carbamoylalkyl, carbamoylalkyloxy preferably carbamoylmethyloxy carbamoylamino, alkylcarbamoylamino, carbamimidoyl, hydroxycarbamimidoyl, alkylsulfonyl, haloalkylsulfonyl, cycloalkylsulfonyl, arylsulfonyl preferably phenylsulfonyl, sulfamoyl, alkylsulfamoyl, alkylsulfonylamino, cycloalkylsulfonylamino, haloalkylsulfonylamino and oxo, preferably **R^{11}, $R^{11'}$, R^{12}, $R^{12'}$** and **R^{16}** are independently selected from H, halo preferably chloro and fluoro more preferably chloro, cyano, nitro, alkyl,

haloalkyl preferably CF_3 or CHF_2, cycloalkyl, cycloalkylalkyl, heteroalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, hydroxyl, hydroxyalkyl, alkoxy, haloalkoxy preferably $-OCF_3$ or $-OCHF_2$, alkoxyalkoxy, cycloalkyloxy, heterocyclyloxy, aryloxy, heteroaryloxy, alkoxyalkyl, haloalkoxyalkyl, cycloalkylalkyloxy, arylalkyloxy, heteroarylalkyloxy, aryloxyalkyl, heteroaryloxyalkyl, arylcarbonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, alkylcarbonyloxy, arylcarbonyloxy, heteroarylcarbonyloxy, alkylcarbonylamino, carbamoyl, hydroxycarbamoyl, alkylcarbamoyl, arylcarbamoyl, heteroarylcarbamoyl, carbamoylamino, alkylcarbamoylamino, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, heteroarylsulfamoyl, alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, or one or more of $\mathbf{R^{11}}$ and $\mathbf{R^{12}}$, or $\mathbf{R^{12}}$ and $\mathbf{R^{16}}$, or $\mathbf{R^{16}}$ and $\mathbf{R^{12'}}$, or $\mathbf{R^{12'}}$ and $\mathbf{R^{11'}}$ form an alkylenedioxy group or a haloalkylenedioxy group together with the phenyl group they are attached to, or one or more of $\mathbf{R^{11}}$ and $\mathbf{R^{12}}$, or $\mathbf{R^{12}}$ and $\mathbf{R^{16}}$, or $\mathbf{R^{16}}$ and $\mathbf{R^{12'}}$, or $\mathbf{R^{12'}}$ and $\mathbf{R^{11'}}$ form together an aryl or heteroaryl moiety fused to the phenyl group they are attached to, each of said substituents being optionally substituted by one or more further substituents selected from halo preferably chloro or fluoro, cyano, alkyl, hydroxyalkyl, alkoxyalkyl, haloalkyl, cyanomethyl, cycloalkyl, heterocyclyl, aryl optionally substituted by one a chloro or methyl group, heteroaryl, heteroalkyl, hydroxyl, alkoxy, alkoxyalkoxy, haloalkoxy preferably 1,1,1-trifluoroethyloxy, cycloalkyloxy, cycloalkylalkyloxy preferably cyclopropylmethyloxy, aryloxy, aralkyloxy optionally substituted by one fluoro, amino, alkylamino, carboxy, alkoxycarbonyl, alkylcarbonyloxy, alkylcarbonylamino, haloalkylcarbonylamino, carbamoyl, hydroxycarbamoyl, alkylcarbamoyl, carbamoylalkyloxy preferably carbamoylmethyloxy carbamoylamino, alkylcarbamoylamino, carbamimidoyl, hydroxycarbamimidoyl, alkylsulfonyl, haloalkylsulfonyl, cycloalkylsulfonyl, arylsulfonyl preferably phenylsulfonyl, sulfamoyl, alkylsulfamoyl, alkylsulfonylamino, haloalkylsulfonylamino and oxo, more preferably $\mathbf{R^{11}}$, $\mathbf{R^{11'}}$, $\mathbf{R^{12}}$, $\mathbf{R^{12'}}$ and $\mathbf{R^{16}}$ are independently selected from H, halo preferably chloro and fluoro, cyano, nitro, alkyl, haloalkyl preferably CF_3 or CHF_2, heterocyclyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, hydroxyl, alkoxy, haloalkoxy preferably OCF_3 or $OCHF_2$, alkoxyalkoxy, aryloxy, cycloalkylalkyloxy, arylalkyloxy, heteroarylalkyloxy, alkoxyalkyl, aryloxyalkyl, heteroaryloxyalkyl, arylcarbonyl, or one or more of $\mathbf{R^{11}}$ and $\mathbf{R^{12}}$, or $\mathbf{R^{12}}$ and $\mathbf{R^{16}}$, or $\mathbf{R^{16}}$ and $\mathbf{R^{12'}}$, or $\mathbf{R^{12'}}$ and $\mathbf{R^{11'}}$ form an alkylenedioxy group or a haloalkylenedioxy group together with the phenyl group they are attached to, or one or more of $\mathbf{R^{11}}$ and $\mathbf{R^{12}}$, or $\mathbf{R^{12}}$ and $\mathbf{R^{16}}$, or $\mathbf{R^{16}}$ and $\mathbf{R^{12'}}$, or $\mathbf{R^{12'}}$ and $\mathbf{R^{11'}}$ form together an aryl, or heteroaryl moiety fused to the phenyl group they are attached to, each of said substituents being optionally substituted by one or more further substituents selected from halo preferably chloro or fluoro, cyano, alkyl preferably methyl, ethyl, propyl, isopropyl, *tert*-butyl, cyanomethyl, cycloalkyl, heterocyclyl, alkoxy preferably methoxy, ethoxy, isopropoxy, alkoxyalkyl, alkoxyalkoxy, cycloalkylalkyloxy, aryloxy, aralkyloxy optionally substituted by one fluoro, amino, alkylamino, alkylcarbonylamino, carbamoyl, hydroxycarbamimidoyl, alkylsulfonyl, alkylsulfonylamino, still more preferably $\mathbf{R^{11}}$, $\mathbf{R^{11'}}$, $\mathbf{R^{12}}$, $\mathbf{R^{12'}}$ and $\mathbf{R^{16}}$ are independently selected from H, halo preferably chloro and fluoro, cyano, nitro, alkyl preferably methyl, ethyl, isopropyl or isobutyl, haloalkyl preferably CF_3 or CHF_2, cycloalkyl preferably cyclohexyl, heterocyclyl preferably pyrrolidin-1-yl, 4-methylpiperidin-1-yl, aryl preferably phenyl, heteroaryl preferably

thiophenyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, aralkyl preferably benzyl, alkoxy preferably methoxy, ethoxy or isopropyloxy, cycloalkylalkyloxy, arylalkyloxy preferably benzyloxy, phenethyloxy or 3,3-diphenylpropan-1-oxy, heteroarylalkyloxy preferably pyridylmethyloxy or pyridylethyloxy, aryloxyalkyl preferably phenoxymethyl, heteroaryloxyalkyl preferably pyridyloxymethyl, or two substituents form an haloalkylenedioxy group each of said substituents being optionally substituted by one or more further substituents selected from halo preferably chloro or fluoro, cyano, alkyl preferably methyl, haloalkyl preferably trifluoromethyl, alkoxy preferably methoxy, isopropyloxy, isobutyloxy, alkoxyalkyl preferably methoxymethyl, alkoxyalkoxy preferably 2-methoxyethoxy, cycloalkylalkyloxy preferably cyclopropylmethyloxy, aryloxy preferably phenoxy, aralkyloxy optionally substituted by one fluoro, preferably benzyloxy, 4-fluorobenzyloxy, amino, alkylcarbonylamino preferably acetylamino, alkylsulfonyl preferably methylsulfonyl, alkylsulfonylamino preferably methylsulfonylamino, (N-methyl-N-methylsulfonyl)amino.

[0027] Preferred compounds of formula Ib-1g are those of formula Ib-1g1



Ib-1g1

and pharmaceutically acceptable salts and solvates thereof, wherein

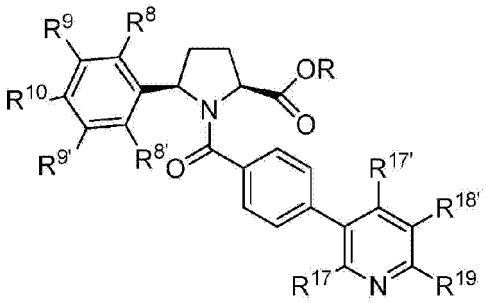
R is as defined above in respect of formula Ia-1b';

R^8, $R^{8'}$, R^9, $R^{9'}$ and **R^{10}** are as defined above in respect of formula Ib-1e;

R^{16} is as defined above in respect to formula Ib-1g, preferably **R^{16}** is selected from halo preferably chloro, alkyl preferably methyl or isobutyl, cycloalkyl preferably cyclohexyl, aryl preferably phenyl, heteroaryl preferably pyridyl, thiophen-3-yl, pyrimidinyl, pyrazinyl, pyridazinyl, aralkyl preferably benzyl, alkoxy preferably methoxy, isopropyloxy more preferably isopropyloxy, haloalkoxy, preferably OCF_3, $OCHF_2$, more preferably OCF_3, cycloalkylalkyloxy preferably cyclopropylmethyloxy, arylalkyloxy preferably phenethyloxy or benzyloxy, heteroarylalkyloxy preferably pyridylethyloxy, aryloxyalkyl preferably phenoxymethyl, heteroaryloxyalkyl preferably pyridyloxymethyl, arylcarbonyl preferably phenylcarbonyl, each of said substituents being optionally substituted by one or more further substituents selected from halo preferably chloro or fluoro, more preferably fluoro, cyano, alkyl preferably methyl, ethyl, propyl, isopropyl, *tert*-butyl, trifluoromethyl, cyanomethyl, cycloalkyl, aryl optionally substituted by a chloro or methyl group, hydroxyl, alkoxy preferably methoxy, ethoxy, isopropoxy, haloalkoxy preferably trifluoromethoxy, 1,1,1-trifluoroethyloxy, aryloxy preferably phenoxy, cycloalkylalkyloxy preferably cyclopropylmethyloxy, aralkyloxy optionally substituted by one

fluoro preferably benzyloxy, 4-fluorobenzyloxy, alkoxyalkyl preferably methoxymethyl, alkoxyalkoxy preferably 2-methoxyethoxy, amino, alkylcarbonylamino preferably acetylamino, carbamoyl, carbamoylmethyloxy, carbamimidoyl, hydroxycarbamimidoyl, alkylsulfonylamino preferably methylsulfonylamino, (N-methyl-N-methylsulfonyl)amino, oxo, more preferably R^{16} is selected from alkyl preferably isobutyl, or R^{16} is alkoxy preferably isopropyloxy, or R^{16} is heterocyclyl preferably pyrrolidin-1-yl, 4-methylpiperidin-1-yl, or R^{16} is aryl preferably a phenyl, preferably a phenyl monosubstituted at position 2 by one group selected from halo preferably chloro or fluoro, more preferably fluoro, cyano, alkyl preferably methyl, alkoxy preferably methoxy, alkoxyalkyl preferably methoxymethyl, alkoxyalkoxy preferably 2-methoxyethoxy, or R^{16} is 2,4-difluorophenyl, 2-fluoro-4-methoxyphenyl, 4-fluoro-2-methoxyphenyl, 2,3-dimethoxyphenyl, 3,4-dimethoxyphenyl, 3,5-dimethoxyphenyl, 2,5-dimethoxyphenyl, 2-methoxy-4-methylsulfonylaminophenyl, 4-acetylamino-2-methoxyphenyl, 4-amino-2-methoxyhenyl, 5-cyano-2,3-dimethoxyphenyl, 2-cyano-4,5-dimethoxyphenyl, 3,4,5-trimethoxyphenyl, 2-cyano-4-methoxyphenyl, 3-methylsulfonylaminophenyl, 4-methylsulfonylaminophenyl, 2-chloro-5-cyanophenyl, 2-cyano-4-trifluoromethylphenyl, 2-methyl-3-(N-methyl-N-methylsulfonyl)aminophenyl, 2-methoxy-4-(N-methyl-N-methylsulfonyl)aminophenyl, 4-methylsulfonylphenyl, 3-methylsulfonylaminophenyl, 4-methylsulfonylaminophenyl, 3-amino-2-methyl, 5-cyano-2-methylphenyl, 5-cyano-2-methoxyphenyl, 2-methyl-3-methylsulfonylamino, 3-cyano-2-methoxyphenyl, or R^{16} is aralkyl preferably benzyl, or R^{16} is heteroaryl preferably 4,6-dimethoxypyrimidin-2-yl, 2-methoxypyrimidin-3-yl, 2,4-dimethoxypyrimidin-5-yl, 2-methoxypyridin-3-yl, 2,6-dimethoxy-pyridin-3-yl, 2-(2-methoxyethoxy)-pyridin-3-yl, 2-methoxypyrimidin-5-yl, 2,4-dimethoxypyrimidin-6-yl, preferably 2-methoxypyrimidin-3-yl, (2,4-dimethoxy)pyrimidin-5-yl, 2-methoxypyrimidin-5-yl, 2,6-dimethoxy-pyridin-3-yl, more preferably (2,4-dimethoxy)pyrimidin-5-yl, 2,6-dimethoxy-pyridin-3-yl, 2-chloro-6-methoxypyrimidin-5-yl, 2-methoxy-6-methylpyridin-5-yl, 2,6-dimethylpyridin-5-yl, 2,6-dimethoxypyrimidin-5-yl, 4-methoxypyridin-3-yl, 2-methoxypyridin-5-yl, 2,4-dimethoxypyridin-5-yl, 2,6-dimethoxypyridazin-5-yl, 2,6-dimethoxypyridin-5-yl, 5-methoxypyridin-3-yl, 4,6-dimethoxypyrimidin-5-yl, 3-methoxypyridin-4-yl, 4-methoxypyridin-3-yl, or R^{16} is, arylalkyloxy preferably phenethyloxy, benzyloxy, 2-fluorobenzyloxy, more preferably 2-fluorobenzyloxy, or R^{16} is aryloxyalkyl preferably phenoxymethyl.

[0028] Preferred compounds of formula Ib-1g1 are those of formula Ib-1g1a



Ib-1g1a

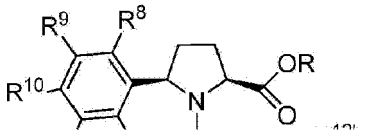
and pharmaceutically acceptable salts and solvates thereof, wherein

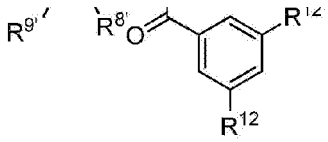
R is as defined above in respect of formula Ia-1b';

R^8, $R^{8'}$, R^9, $R^{9'}$ and R^{10} are as defined above in respect of formula Ib-1e;

R^{17}, $R^{17'}$, $R^{18'}$ and R^{19} are independently selected from H, halo preferably chloro and fluoro more preferably fluoro, cyano, alkyl preferably methyl, haloalkyl preferably CF_3 or CHF_2, cycloalkyl, cycloalkylalkyl, heteroalkyl, heterocyclyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, hydroxyl, hydroxyalkyl, alkoxy preferably methoxy, ethoxy, isopropyloxy, haloalkoxy preferably OCF_3 or $OCHF_2$, alkoxyalkoxy, cycloalkyloxy, alkoxyalkyl, cycloalkylalkyloxy, aryloxy, aralkyloxy, haloalkoxyalkyl, alkylamino, alkylsulfonyl preferably methylsulfonyl, alkylcarbonylamino, haloalkylcarbonylamino, cycloalkylcarbonylamino, alkylcarbonylaminoalkyl, carbamoyl, hydroxycarbamoyl, alkylcarbamoyl, carbamoylamino, alkylcarbamoylamino, alkylsulfonyl, haloalkylsulfonyl, cycloalkylsulfonyl, sulfamoyl, alkylsulfamoyl, alkylsulfonylamino, haloalkylsulfonylamino, preferably R^{17}, $R^{17'}$, $R^{18'}$ and R^{19} are independently selected from H, halo preferably chloro and fluoro more preferably fluoro, cyano, alkyl preferably methyl, haloalkyl preferably CF_3 or CHF_2, cycloalkyl, heteroalkyl, heterocyclyl, aryl, heteroaryl, hydroxyl, alkoxy preferably methoxy, ethoxy, isopropyloxy, haloalkoxy preferably OCF_3 or $OCHF_2$, alkoxyalkoxy, cycloalkyloxy, alkoxyalkyl, cycloalkylalkyloxy, aryloxy, aralkyloxy, alkylamino, alkylsulfonyl preferably methylsulfonyl, alkylcarbonylamino, haloalkylcarbonylamino, carbamoyl, hydroxycarbamoyl, alkylcarbamoyl, carbamoylamino, alkylcarbamoylamino, haloalkylsulfonyl, cycloalkylsulfonyl, sulfamoyl, alkylsulfamoyl, alkylsulfonylamino, haloalkylsulfonylamino, more preferably R^{17}, $R^{17'}$, $R^{18'}$ and R^{19} are independently selected from H, halo preferably chloro and fluoro more preferably chloro, cyano, alkyl preferably methyl, haloalkyl preferably CF_3 or CHF_2, alkoxy preferably methoxy, haloalkoxy preferably OCF_3 or $OCHF_2$, alkoxyalkoxy preferably (2-methoxy)ethoxy, alkylamino preferably dimethylamino, more preferably $R^{17'}$, $R^{18'}$ and R^{19} are H and R^{17} is methoxy, (2-methoxy)ethoxy or R^{17}, $R^{18'}$ and R^{19} are H and $R^{17'}$ is methoxy, or R^{17}, $R^{17'}$ and $R^{18'}$ are H and R^{19} is chloro, methyl, methoxy, dimethylamino, or $R^{17'}$ and $R^{18'}$ are H and: *a)* both R^{17} and R^{19} are methyl or methoxy, or *b)* R^{17} is methyl and R^{19} is methoxy, or R^{17}, $R^{17'}$ and R^{19} are H and $R^{18'}$ is methoxy even more preferably $R^{17'}$, $R^{18'}$ and R^{19} are H and R^{17} is methoxy, or $R^{17'}$ and $R^{18'}$ are H and: *a)* both R^{17} and R^{19} are methyl or methoxy, or *b)* R^{17} is methyl and R^{19} is methoxy, or R^{17}, $R^{17'}$ and R^{19} are H and $R^{18'}$ is methoxy.

[0029] Other preferred compounds of formula Ib-1g are those of formula Ib-1g2





Ib-1g2

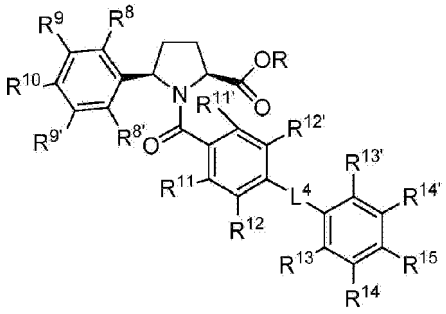
and pharmaceutically acceptable salts and solvates thereof, wherein

R is as defined above in respect of formula Ia-1b';

R^8, $R^{8'}$, R^9, $R^{9'}$ and **R^{10}** are as defined above in respect to formula Ib-1e;

R^{12} and **$R^{12'}$** are as defined above in respect to formula Ib-1g, preferably **R^{12}** and **$R^{12'}$** are independently selected from H, halo preferably chloro, cyano, nitro, alkyl preferably ethyl, isopropyl, haloalkyl preferably CF_3 or CHF_2, aryl preferably phenyl, hydroxyl, alkoxy preferably methoxy or ethoxy, haloalkoxy preferably OCF_3 or $OCHF_2$, alkoxyalkoxy, aryloxy, arylalkyloxy preferably phenethyloxy or benzyloxy, heteroarylalkyloxy, aryloxyalkyl, heteroaryloxyalkyl, each of said substituents being optionally substituted by one or more further substituents selected from halo preferably chloro or fluoro, alkoxy, alkyl, cycloalkyl, alkylsulfonyl preferably methylsulfonyl, more preferably **R^{12}** is H or alkoxy preferably methoxy or ethoxy, more preferably methoxy and **$R^{12'}$** is halo preferably chloro, alkoxy preferably methoxy or ethoxy, more preferably methoxy, arylalkyloxy preferably phenethyloxy, benzyloxy or 3,3-diphenylpropan-1-oxy, optionally substituted by halo preferably chloro or fluoro, alkoxy, alkyl, alkylsulfonyl preferably methylsulfonyl, even more preferably **R^{12}** is methoxy and **$R^{12'}$** is methoxy, chloro, benzyloxy, (4-chlorobenzyl)oxy, (4-methylsulfonylbenzyl)oxy.

[0030] Other preferred compounds of formula Ib-1g are those of formula Ib-1h



Ib-1h

and pharmaceutically acceptable salts and solvates thereof, wherein

R is as defined above in respect to formula Ia-1b';

R^8, $R^{8'}$, R^9, $R^{9'}$ and **R^{10}** are as defined above in respect to formula Ib-1e;

L^4 is a single bond, -C(O)-, -O-, -O-C_1-C_3-alkylene or -C_1-C_3-alkylene-O- optionally substituted

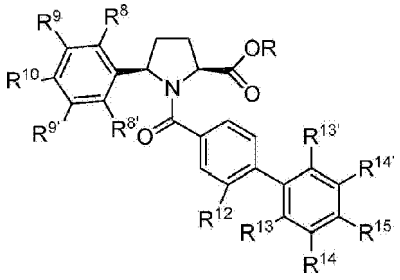
by one or more group selected from fluoro or methyl, preferably **L^4** is a single bond, -O-, -O-C_1-C_2-alkylene, -C_1-alkylene-O- optionally substituted by one or more group selected from fluoro or methyl, more preferably **L^4** is a single bond,-OCH_2, -$O(CH_2)_2$- or -CH_2O-;

R^{11}, $R^{11'}$, R^{12} and **$R^{12'}$** are as defined above in respect to formula Ib-1g, preferably **R^{11}** and **$R^{11'}$** are H and **R^{12}** and **$R^{12'}$** are independently selected from H, halo preferably chloro or fluoro, cyano, nitro, alkyl preferably methyl, ethyl, isopropyl, haloalkyl preferably CF_3 or CHF_2, hydroxyl, alkoxy preferably methoxy or ethoxy, haloalkoxy preferably OCF_3 or $OCHF_2$, alkoxyalkoxy, more preferably **R^{11}** and **$R^{11'}$** are H, **R^{12}** is H, fluoro, chloro, methyl, -CF_3, alkoxy preferably methoxy or ethoxy, more preferably methoxy and **$R^{12'}$** is halo preferably chloro, alkoxy preferably methoxy or ethoxy, more preferably methoxy, or **R^{11}, $R^{11'}$** and **$R^{12'}$** are H and **R^{12}** is fluoro, chloro, methyl, CF_3, methoxy, even more preferably **R^{11}** and **$R^{11'}$** are H, **R^{12}** is H or methoxy and **$R^{12'}$** is methoxy,chloro, or **R^{11}, $R^{11'}$** and **$R^{12'}$** are H and **R^{12}** is fluoro, chloro, methyl, CF_3, methoxy;

R^{13}, $R^{13'}$, R^{14}, $R^{14'}$ and **R^{15}** are independently selected from H, halo preferably chloro and fluoro more preferably fluoro, cyano, alkyl preferably methyl, ethyl, propyl, isopropyl, *tert*-butyl, haloalkyl preferably CF_3 or CHF_2, cyanomethyl, cycloalkyl, heteroalkyl, heterocyclyl, aryl, heteroaryl, hydroxyl, hydroxyalkyl, alkoxy preferably methoxy, haloalkoxy preferably OCF_3, $OCHF_2$, or 1,1,1-trifluoroethyloxy, alkoxyalkoxy, cycloalkyloxy, alkoxyalkyl, cycloalkylalkyloxy, aralkyloxy optionally substituted by one fluoro, amino, alkylamino, alkylcarbonylamino, haloalkylcarbonylamino, carbamoyl, hydroxycarbamoyl, alkylcarbamoyl, carbamoylalkyloxy, alkylcarbamoylamino, carbamimidoyl, hydroxycarbamimidoyl, alkylsulfonyl preferably methylsulfonyl, haloalkylsulfonyl, cycloalkylsulfonyl, sulfamoyl, alkylsulfamoyl, alkylsulfonylamino, haloalkylsulfonylamino, preferably **R^{13}, $R^{13'}$, R^{14}, $R^{14'}$** and **R^{15}** are independently selected from H, halo preferably chloro and fluoro more preferably fluoro, cyano, alkyl preferably methyl, ethyl, propyl, isopropyl, *tert*-butyl, haloalkyl preferably CF_3 or CHF_2, cycloalkyl, cycloalkylalkyl, heteroalkyl, heterocyclyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, hydroxyl, hydroxyalkyl, alkoxy preferably methoxy, haloalkoxy preferably OCF_3, $OCHF_2$, or 1,1,1-trifluoroethyloxy, alkoxyalkoxy, cycloalkyloxy, alkoxyalkyl, cycloalkylalkyloxy, aralkyloxy optionally substituted by one fluoro, amino, alkylamino, alkylcarbonylamino, haloalkylcarbonylamino, carbamoyl, hydroxycarbamoyl, alkylcarbamoyl, carbamoylalkyloxy, carbamoylamino, alkylcarbamoylamino, carbamimidoyl, hydroxycarbamimidoyl, alkylsulfonyl preferably methylsulfonyl, haloalkylsulfonyl, cycloalkylsulfonyl, sulfamoyl, alkylsulfamoyl, alkylsulfonylamino, haloalkylsulfonylamino, more preferably **R^{13}, $R^{13'}$, R^{14}, $R^{14'}$** and **R^{15}** are independently selected from H, halo preferably chloro and fluoro more preferably fluoro, cyano, alkyl preferably methyl, ethyl, propyl, isopropyl, *tert*-butyl, haloalkyl preferably -CF_3 or CHF_2, hydroxyl, hydroxyalkyl, alkoxy preferably methoxy, haloalkoxy preferably OCF_3 or $OCHF_2$, alkoxyalkoxy preferably 2-methoxyethoxy, cycloalkyloxy, cycloalkylalkyloxy, alkoxyalkyl preferably methoxymethyl, amino, alkylcarbonylamino preferably acetylamino, carbamoyl,

hydroxycarbamimidoyl, alkylsulfonyl preferably methylsulfonyl, haloalkylsulfonyl, cycloalkylsulfonyl, alkylsulfonylamino preferably methylsulfonylamino, (N-methyl-N-methylsulfonyl)amino, still more preferably **R^{13}, $R^{13'}$, R^{14}, $R^{14'}$** and **R^{15}** are independently selected from H, halo preferably chloro and fluoro, more preferably fluoro, cyano, nitro, alkyl preferably methyl, haloalkyl preferably -CF_3 or -CHF_2, alkoxyalkyl preferably methoxymethyl, alkoxy preferably methoxy, cycloalkylalkyloxy preferably cyclopropylmethyloxy, haloalkoxy preferably OCF_3 or $OCHF_2$, alkoxyalkoxy preferably 2-methoxyethoxy, amino, alkylcarbonylamino preferably acetylamino, alkylsulfonyl preferably methylsulfonyl, alkylsulfonylamino preferably methylsulfonylamino, (N-methyl-N-methylsulfonyl)amino, even more preferably **R^{13}, $R^{13'}$, R^{14}** and **$R^{14'}$** are H and **R^{15}** is H, chloro, methyl or methoxy, methylsulfonyl, methylsulfonylamino, preferably H, methylsulfonyl, methylsulfonylamino, or **$R^{13'}$, R^{14}, $R^{14'}$** and **R^{15}** are H and **R^{13}** is methoxy or chloro, preferably chloro, or **R^{13}, $R^{13'}$, $R^{14'}$** and **R^{15}** are H and **R^{14}** is methylsulfonylamino, or **$R^{13'}$, R^{14}** and **$R^{14'}$** are H and **R^{13}** and **R^{15}** are *a)* both F, or *b)* **R^{13}** is F and **R^{15}** is methoxy, or *c)* **R^{13}** is methoxy and **R^{15}** is F, or *d)* **R^{13}** is methoxy and **R^{15}** is acetylamino, or *e)* **R^{13}** is methoxy and **R^{15}** is amino, or *f)* **R^{13}** is cyano and **R^{15}** is methoxy, or *g)* **R^{13}** is chloro and **R^{15}** is cyano, or *h)* **R^{13}** is cyano and **R^{15}** is trifluoromethyl, or *i)* **R^{13}** is methoxy and **R^{15}** is (N-methyl-N-methylsulfonyl)amino, or **$R^{13'}$, $R^{14'}$** and **R^{15}** are H and **R^{13}** and **R^{14}** are *a)* both methoxy, or *b)* **R^{13}** is methyl and **R^{14}** is methylsulfonylamino, or c) **R^{13}** is methoxy and **R^{14}** is cyano, or *d)* **R^{13}** is methyl and **R^{14}** is amino, or **R^{13}, R^{13}** and **$R^{14'}$** are H and **R^{14}** and **R^{15}** are both methoxy, or **$R^{13'}$, R^{14}** and **R^{15}** are H and **R^{13}** and **$R^{14'}$** are *a)* both methoxy, or *b)* **R^{14}** is methoxy and **$R^{14'}$** is cyano, or *c)* **R^{14}** is methyl and **$R^{14'}$** is cyano, or **R^{13}, $R^{13'}$** and **R^{15}** are H and **R^{14}** and **$R^{14'}$** are both methoxy, or **R^{13}** and **R^{14}** are H and **$R^{13'}$, $R^{14'}$** and **R^{15}** are methoxy, or **R^{14}** and **R^{15}** are H and **R^{13}, $R^{13'}$** and **$R^{14'}$** are methoxy, or **R^{13}** and **R^{14}** are methoxy and **$R^{13'}$** and **R^{15}** are H and **$R^{14'}$** is cyano, or **R^{14}** and **R^{15}** are methoxy and **R^{13}** and **$R^{14'}$** are H and **$R^{13'}$** is cyano, or **R^{13}** and **$R^{13'}$** are H and **R^{14}, $R^{14'}$** and **R^{15}** are methoxy.

[0031] Preferred compounds of formula Ib-1h are those of formula Ib-1h1



Ib-1h1

and pharmaceutically acceptable salts and solvates thereof, wherein

R is as defined above in respect to formula Ia-1b';

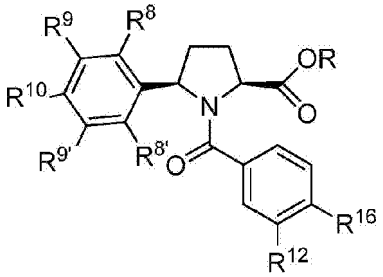
R^8, $R^{8'}$, R^9, $R^{9'}$ and **R^{10}** are as defined above in respect to formula Ib-1e;

R^{12} is as defined above in respect to formula Ib-1h, preferably **R^{12}** is H, fluoro, chloro, methyl, CF_3, nitro, cyano, methoxy or cyclopropylmethyloxy;

R^{13}, $R^{13'}$, R^{14}, $R^{14'}$ and **R^{15}** are as defined above in respect to formula Ib-1h, preferably **$R^{13'}$, R^{14}, $R^{14'}$** and **R^{15}** are H and **R^{13}** is chloro, cyano, hydroxyl, methyl, trifluoromethyl, cyanomethyl, methoxy, isopropoxy, isobutyloxy, OCF_3, cyclopropylmethyloxy, phenoxy, cyclopropylmethyloxy, benzyloxy, (4-fluorobenzyl)oxy, methoxymethyl, 2-methoxyethoxy, carbamoylmethyloxy, or **R^{13}, $R^{13'}$, $R^{14'}$** and **R^{15}** are H and **R^{14}** is chloro, methylsulfonylamino, or **R^{13}, $R^{13'}$, R^{14}** and **$R^{14'}$** are H and **R^{15}** is chloro, methylsulfonylamino, **$R^{13'}$, R^{14}** and **$R^{14'}$** are H and **R^{13}** and **R^{15}** are *a)* independently selected from chloro or methoxy, or *b)* both F, or *c)* **R^{13}** is F and **R^{15}** is methoxy, or *d)* **R^{13}** is methoxy and **R^{15}** is F, or *e)* **R^{13}** is methoxy and **R^{15}** is acetylamino, or *f)* **R^{13}** is methoxy and **R^{15}** is amino, or *g)* **R^{13}** is cyano and **R^{15}** is methoxy, or *h)* **R^{13}** is chloro and **R^{15}** is cyano, or *i)* **R^{13}** is cyano and **R^{15}** is trifluoromethyl, or *j)* **R^{13}** is methoxy and **R^{15}** is (N-methyl-N-methylsulfonyl)amino, or **R^{14}, $R^{14'}$** and **R^{15}** are H and both **R^{13}** and **$R^{13'}$** are methoxy, or **R^{13}, $R^{13'}$** and **R^{15}** are H and both **R^{14}** and **$R^{14'}$** are fluoro, methoxy, or **R^{13}, $R^{13'}$** and **$R^{14'}$** are H and *a)* **R^{14}** forms together with **R^{15}** a phenyl moiety fused to the phenyl ring they are attached to, or *b)* both **R^{14}** and **R^{15}** are methoxy, or **$R^{13'}$, $R^{14'}$** and **R^{15}** are H and **R^{13}** and **R^{14}** are *a)* both methoxy, or *b)* **R^{13}** is methyl and **R^{14}** is methylsulfonylamino, or *c)* **R^{13}** is methoxy and **R^{14}** is cyano, or *d)* **R^{13}** is methyl and **R^{14}** is amino, or **$R^{13'}$, R^{14}** and **R^{15}** are H and **R^{13}** and **$R^{14'}$** are *a)* both methoxy, or *b)* **R^{13}** is methoxy and **$R^{14'}$** is cyano, or *c)* **R^{13}** is methyl and **$R^{14'}$** is cyano, or **R^{13}** and **R^{14}** are H and **$R^{13'}$, $R^{14'}$** and **R^{15}** are methoxy, or **R^{14}** and **R^{15}** are H and **R^{13}, $R^{13'}$** and **$R^{14'}$** are methoxy, or **R^{13}** and **R^{14}** are methoxy and **$R^{13'}$** and **R^{15}** are H and **$R^{14'}$** is cyano, or **R^{14}** and **R^{15}** are methoxy and **R^{13}** and **$R^{14'}$** are H and **$R^{13'}$** is cyano, or **R^{13}** and **$R^{13'}$** are H and **R^{14}, $R^{14'}$** and **R^{15}** are methoxy, more preferably **$R^{13'}$, R^{14}, $R^{14'}$** and **R^{15}** are H and **R^{13}** is chloro, cyano, trifluoromethyl, methoxy, isopropoxy, cyclopropylmethyloxy, or **R^{13}, $R^{13'}$, $R^{14'}$** and **R^{15}** are H and **R^{14}** is chloro, or **R^{13}, $R^{13'}$, R^{14}** and **$R^{14'}$** are H and **R^{15}** is chloro, methylsulfonylamino, or **$R^{13'}$, R^{14}** and **$R^{14'}$** are H and **R^{13}** and **R^{15}** are *a)* independently selected from chloro or methoxy, or *b)* both F, or *c)* **R^{13}** is F and **R^{15}** is methoxy, or *d)* **R^{13}** is methoxy and **R^{15}** is F, or *e)* **R^{13}** is methoxy and **R^{15}** is acetylamino, or *f)* **R^{13}** is methoxy and **R^{15}** is amino, or *g)* **R^{13}** is cyano and **R^{15}** is methoxy, or *h)* **R^{13}** is chloro and **R^{15}** is cyano, or *i)* **R^{13}** is cyano and **R^{15}** is trifluoromethyl, or *j)* **R^{13}** is methoxy and **R^{15}** is (N-methyl-N-methylsulfonyl)amino, or **R^{14}, $R^{14'}$** and **R^{15}** are H and both **R^{13}** and **$R^{13'}$** are methoxy, or **R^{13}, $R^{13'}$** and **$R^{14'}$** are H and *a)* **R^{14}** forms together with **R^{15}** a phenyl moiety fused to the

phenyl ring they are attached to, or *b)* both **R14** and **R15** are methoxy, or **R13'**, **R14'** and **R15** are H and **R13** and **R14** are *a)* both methoxy, or *b)* **R13** is methyl and **R14** is methylsulfonylamino, or *c)* **R13** is methoxy and **R14** is cyano, or *d)* **R13** is methyl and **R14** is amino, or **R13'**, **R14** and **R15** are H and **R13** and **R14'** are *a)* both methoxy, or *b)* **R13** is methoxy and **R14'** is cyano, or *c)* **R13** is methyl and **R14'** is cyano, or **R13** and **R14** are H and **R13'**, **R14'** and **R15** are methoxy, or **R14** and **R15** are H and **R13**, **R13'** and **R14'** are methoxy, or **R13** and **R14** are methoxy and **R13'** and **R15** are H and **R14'** is cyano, or **R14** and **R15** are methoxy and **R13** and **R14'** are H and **R13'** is cyano, or **R13** and **R13'** are H and **R14**, **R14'** and **R15** are methoxy.

[0032] Other preferred compounds of formula Ib-1g are those of formula Ib-1h'



Ib-1h'

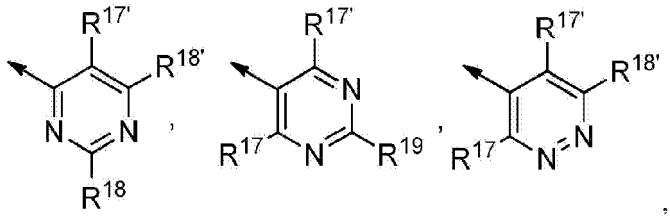
and pharmaceutically acceptable salts and solvates thereof, wherein

R is as defined above in respect to formula Ia-1b';

R8, **R8'**, **R9**, **R9'** and **R10** are as defined above in respect to formula Ib-1e;

R12 is as defined above in respect to formula Ib-1g, preferably **R12** is H, fluoro, chloro, methyl, CF_3, or methoxy more preferably **R12** is H or methoxy;

R16 is selected from the group of heteroaryl moieties consisting of:



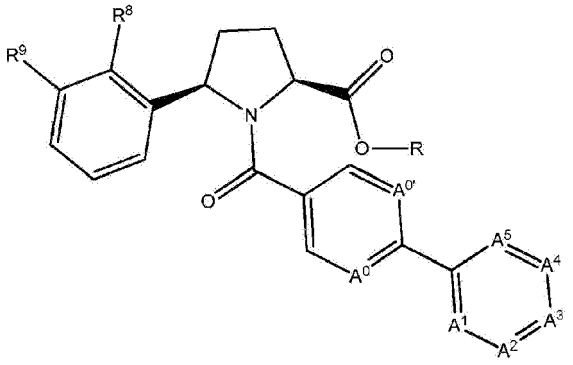
wherein the arrow marks the attachment point to the phenyl ring;

R17, **R17'**, **R18**, **R18'** and **R19** are independently selected from H, halo preferably chloro and fluoro, cyano, alkyl preferably methyl, ethyl, propyl, isopropyl, *tert*-butyl, haloalkyl preferably CF_3 or CHF_2, hydroxyl, hydroxyalkyl, alkoxy preferably methoxy, ethoxy, isopropyloxy, haloalkoxy preferably OCF_3, $OCHF_2$, or 1,1,1-trifluoroethyloxy, alkoxyalkoxy, cycloalkyloxy, alkoxyalkyl preferably methoxymethyl, cycloalkylalkyloxy preferably cyclopropylmethyloxy,

aralkyloxy preferably benzyloxy, amino, alkylamino, alkylcarbonylamino, haloalkylcarbonylamino, carbamoyl, hydroxycarbamoyl, alkylcarbamoyl, carbamoylamino, alkylcarbamoylamino, carbamimidoyl, hydroxycarbamimidoyl, alkylsulfonyl preferably methylsulfonyl, haloalkylsulfonyl, sulfamoyl, alkylsulfamoyl, alkylsulfonylamino preferably methylsulfonylamino, (N-methyl-N-methylsulfonyl)amino, haloalkylsulfonylamino, preferably R^{17}, $R^{17'}$, $R^{18'}$ and R^{19} are independently selected from H, halo preferably chloro and fluoro, cyano, alkyl preferably methyl, ethyl, propyl, isopropyl, *tert-butyl,* haloalkyl preferably CF_3, alkoxy preferably methoxy, ethoxy, isopropyloxy, haloalkoxy preferably OCF_3, $OCHF_2$, or 1,1,1-trifluoroethyloxy, alkoxyalkyl preferably methoxymethyl, aralkyloxy preferably benzyloxy, amino, alkylcarbonylamino, carbamoyl, carbamimidoyl, hydroxycarbamimidoyl, alkylsulfonyl preferably methylsulfonyl, alkylsulfonylamino preferably methylsulfonylamino, (N-methyl-N-methylsulfonyl)amino, more preferably R^{17}, $R^{17'}$, $R^{18'}$ and R^{19} are independently selected from H, halo preferably chloro, alkoxy preferably methoxy, even more preferably R^{17}, $R^{17'}$, $R^{18'}$ and R^{19} are independently selected from H, halo preferably chloro, alkoxy preferably methoxy.

[0033] Preferred compounds of formula Ib-1h' are those wherein R^{16} is selected from 2-2-methoxypyrimidin-4-yl, 2,4-dibenzyloxypyrimidin-5-yl, 2,4-dimethoxypyrimidin-5-yl, 3,6-dimethoxypyridazin-5-yl, 2-methoxypyrimidin-5-yl, 2-methoxypyrimidin-3-yl.

[0034] Still other preferred compounds of formula Ib-1g are those of formula Ib-1h"



Ib-1h"

and pharmaceutically acceptable salts and solvates thereof, wherein

R^8 is F or Cl and R^9 is H, or both R^8 and R^9 are F;

R is H, methyl, ethyl or *tert*-butyl;

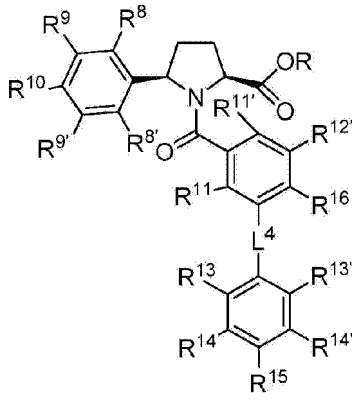
A^0, $A^{0'}$, A^1, A^2, A^3, A^4 and A^5 are selected from the combinations ***1*** to ***24***:

Combination No.	A^0	$A^{0'}$	A^1	A^2	A^3	A^4	A^5
1	CH	CH	C-OCH_3	CH	C-$NHSO_2CH_3$	CH	CH
2	CH	CH	C-CH_3	C-$NHSO_2CH_3$	CH	CH	CH

Combination No.	A^0	$A^{0'}$	A^1	A^2	A^3	A^4	A^5
3	CH	CH	C-OCH_3	N	CH	CH	CH
4	CH	CH	C-OCH_3	N	C-OCH_3	N	CH
5	C-OCH_3	CH	CH	N	C-OCH_3	N	CH
6	CH	CH	C-OCH_3	N	N	C-OCH_3	CH
7	CH	CH	C-OCH_3	CH	CH	C-CN	CH
8	CH	CH	C-CH_3	CH	CH	C-CN	CH
9	C-F	CH	C-OCH_3	N	N	C-OCH_3	CH
10	CH	CH	CH	N	CH	CH	C-OCH_3
11	CH	CH	CH	CH	C-$NHSO_2CH_3$	CH	CH
12	CH	CH	CH	C-$NHSO_2CH_3$	CH	CH	CH
13	CH	CH	CH	N	C-OCH_3	N	C-OCH_3
14	N	C-OCH_3	CH	CH	CH	CH	CH
15	CH	CH	C-OCH_3	N	CH	N	CH
16	CH	C-OCH_3	C-OCH_3	CH	CH	CH	CH
17	C-OCH_3	CH	CH	N	CH	CH	C-OCH_3
18	C-OCH_3	CH	C-OCH_3	N	C-OCH_3	N	CH
19	CH	CH	C-OCH_3	CH	C-$NHCOCH_3$	CH	CH
20	CH	CH	C-CN	CH	C-OCH_3	C-OCH_3	CH
21	CH	CH	C-OCH_3	CH	C-$N(CH_3)SO_2CH_3$	CH	CH

Combination No.	A^0	$A^{0'}$	A^1	A^2	A^3	A^4	A^5
22	N	CH	C-OCH_3	CH	C-OCH_3	CH	CH
23	CH	CH	C-OCH_3	N	CH	N	C-OCH_3
24	CH	CH	C-OCH_3	CH	N	CH	CH

[0035] Still other preferred compounds of formula Ib-1g are those of formula Ib-1i



Ib-1i

and pharmaceutically acceptable salts and solvates thereof, wherein

R is as defined above in respect to formula Ia-1b';

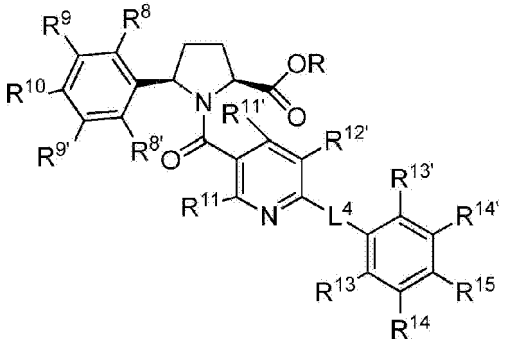
R^8, $R^{8'}$, R^9, $R^{9'}$ and **R^{10}** are as defined above in respect to formula Ib-1f;

L^4, R^{11}, $R^{11'}$, $R^{12'}$ R^{13}, $R^{13'}$, R^{14}, $R^{14'}$ and **R^{15}** is as defined above in respect to formula Ib-1h;

R^{16} is as defined above in respect to formula Ib-1g, preferably **R^{16}** is selected from H, halo preferably chloro or fluoro more preferably chloro, alkyl, haloalkyl preferably CF_3 or CHF_2, aryl, hydroxyl, alkoxy, haloalkoxy preferably OCF_3 or $OCHF_2$, alkoxyalkoxy, cycloalkyloxy, heterocyclyloxy, aryloxy, heteroaryloxy, alkoxyalkyl, haloalkoxyalkyl, arylalkyloxy, heteroarylalkyloxy, aryloxyalkyl, heteroaryloxyalkyl, or **R^{16}** forms together with **$R^{12'}$** an alkylenedioxy group or a haloalkylenedioxy group, each of said substituents being optionally substituted by one or more further substituents selected from halo preferably chloro or fluoro, alkoxy, alkyl, alkylsulfonyl, more preferably **R^{16}** is selected from H, halo preferably chloro and fluoro more preferably chloro, alkyl, haloalkyl preferably CF_3 or CHF_2, hydroxyl, alkoxy, haloalkoxy preferably OCF_3 or $OCHF_2$, alkoxyalkoxy, haloalkoxyalkyl, or **R^{16}** forms together with **$R^{12'}$** an alkylenedioxy group or a haloalkylenedioxy group, each of said substituents being optionally substituted by one or more further substituents selected from halo preferably chloro

or fluoro, alkoxy, alkyl, cycloalkyl, alkylsulfonyl.

[0036] Other preferred compounds of formula Ib-1f are those of formula Ib-1j



Ib-1j

and pharmaceutically acceptable salts and solvates thereof, wherein

R is as defined above in respect of formula Ia-1b';

R^8, $R^{8'}$, R^9, $R^{9'}$ and **R^{10}** are as defined above in respect of formula Ib-1f;

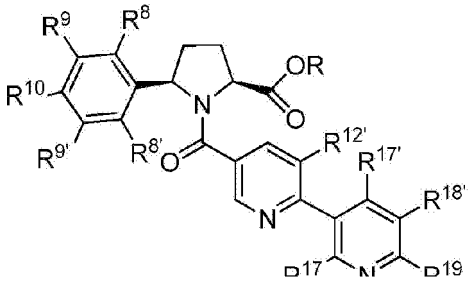
L^4 is as defined above in respect to formula Ib-1h, preferably **L^4** is a single bond;

R^{11} and **$R^{11'}$** are as defined above in respect to formula Ib-1h, preferably **R^{11}** and **$R^{11'}$** are H;

$R^{12'}$ is as defined above in respect to formula Ib-1h, preferably **$R^{12'}$** is H or methoxy, more preferably **$R^{12'}$** is H;

R^{13}, $R^{13'}$, R^{14}, $R^{14'}$ and **R^{15}** are as defined above in respect to formula Ib-1h, preferably **$R^{13'}$, R^{14}, $R^{14'}$** and **R^{15}** are H and **R^{13}** is chloro, fluoro, methoxy, or **R^{13}, $R^{13'}$, $R^{14'}$** and **R^{15}** are H and **R^{14}** is methoxy, or **$R^{13'}$, R^{14}** and **R^{15}** are H and *a)* both **R^{13}** and **$R^{14'}$** are chloro or *b)* **R^{13}** is methoxy and **$R^{14'}$** is cyano, or **$R^{13'}$, R^{14}** and **$R^{14'}$** are H and both **R^{13}** and **R^{15}** are methoxy more preferably **$R^{13'}$, R^{14}, $R^{14'}$** and **R^{15}** are H and **R^{13}** is chloro, or **$R^{13'}$, R^{14}** and **R^{15}** are H and both **R^{13}** and **$R^{14'}$** are chloro.

[0037] Other preferred compounds of formula Ib-1f are those of formula Ib-1k



Ib-1k

and pharmaceutically acceptable salts and solvates thereof, wherein

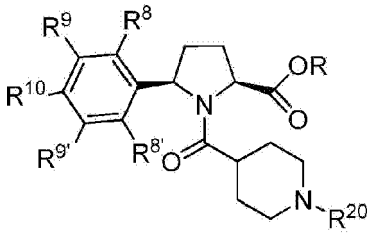
R is as defined above in respect of formula Ia-1b';

R^8, $R^{8'}$, R^9, $R^{9'}$ and **R^{10}** are as defined above in respect of formula Ib-1e;

$R^{12'}$ is H, fluoro, chloro, CF_3, methyl or methoxy, preferably **$R^{12'}$** is H or methoxy, more preferably **$R^{12'}$** is methoxy;

R^{17}, $R^{17'}$, $R^{18'}$ and **R^{19}** are independently selected from H, halo preferably chloro and fluoro, more preferably fluoro, cyano, nitro, alkyl preferably methyl, haloalkyl preferably CF_3 or CHF_2, alkoxyalkyl preferably methoxymethy, alkoxy preferably methoxy, cycloalkylalkyloxy preferably cyclopropylmethyloxy, haloalkoxy preferably OCF_3 or $OCHF_2$, alkoxyalkoxy preferably 2-methoxyethoxy, amino, alkylcarbonylamino preferably acetylamino, alkylsulfonyl preferably methylsulfonyl, alkylsulfonylamino preferably methylsulfonylamino, (N-methyl-N-methylsulfonyl)amino, preferably **$R^{17'}$** and **$R^{18'}$** are H and both **R^{17}** and **R^{19}** are methoxy.

[0038] Other preferred compounds of formula Ib-1f are those of formula Ib-1l



Ib-1l

and pharmaceutically acceptable salts and solvates thereof, wherein

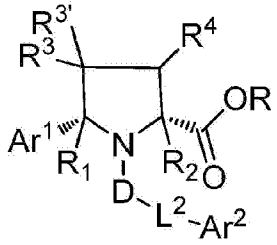
R is as defined above in respect of formula Ia-1b';

R^8, $R^{8'}$, R^9, $R^{9'}$ and **R^{10}** are as defined above in respect of formula Ib-1e;

R^{20} is an aryl or heteroaryl, each of said aryl or heteroaryl being optionally substituted by one or more substituent(s) selected from halo, alkyl, haloalkyl, cyano, nitro, phenyl optionally substituted by one chloro, alkoxy, heterocyclylsulfonyl, alkylsulfamoyl or alkylsulfonylamino, preferably **R^{20}** is a phenyl optionally substituted by one or more substituent(s) selected from halo preferably chloro or fluoro, alkyl preferably methyl, haloalkyl preferably CF_3, cyano, nitro, alkoxy preferably methoxy, heterocyclylsulfonyl preferably (piperidin-1-yl)sulfonyl, (morpholin-4-yl)sulfonyl, alkylsulfamoyl preferably diethylaminosulfonyl, alkylsulfonylamino preferably methylsulfonylamino, or **R^{20}** is 4-(4-chlorophenyl)thiazol-2-yl, or **R^{20}** is a benzoxazol-2-yl, more preferably **R^{20}** is 2-methoxyphenyl, 2-cyano-4-trifluoromethylphenyl, 2-chloro-4-

trifluoromethylphenyl, 2-nitro-4-trifluoromethylphenyl, 2-nitro-4-(piperidin-1-yl)sulfonyl phenyl, 4-(morpholin-4-yl)sulfonylphenyl, 2-nitro-4- diethylaminosulfonyl phenyl, 2-nitro-4-tolyl, 2-cyano-4-nitrophenyl, 4-nitrophenyl, 2-fluoro-4-nitrophenyl, 3-methoxy-4-nitrophenyl, 5-chloro-2-nitrophenyl, 2-cyano-4-methylsulfonylaminophenyl, 2-cyano-4-methoxyphenyl, 2-methylsulfonylamino-4-trifluoromethylphenyl, 2-nitrophenyl, 4-cyanophenyl, 2-methoxy-4-trifluoromethylphenyl, or **R**^{20} is 4-(4-chlorophenyl)thiazol-2-yl, or **R**^{20} is a benzoxazol-2-yl, even more preferably **R**^{20} is 2-cyano-4-trifluoromethylphenyl, 2-nitro-4-trifluoromethylphenyl, 2-methoxy-4-trifluoromethylphenyl.

[0039] Other preferred compounds are those of formula Ic-1b':



Ic-1b'

and pharmaceutically acceptable salts and, solvates thereof, wherein

R^{2} and **R** are as defined above in respect of formula Ia-1b';

R^{1} is H;

D is C=O;

L^{2} is single bond;

Ar^{1} is a 5- to 6-membered aryl or heteroaryl group, 3- to 6-membered cycloalkyl group, or a linear or branched C_3-C_6 alkyl group, each of which being optionally substituted by one or more group(s) selected from halo, cyano, alkyl, haloalkyl, cycloalkyl, aryl, heteroaryl, hydroxyl, alkoxy, haloalkoxy, amino, alkylamino, carboxy, alkoxycarbonyl, alkylcarbonyloxy, alkylcarbonylamino, haloalkylcarbonylamino, carbamoyl, hydroxycarbamoyl, alkylcarbamoyl, carbamoylamino, alkylcarbamoylamino, alkylsulfonyl, haloalkylsulfonyl, sulfamoyl, alkylsulfamoyl, alkylsulfonylamino, or two substituents form an alkylenedioxy group or a haloalkylenedioxy group, each of said aryl or heteroaryl substituents being optionally substituted by one or more further substituents selected from halo, cyano, alkyl, haloalkyl, hydroxyl, alkoxy, haloalkoxy, preferably **Ar**^{1} is a 5- to 6-membered aryl preferably phenyl, 5- to 6-membered heteroaryl group preferably pyridin-2-yl, pyridin-3-yl, cyclohexyl, cyclopentyl, isopropyl, isobutyl or isopentyl each of said phenyl, pyridin-2-yl, pyridin-3-yl, cyclohexyl or cyclopentyl group being optionally substituted by one or more group(s) selected from halo preferably bromo, chloro or fluoro, cyano, C_1-C_4 alkyl preferably methyl, C_1-C_4 alkoxy

preferably methoxy, aryl preferably phenyl, still more preferably **Ar^1** is aryl preferably phenyl, cyclohexyl, isobutyl or isopentyl, said phenyl group being optionally substituted by one or more halo group preferably bromo, chloro or fluoro, cyano, methyl, phenyl or methoxy, further more preferably **Ar^1** is phenyl, cyclohexyl, isobutyl, 2-chlorophenyl, 2-tolyl, 2-methoxyphenyl, 3-chlorophenyl, 4-chlorophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2,6-difluorophenyl, 2,4-difluorophenyl, 2,4-dichlorophenyl, 2-bromophenyl, 2-cyanophenyl, 3,5-difluorophenyl, 3,4-difluorophenyl, 2,3-difluorophenyl, 2,5-difluorophenyl, 1,1'-biphenyl-2-yl, 4-cyanophenyl, even more preferably **Ar^1** is isobutyl, cyclohexyl, phenyl , 2-chlorophenyl, 2-tolyl, 2-methoxyphenyl, 3-chlorophenyl, 4-chlorophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2,4-difluorophenyl, 2,4-dichlorophenyl, 2-bromophenyl, 2,3-difluorophenyl, 2,5-difluorophenyl, still even more preferably **Ar^1** is isobutyl, 2-chlorophenyl, 2-tolyl, 2-methoxyphenyl, 2-fluorophenyl, 2,4-difluorophenyl, 2-bromophenyl, 2,3-difluorophenyl, 2,5-difluorophenyl;

Ar^2 is an aryl or heteroaryl, cycloalkyl, monocyclic heterocyclyl or C_2-C_6 alkyl group, each of which being optionally substituted by one or more group(s) selected from halo, cyano, nitro, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, heteroalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, benzoxazol-2-yl heteroarylalkyl, hydroxyl, hydroxyalkyl, alkoxy, haloalkoxy, alkoxyalkoxy, cycloalkyloxy, cycloalkylalkyloxy, heterocyclyloxy, aryloxy, heteroaryloxy, alkoxyalkyl, haloalkoxyalkyl, arylalkyloxy, heteroarylalkyloxy, aryloxyalkyl, heteroaryloxyalkyl, amino, alkylamino, arylcarbonyl, carboxy, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, alkylcarbonyloxy, arylcarbonyloxy, heteroarylcarbonyloxy, alkylcarbonylamino, carbamoyl, hydroxycarbamoyl, alkylcarbamoyl, arylcarbamoyl, heteroarylcarbamoyl, carbamoylamino, alkylcarbamoylamino, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, heteroarylsulfamoyl, alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, oxo, or two substituents form an alkylenedioxy group or a haloalkylenedioxy group, or fused to the aryl, heteroaryl, cycloalkyl or heterocyclyl group may be one or more aryl or heteroaryl moiety, each of said substituents being optionally substituted by one or more further substituents selected from halo, cyano, nitro, alkyl, hydroxyalkyl, haloalkyl, cyanomethyl, cycloalkyl, heterocyclyl, aryl optionally substituted by a chloro or methyl group, heteroaryl, heteroalkyl, hydroxyl, alkoxy, alkoxyalkyl, alkoxyalkoxy, haloalkoxy, cycloalkyloxy, cycloalkylalkyloxy, aryloxy, aralkyloxy optionally substituted by a fluoro group, carboxy, alkoxycarbonyl, alkylcarbonyloxy, amino, alkylamino, alkylcarbonylamino, haloalkylcarbonylamino, carbamoyl, hydroxycarbamoyl, alkylcarbamoyl, carbamoylalkyloxy, carbamoylamino, alkylcarbamoylamino, carbamimidoyl, hydroxycarbamimidoyl, alkylsulfonyl, haloalkylsulfonyl, cycloalkylsulfonyl, heterocyclylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, alkylsulfonylamino, haloalkylsulfonylamino, oxo, and haloalkoxyalkyl; preferably **Ar^2** is an aryl or heteroaryl preferably pyridyl, pyrazinyl, cycloalkyl, monocyclic heterocyclyl or C_2-C_6 alkyl group, each of each of said aryl, heteroaryl, cycloalkyl and heterocyclyl groups being optionally substituted by one or more group(s) selected from halo preferably chloro and fluoro, cyano, nitro, alkyl, haloalkyl preferably CF_3 or CHF_2, heterocyclyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, hydroxyl, alkoxy, haloalkoxy preferably OCF_3 or $OCHF_2$, alkoxyalkoxy, aryloxy, alkoxyalkyl, arylalkyloxy, heteroarylalkyloxy,

cycloalkylalkyloxy, aryloxyalkyl, heteroaryloxyalkyl, arylcarbonyl, or two substituents form an alkylenedioxy group or a haloalkylenedioxy group, or fused to the cycloalkyl or heterocycloalkyl group may be one aryl moiety, each of said substituents being optionally substituted by one or more further substituents selected from halo preferably chloro or fluoro, cyano, nitro, alkyl preferably methyl, ethyl, propyl, isopropyl, *tert-butyl,* haloalkyl preferably CF_3, cyanomethyl, alkoxy preferably methoxy, ethoxy, isopropoxy, alkoxyalkyl, alkoxyalkoxy, cycloalkylalkyloxy, aryloxy, aralkyloxy optionally substituted by one fluoro, amino, alkylcarbonylamino, carbamoyl, hydroxycarbamimidoyl, alkylsulfonyl, alkylsulfonylamino, still more preferably **Ar^2** is an aryl preferably phenyl, heteroaryl preferably pyridyl, monocyclic heterocyclyl preferably piperidinyl, C_2-C_6 alkyl group preferably isobutyl, each of said aryl, heteroaryl and heterocyclyl groups being optionally substituted by one or more group(s) selected from halo preferably chloro and fluoro, cyano, nitro, alkyl, preferably methyl, heterocyclyl preferably pyrrolidin-1-yl, 4-methylpiperidin-1-yl, aryl preferably phenyl, heteroaryl preferably pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, alkoxy preferably methoxy, ethoxy or isopropyloxy, alkoxyalkyl, cycloalkylalkyloxy, arylalkyloxy preferably benzyloxy, phenethyloxy or 3,3-diphenylpropan-1-oxy, heteroarylalkyloxy preferably pyridylmethyloxy or pyridylethyloxy, aryloxyalkyl preferably phenoxymethyl, heteroaryloxyalkyl preferably pyridinyloxymethyl, arylcarbonyl preferably phenylacetyl, or two substituents form an haloalkylenedioxy group each of said substituents being optionally substituted by one or more further substituents selected from halo preferably chloro or fluoro, more preferably fluoro, cyano, nitro, alkyl preferably methyl, cycloalkyl, alkoxy preferably methoxy, isopropyloxy, isobutyloxy, cycloalkylalkyloxy preferably cyclopropylmethyloxy, alkoxyalkyl preferably methoxymethyl, alkoxyalkoxy preferably 2-methoxyethoxy, aryloxy preferably phenoxy, aralkyloxy optionally substituted by one fluoro, preferably benzyloxy or 4-fluorobenzyloxy, amino, alkylcarbonylamino preferably acetylamino, alkylsulfonyl preferably methylsulfonylalkyl, sulfonylamino preferably methylsulfonylamino, (N-methyl-N-methylsulfonyl)amino, further more preferably **Ar^2** is a biaryl consisting of two 6-membered aryl moieties preferably biphenyl, more preferably a biphenyl linked to **L^2** at position 4' and monosubstituted at position 2, or **Ar^2** is a heterobiaryl consisting of one 6-membered aryl moiety and one 6-membered heteroaryl moiety or two 6-membered heteroaryl moieties, said heterobiaryl being linked to **L^2** either on the aryl or on the heteroaryl moiety and being preferably phenylpyridyl, pyrimidinylphenyl, pyridazinylphenyl, pyrazinylphenyl, or **Ar^2** is an aryl or heteroaryl optionally substituted by one group selected from arylalkyloxy, aryloxyalkyl, arylcarbonyl, each of said biaryl, heterobiaryl, aryl and heteroaryl groups being optionally substituted by one or more group(s) selected from halo preferably chloro or fluoro, cyano, nitro, alkyl preferably methyl, ethyl, propyl, isopropyl, *tert*-butyl, alkoxy preferably methoxy, isopropyloxy, isobutyloxy, cycloalkylalkyloxy, aryloxy preferably phenoxy, aralkyloxy optionally substituted by one fluoro preferably benzyloxy or 4-fluorobenzyloxy, amino, alkylcarbonylamino preferably acetylamino, alkylsulfonylamino preferably methylsulfonylamino, (N-methyl-N-methylsulfonyl)amino, or **Ar^2** is a piperidinyl ring linked to **L^2** at position 4 and N substituted with a phenyl, 4-(4-chlorophenyl)thiazol-2-yl or benzoxazol-2-yl moiety, said phenyl moiety being further substituted by one or more substituents selected from halo preferably chloro and fluoro, cyano, nitro, alkyl preferably methyl, haloalkyl preferably CF_3, alkoxy preferably

methoxy, heterocyclylsulfonyl preferably (piperidin-1-yl)sulfonyl, (morpholin-4-yl)sulfonyl, alksulfamoyl preferably methylsulfonylamino, diethylaminosulfonyl, even more preferably **Ar^2** is 4'-(2-methoxy-1,1'-biphenyl), 4'-(2-methyl-1,1'-biphenyl), 4'-(2-fluoro-1,1'-biphenyl), 4'-(4-chloro-1,1'-biphenyl), 4'-(2-chloro-1,1'-biphenyl), 4'-(2-chloro-2'-methoxy-1,1'-biphenyl), 4' -(2-(2-methoxyethoxy)-1,1'-biphenyl), 4'-(2-(methoxymethyl)-1,1'-biphenyl), 4'-(4-methoxy-1,1'-biphenyl), 4'-(4-cyano-1,1'-biphenyl), 4'-(3-chloro-1,1'-biphenyl), 4'-(2-chloro-1,1'-biphenyl), 4'-(4-methylsulfonylamino-1,1'-biphenyl), 4'-(2-trifluoromethoxy-1,1'-biphenyl), 4'-(2-isopropoxy-1,1'-biphenyl), 4'-(2-cyclopropylmethyloxy-1,1'-biphenyl), 4'-(2-cyano-1,1'-biphenyl), 4'-(2,6-dimethoxy-1,1'-biphenyl), 4'-(2,4-dichloro-1,1'-biphenyl), 4'-(2-trifluoromethyl-1,1'-biphenyl), 4'-(2-methoxy-4-chloro-1,1'-biphenyl), 4'-(2,4-dimethoxy-1,1'-biphenyl), 4-(2,2'-dimethoxy-1,1'-biphenyl), 4-(naphtalen-2-yl)phenyl, 5-(2-phenyl)pyridyl, 4-cyclohexylphenyl, 4-benzylphenyl, 4-(3-thienyl)phenyl, 4-(pyridin-3-yl)phenyl, 4-(2-methoxypyridin-3-yl)phenyl, 4-(2,6-dimethoxy-pyridin-3-yl)phenyl, 4-(2-(2-methoxyethoxy)-pyridin-3-yl)phenyl, 4-(pyrimidin-2-yl)phenyl, 4-(pyrimidin-5-yl)phenyl, 4-(2-methoxypyrimidin-5-yl)-3-methoxyphenyl, 4-(2,4-dimethoxypyrimidin-6-yl)phenyl, 4-(2,4-dimethoxypyrimidin-5-yl)phenyl, (4-benzyloxy)phenyl, 4-phenoxyphenyl, (3-phenethyloxy)phenyl, (4-phenethyloxy)phenyl, (4-phenoxymethyl)phenyl, optionally substituted by one or more group(s) selected from halo preferably chloro or fluoro, more preferably fluoro, alkyl preferably methyl, alkoxy preferably methoxy, or **Ar^2** is 4'-(2,4-difluoro-1,1'-biphenyl), 4'-(3'-methyl-1,1'-biphenyl), 4'-(3'-fluoro-1,1'-biphenyl), 4'-(2-fluoro-4-methoxy-1,1'-biphenyl), 4'-(4-fluoro-2-methoxy-1,1'-biphenyl), 4'-(2,3-dimethoxy-1,1'-biphenyl), 4'-(3,4-dimethoxy-1,1'-biphenyl), 4'-(2,3,4-trimethoxy-1,1'-biphenyl), 4'-(2,3,6-trimethoxy-1,1'-biphenyl), 4'-(3,5-dimethoxy-1,1'-biphenyl), 4'-(2,5-dimethoxy-1,1'-biphenyl), 4'-(2-isopropyl-1,1'-biphenyl), 4'-(2,2'-dimethoxy-1,1'-biphenyl), 4'-(2'-fluoro,2-dimethoxy-1,1'-biphenyl), 4'-(2-ethyl-1,1'-biphenyl), 4'-(4-propyl-1,1'-biphenyl), 4'-(4-*tert*-butyl-1,1'-biphenyl), 4'-(2-methoxy-4-methylsulfonylamino-1,1'-biphenyl), 4'-(2-methoxy-4-acetylamino-1,1'-biphenyl), 4'-(3-hydroxycarbamimidoyl-1,1'-biphenyl), 4'-(4-amino-2-methoxy-1,1'-biphenyl), 4'-(3-carbamoyl-1,1'-biphenyl), 4'-(5-cyano-2,3-dimethoxy-1,1'-biphenyl), 4'-(2-cyano-4,5-dimethoxy-1,1'-biphenyl), 4'-(3,4,5-trimethoxy-1,1'-biphenyl), 4'-(2-cyanomethyl-4,5-dimethoxy-1,1'-biphenyl), 4'-(2-fluoro-5-cyano-1,1'-biphenyl), 4'-(2'-fluoro-3,4-dimethoxy-1,1'-biphenyl), 4'-(3-carbamoyl-4-cyano-1,1'-biphenyl), 4'-(2-cyano-4-methoxy-1,1'-biphenyl), 4'-(2'-fluoro-4-methylsulfonylamino-1,1'-biphenyl), 4'-(2'-fluoro-3-methylsulfonylamino-1,1'-biphenyl), 4'-(2-cyano-2'-fluoro-1,1'-biphenyl), 4'-(2-chloro-5-cyano-1,1'-biphenyl), 4'-(2-cyano-4-trifluoromethyl-1,1'-biphenyl), 4'-(2-methyl-3-(N-methyl-N-methylsulfonyl)amino-1,1'-biphenyl), 4'-(2-methyl-4-(N-methyl-N-methylsulfonyl)amino-1,1'-biphenyl), 4'-(4-methylsulfonyl-1,1'-biphenyl), 4'-(3-methylsulfonylamino-1,1'-biphenyl), 4'-(4-amino-2-methyl-1,1'-biphenyl), 4'-(5-cyano-2-methyl-1,1'-biphenyl), 4'-(5-cyano-2-methoxy-1,1'-biphenyl), 4'-(3-cyano-1,1'-biphenyl), 4'-(2-cyano-3-methoxy-1,1'-biphenyl), 4'-(2-methyl-3-methylsulfonylamino-1,1'-biphenyl), 4'-(2-methyl-3-acetylamino-1,1'-biphenyl), 4-(2-chloro-6-methoxypyrimidin-5-yl)phenyl, 4-(2-ethoxypyridin-5-yl)phenyl, 4-(2-isopropoxypyridin-5-yl)phenyl, 4-(2-methoxy-6-methylpyridin-5-yl)phenyl, 4-(2-methoxy-pyrimidin-4-yl)-3-chlorophenyl, 4-(2,6-dimethylpyridin-5-yl)phenyl, 4-(2,6-dimethoxy-pyrimidin-5-yl)-3-chlorophenyl, 4-(4-methoxy-pyridin-3-yl)-3-methoxyphenyl, 4-(6-methoxy-pyridin-3-yl)-3-methoxyphenyl, 4-(6-methoxy-pyridin-3-yl)-3-chlorophenyl, 4-(4,6-dimethoxy-pyridin-3-yl)phenyl, 4-(3,6-dimethoxypyridazin-5-yl)phenyl, 4-

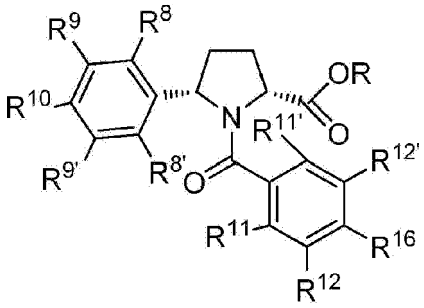
(2,6-dimethoxy-pyridin-3-yl)phenyl, 4-(5-methoxy-pyridin-3-yl)-3-methoxyphenyl, 4-(2,6-dimethoxy-pyridin-3-yl)-3-fluorophenyl, 4-(6-methoxypyridin-3-yl)-3-fluorophenyl, 4-(3,6-dimethoxy-pyridazin-5-yl)-3-fluorophenyl, 4-(4,6-dimethoxy-pyrimidin-5-yl)phenyl, 4-(2-methoxy-pyrimidin-5-yl)-3-methoxyphenyl, 4-(3-methoxy-pyridin-4-yl)phenyl, 4-(4-methoxy-pyridin-3-yl)phenyl, 4-(2-methoxypyrimidin-3-yl)phenyl, 3-methoxy-2-(2-methoxyphenyl)pyridin-5-yl, 3-methoxy-2-(5-cyano-2-methoxyphenyl)pyridin-5-yl, 3-methoxy-2-(2,4-dimethoxyphenyl)pyridin-5-yl, 2-(2,4-dimethoxyphenyl)pyridin-5-yl, 1-(2-cyano-4-trifluoromethyl)piperidin-4-yl, 1-(2-nitro-4-trifluoromethyl)piperidin-4-yl, 1-(2-methoxy-4-trifluoromethyl)piperidin-4-yl;

R^3 is H, cyano, alkyl, hydroxyalkyl, aralkyl, alkoxyalkyl, acetyl, arylsulfonyl;

$R^{3'}$ is H or C_1-C_4 alkyl;

R^4 is H, cyano, C_1-C_4 alkyl.

[0040] Preferred compounds of formula Ic-1b' are those of formula Ic-1g:



Ic-1g

and pharmaceutically acceptable salts and solvates thereof, wherein

R is as defined above in respect of formula Ia-1b';

R^8, $R^{8'}$, R^9, $R^{9'}$ and **R^{10}** are independently selected from H, halo preferably fluoro, chloro, bromo, cyano, alkyl, hydroxyalkyl, haloalkyl preferably CF_3 or CHF_2, cycloalkyl, cycloalkylalkyl, heteroalkyl, heterocyclyl, heterocyclylalkyl, aryl preferably phenyl, aralkyl, heteroaryl, heteroarylalkyl, hydroxyl, haloalkoxy preferably OCF_3 or $OCHF_2$, heterocyclyloxy, alkylamino, alkoxycarbonyl, cycloalkyloxycarbonyl, heterocyclyloxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, alkylcarbonyloxy, cycloalkylcarbonyloxy, heterocyclylcarbonyloxy, arylcarbonyloxy, heteroarylcarbonyloxy, arylalkyloxy, alkylcarbonylamino, haloalkylcarbonylamino, cycloalkylcarbonylamino, heterocyclylcarbonylamino arylcarbonylamino, heteroarylcarbonylamino, alkylcarbonylaminoalkyl, carbamoyl, hydroxycarbamoyl, alkylcarbamoyl, arylcarbamoyl, heteroarylcarbamoyl, carbamoylalkyl, carbamoylamino, alkylcarbamoylamino, alkylsulfonyl, haloalkylsulfonyl, cycloalkylsulfonyl, heterocyclylsulfonyl, arylsulfonyl, heteroarylsulfonyl sulfamoyl, alkylsulfamoyl, arylsulfamoyl, heteroarylsulfamoyl, alkylsulfonylamino, cycloalkylsulfonylamino, heterocyclylsulfonylamino,

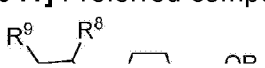
arylsulfonylamino, heteroarylsulfonylamino, or one or more of **R^8** and **R^9**, or **R^9** and **R^{10}**, or **R^{10}** and **$R^{9'}$**, or **$R^{9'}$** and **$R^{8'}$** form an alkylenedioxy group or a haloalkylenedioxy group together with the phenyl group they are attached to, or one or more of **R^8** and **R^9**, or **R^9** and **R^{10}**, or **R^{10}** and **$R^{9'}$**, or **$R^{9'}$** and **$R^{8'}$** form together a cycloalkyl, aryl, heterocycloalyl or heteroaryl moiety fused to the phenyl group they are attached to, each of said substituents being optionally substituted by one or more further substituents selected from halo, cyano, alkyl, hydroxyalkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, heteroalkyl, hydroxyl, alkoxy, haloalkoxy, cycloalkyloxy, alkylamino, carboxy, alkoxycarbonyl, alkylcarbonyloxy, cycloalkylcarbonyloxy, alkylcarbonylamino, haloalkylcarbonylamino, cycloalkylcarbonylamino, alkylcarbonylaminoalkyl, carbamoyl, hydroxycarbamoyl, alkylcarbamoyl, carbamoylalkyl, carbamoylamino, alkylcarbamoylamino, alkylsulfonyl, haloalkylsulfonyl, cycloalkylsulfonyl, sulfamoyl, alkylsulfamoyl, alkylsulfonylamino, cycloalkylsulfonylamino or oxo, preferably **R^8**, **$R^{8'}$**, **R^9**, **$R^{9'}$** and **R^{10}** are independently selected from H, halo preferably fluoro, chloro, bromo, cyano, alkyl, haloalkyl preferably CF_3 or CHF_2, cycloalkyl, aryl preferably phenyl, heteroaryl, hydroxyl, haloalkoxy preferably OCF_3 or $OCHF_2$, alkylamino, alkoxycarbonyl, alkylcarbonyloxy, alkylcarbonylamino, haloalkylcarbonylamino, carbamoyl, hydroxycarbamoyl, alkylcarbamoyl, carbamoylamino, alkylcarbamoylamino, alkylsulfonyl, haloalkylsulfonyl, sulfamoyl, alkylsulfamoyl, alkylsulfonylamino, or one or more of **R^8** and **R^9**, or **R^9** and **R^{10}**, or **R^{10}** and **$R^{9'}$**, or **$R^{9'}$** and **$R^{8'}$** form an alkylenedioxy group or a haloalkylenedioxy group together with the phenyl group they are attached to, each of said substituents being optionally substituted by one or more further substituents selected from halo, cyano, alkyl, haloalkyl, hydroxyl, alkoxy, haloalkoxy, more preferably **R^8**, **$R^{8'}$**, **R^9**, **$R^{9'}$** and **R^{10}** are independently selected from H, halo preferably bromo, fluoro or chloro, cyano, C_1-C_4 alkyl preferably methyl, aryl preferably phenyl, alkoxy preferably methoxy, still more preferably **R^8**, **$R^{8'}$**, **R^9**, **$R^{9'}$** and **R^{10}** are independently selected from H, halo preferably bromo, fluoro or chloro, alkyl preferably methyl, still more preferably **R^8** is Br, Cl or F, preferably Cl and **$R^{8'}$**, **R^9**, **$R^{9'}$** and **R^{10}** are independently selected from H or F, or **R^9** is Cl or F and **R^8**, **$R^{8'}$**, **$R^{9'}$** and **R^{10}** are H, or **R^9** and **$R^{9'}$** are F and **R^8**, **$R^{8'}$** and **R^{10}** are H, or **R^{10}** is Cl or F and **R^8**, **$R^{8'}$**, **R^9** and **$R^{9'}$** are H, even more preferably **R^8** is Br, Cl or F and **$R^{8'}$**, **R^9**, **$R^{9'}$** and **R^{10}** are H, or **R^8** and **R^9** are F and **$R^{8'}$**, **$R^{9'}$** and **R^{10}** are H, or **R^8** and **R^{10}** are F and **$R^{8'}$**, **R^9** and **$R^{9'}$** are H;

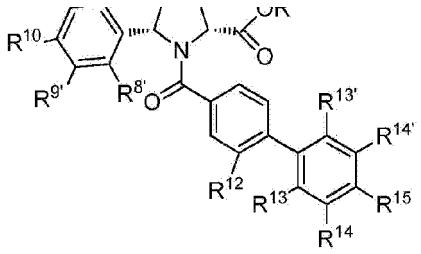
R^{11}, **$R^{11'}$**, **R^{12}**, **$R^{12'}$** and **R^{16}** are independently selected from H, halo preferably chloro and fluoro more preferably chloro, cyano, nitro, alkyl, haloalkyl preferably CF_3 or CHF_2, cycloalkyl, cycloalkylalkyl, heteroalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, hydroxyl, hydroxyalkyl, alkoxy, haloalkoxy preferably -OCF_3 or -$OCHF_2$, alkoxyalkoxy, cycloalkyloxy, heterocyclyloxy, aryloxy, heteroaryloxy, alkoxyalkyl, haloalkoxyalkyl, cycloalkylalkyloxy, arylalkyloxy, heteroarylalkyloxy, aryloxyalkyl, heteroaryloxyalkyl, arylcarbonyl, alkyloxycarbonyl, aminoalkylalkoxycarbonyl, cycloalkyloxycarbonyl, heterocyclyloxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, alkylcarbonyloxy, cycloalkylcarbonyloxy, heterocyclylcarbonyloxy, arylcarbonyloxy, heteroarylcarbonyloxy, alkylcarbonylamino, haloalkylcarbonylamino, cycloalkylcarbonylamino,

heterocyclylcarbonylamino arylcarbonylamino, heteroarylcarbonylamino, alkylcarbonylaminoalkyl, carbamoyl, hydroxycarbamoyl, alkylcarbamoyl, arylcarbamoyl, heteroarylcarbamoyl, carbamoylalkyl, carbamoylamino, alkylcarbamoylamino, alkylsulfonyl, haloalkylsulfonyl, cycloalkylsulfonyl, heterocyclylsulfonyl, arylsulfonyl, heteroarylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, heteroarylsulfamoyl, alkylsulfonylamino, cycloalkylsulfonylamino, heterocyclylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, haloalkylsulfonylamino, or one or more of R^{11} and R^{12}, or R^{12} and R^{16}, or R^{16} and $R^{12'}$, or $R^{12'}$ and $R^{11'}$ form an alkylenedioxy group or a haloalkylenedioxy group together with the phenyl group they are attached to, or one or more of R^{11} and R^{12}, or R^{12} and R^{16}, or R^{16} and $R^{12'}$, or $R^{12'}$ and $R^{11'}$ form together a cycloalkyl, aryl, heterocycloalkyl or heteroaryl moiety fused to the phenyl group they are attached to, each of said substituents being optionally substituted by one or more further substituents selected from halo preferably chloro or fluoro, cyano, alkyl, hydroxyalkyl, alkoxyalkyl, haloalkyl, cyanomethyl, cycloalkyl, heterocyclyl, aryl optionally substituted by one a chloro or methyl group, heteroaryl, cycloalkylalkyl, aralkyl, heteroarylalkyl, heteroalkyl, hydroxyl, alkoxy, alkoxyalkoxy, haloalkoxy preferably trifluoromethoxt, 1,1,1-trifluoroethyloxy, haloalkoxyalkyl, cycloalkyloxy, cycloalkylalkyloxy preferably cyclopropylmethyloxy, aryloxy, aralkyloxy optionally substituted by one fluoro, amino, alkylamino, carboxy, alkoxycarbonyl, alkylcarbonyloxy, alkylcarbonylamino, haloalkylcarbonylamino, cycloalkylcarbonylamino, alkylcarbonylaminoalkyl, carbamoyl, hydroxycarbamoyl, alkylcarbamoyl, carbamoylalkyl, carbamoylalkyloxy preferably carbamoylmethyloxy carbamoylamino, alkylcarbamoylamino, carbamimidoyl, hydroxycarbamimidoyl, alkylsulfonyl, haloalkylsulfonyl, cycloalkylsulfonyl, arylsulfonyl preferably phenylsulfonyl, sulfamoyl, alkylsulfamoyl, alkylsulfonylamino, cycloalkylsulfonylamino, haloalkylsulfonylamino and oxo, preferably R^{11}, $R^{11'}$, R^{12}, $R^{12'}$ and R^{16} are independently selected from H, halo preferably chloro and fluoro more preferably chloro, cyano, nitro, alkyl, haloalkyl preferably CF_3 or CHF_2, cycloalkyl, cycloalkylalkyl, heteroalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, hydroxyl, hydroxyalkyl, alkoxy, haloalkoxy preferably -OCF_3 or -$OCHF_2$, alkoxyalkoxy, cycloalkyloxy, heterocyclyloxy, aryloxy, heteroaryloxy, alkoxyalkyl, haloalkoxyalkyl, cycloalkylalkyloxy, arylalkyloxy, heteroarylalkyloxy, aryloxyalkyl, heteroaryloxyalkyl, arylcarbonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, alkylcarbonyloxy, arylcarbonyloxy, heteroarylcarbonyloxy, alkylcarbonylamino, carbamoyl, hydroxycarbamoyl, alkylcarbamoyl, arylcarbamoyl, heteroarylcarbamoyl, carbamoylamino, alkylcarbamoylamino, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, heteroarylsulfamoyl, alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, or one or more of R^{11} and R^{12}, or R^{12} and R^{16}, or R^{16} and $R^{12'}$, or $R^{12'}$ and $R^{11'}$ form an alkylenedioxy group or a haloalkylenedioxy group together with the phenyl group they are attached to, or one or more of R^{11} and R^{12}, or R^{12} and R^{16}, or R^{16} and $R^{12'}$, or $R^{12'}$ and $R^{11'}$ form together an aryl or heteroaryl moiety fused to the phenyl group they are attached to, each of said substituents being optionally substituted by one or more further substituents selected from halo preferably chloro or fluoro, cyano, alkyl, hydroxyalkyl, alkoxyalkyl, haloalkyl, cyanomethyl, cycloalkyl, heterocyclyl, aryl optionally substituted by one a chloro or methyl group, heteroaryl,

heteroalkyl, hydroxyl, alkoxy, alkoxyalkoxy, haloalkoxy preferably 1,1,1-trifluoroethyloxy, cycloalkyloxy, cycloalkylalkyloxy preferably cyclopropylmethyloxy, aryloxy, aralkyloxy optionally substituted by one fluoro, amino, alkylamino, carboxy, alkoxycarbonyl, alkylcarbonyloxy, alkylcarbonylamino, haloalkylcarbonylamino, carbamoyl, hydroxycarbamoyl, alkylcarbamoyl, carbamoylalkyloxy preferably carbamoylmethyloxy carbamoylamino, alkylcarbamoylamino, carbamimidoyl, hydroxycarbamimidoyl, alkylsulfonyl, haloalkylsulfonyl, cycloalkylsulfonyl, arylsulfonyl preferably phenylsulfonyl, sulfamoyl, alkylsulfamoyl, alkylsulfonylamino, haloalkylsulfonylamino and oxo, more preferably **R^{11}, $R^{11'}$, R^{12}, $R^{12'}$** and **R^{16}** are independently selected from H, halo preferably chloro and fluoro, cyano, nitro, alkyl, haloalkyl preferably CF_3 or CHF_2, heterocyclyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, hydroxyl, alkoxy, haloalkoxy preferably OCF_3 or $OCHF_2$, alkoxyalkoxy, aryloxy, cycloalkylalkyloxy, arylalkyloxy, heteroarylalkyloxy, alkoxyalkyl, aryloxyalkyl, heteroaryloxyalkyl, arylcarbonyl, or one or more of **R^{11}** and **R^{12},** or **R^{12}** and **R^{16},** or **R^{16}** and **$R^{12'}$,** or **$R^{12'}$** and **$R^{11'}$** form an alkylenedioxy group or a haloalkylenedioxy group together with the phenyl group they are attached to, or one or more of **R^{11}** and **R^{12}** or **R^{12}** and **R^{16},** or **R^{16}** and **$R^{12'}$,** or **$R^{12'}$** and **$R^{11'}$** form together an aryl, or heteroaryl moiety fused to the phenyl group they are attached to, each of said substituents being optionally substituted by one or more further substituents selected from halo preferably chloro or fluoro, cyano, alkyl preferably methyl, ethyl, propyl, isopropyl, *tert-butyl,* cyanomethyl, cycloalkyl, heterocyclyl, alkoxy preferably methoxy, ethoxy, isopropoxy, alkoxyalkyl, alkoxyalkoxy, cycloalkylalkyloxy, aryloxy, aralkyloxy optionally substituted by one fluoro, amino, alkylamino, alkylcarbonylamino, carbamoyl, hydroxycarbamimidoyl, alkylsulfonyl, alkylsulfonylamino, still more preferably **R^{11}, $R^{11'}$, R^{12}, $R^{12'}$** and **R^{16}** are independently selected from H, halo preferably chloro and fluoro, cyano, nitro, alkyl preferably methyl, ethyl, isopropyl or isobutyl, haloalkyl preferably CF_3 or CHF_2, cycloalkyl preferably cyclohexyl, heterocyclyl preferably pyrrolidin-1-yl, 4-methylpiperidin-1-yl, aryl preferably phenyl, heteroaryl preferably thiophenyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, aralkyl preferably benzyl, alkoxy preferably methoxy, ethoxy or isopropyloxy, cycloalkylalkyloxy, arylalkyloxy preferably benzyloxy, phenethyloxy or 3,3-diphenylpropan-1-oxy, heteroarylalkyloxy preferably pyridylmethyloxy or pyridylethyloxy, aryloxyalkyl preferably phenoxymethyl, heteroaryloxyalkyl preferably pyridyloxymethyl, or two substituents form an haloalkylenedioxy group each of said substituents being optionally substituted by one or more further substituents selected from halo preferably chloro or fluoro, cyano, alkyl preferably methyl, haloalkyl preferably trifluoromethyl, alkoxy preferably methoxy, isopropyloxy, isobutyloxy, alkoxyalkyl preferably methoxymethyl, alkoxyalkoxy preferably 2-methoxyethoxy, cycloalkylalkyloxy preferably cyclopropylmethyloxy, aryloxy preferably phenoxy, aralkyloxy optionally substituted by one fluoro, preferably benzyloxy, 4-fluorobenzyloxy, amino, alkylcarbonylamino preferably acetylamino, alkylsulfonyl preferably methylsulfonyl, alkylsulfonylamino preferably methylsulfonylamino, (N-methyl-N-methylsulfonyl)amino.

[0041] Preferred compounds of formula Ic-1g are those of formula Ic-1h1:





Ic-1h1

and pharmaceutically acceptable salts and solvates thereof, wherein

R is as defined above in respect to formula Ia-1b';

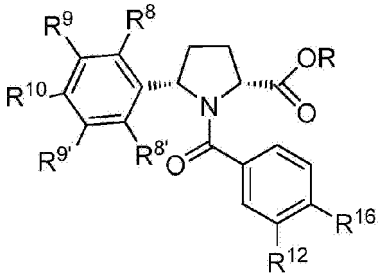
R^8, $R^{8'}$, R^9, $R^{9'}$ and **R^{10}** are as defined above in respect to formula Ic-1g;

R^{12} is as defined above in respect to formula Ic-1g, preferably **R^{12}** is H, fluoro, chloro, methyl, CF_3, nitro, cyano, methoxy or cyclopropylmethyloxy;

R^{13}, $R^{13'}$, R^{14}, $R^{14'}$ and **R^{15}** are as defined above in respect to formula Ic-1g, preferably **$R^{13'}$, R^{14}, $R^{14'}$** and **R^{15}** are H and **R^{13}** is chloro, cyano, hydroxyl, methyl, trifluoromethyl, cyanomethyl, methoxy, isopropoxy, isobutyloxy, OCF_3, cyclopropylmethyloxy, phenoxy, cyclopropylmethyloxy, benzyloxy, (4-fluorobenzyl)oxy, methoxymethyl, 2-methoxyethoxy, carbamoylmethyloxy, or **R^{13}, $R^{13'}$, $R^{14'}$** and **R^{15}** are H and **R^{14}** is chloro, methylsulfonylamino, or **R^{13}, $R^{13'}$, R^{14}** and **$R^{14'}$** are H and **R^{15}** is chloro, methylsulfonylamino, **$R^{13'}$, R^{14}** and **$R^{14'}$** are H and **R^{13}** and **R^{15}** are *a)* independently selected from chloro or methoxy, or *b)* both F, or c) **R^{13}** is F and **R^{15}** is methoxy, or *d)* **R^{13}** is methoxy and **R^{15}** is F, or *e)* **R^{13}** is methoxy and **R^{15}** is acetylamino, or f) **R^{13}** is methoxy and **R^{15}** is amino, or g) **R^{13}** is cyano and **R^{15}** is methoxy, or *h)* **R^{13}** is chloro and **R^{15}** is cyano, or *i)* **R^{13}** is cyano and **R^{15}** is trifluoromethyl, or *j)* **R^{13}** is methoxy and **R^{15}** is (N-methyl-N-methylsulfonyl)amino, or **R^{14}, $R^{14'}$** and **R^{15}** are H and both **R^{13}** and **$R^{13'}$** are methoxy, or **R^{13}, $R^{13'}$** and **R^{15}** are H and both **R^{14}** and **$R^{14'}$** are fluoro, methoxy, or **R^{13}, $R^{13'}$** and **$R^{14'}$** are H and *a)* **R^{14}** forms together with **R^{15}** a phenyl moiety fused to the phenyl ring they are attached to, or *b)* both **R^{14}** and **R^{15}** are methoxy, or **$R^{13'}$, $R^{14'}$** and **R^{15}** are H and **R^{13}** and **R^{14}** are *a)* both methoxy, or *b)* **R^{13}** is methyl and **R^{14}** is methylsulfonylamino, or c) **R^{13}** is methoxy and **R^{14}** is cyano, or *d)* **R^{13}** is methyl and **R^{14}** is amino, or **$R^{13'}$, R^{14}** and **R^{15}** are H and **R^{13}** and **$R^{14'}$** are *a)* both methoxy, or *b)* **R^{13}** is methoxy and **$R^{14'}$** is cyano, or c) **R^{13}** is methyl and **$R^{14'}$** is cyano, or **R^{13}** and **R^{14}** are H and **$R^{13'}$, $R^{14'}$** and **R^{15}** are methoxy, or **R^{14}** and **R^{15}** are H and **R^{13}, $R^{13'}$** and **$R^{14'}$** are methoxy, or **R^{13}** and **R^{14}** are methoxy and **$R^{13'}$** and **R^{15}** are H and **$R^{14'}$** is cyano, or **R^{14}** and **R^{15}** are methoxy and **R^{13}** and **$R^{14'}$** are H and **$R^{13'}$** is cyano, or **R^{13}** and **$R^{13'}$** are H and **R^{14}, $R^{14'}$** and **R^{15}** are methoxy, more preferably **$R^{13'}$, R^{14}, $R^{14'}$** and **R^{15}** are H and **R^{13}** is chloro, cyano, trifluoromethyl, methoxy, isopropoxy, cyclopropylmethyloxy, or **R^{13}, $R^{13'}$, $R^{14'}$** and **R^{15}** are H and **R^{14}** is chloro, or **R^{13}, $R^{13'}$, R^{14}** and

$R^{14'}$ are H and R^{15} is chloro, methylsulfonylamino, or $R^{13'}$, R^{14} and $R^{14'}$ are H and R^{13} and R^{15} are *a)* independently selected from chloro or methoxy, or *b)* both F, or *c)* R^{13} is F and R^{15} is methoxy, or *d)* R^{13} is methoxy and R^{15} is F, or *e)* R^{13} is methoxy and R^{15} is acetylamino, or *f)* R^{13} is methoxy and R^{15} is amino, or *g)* R^{13} is cyano and R^{15} is methoxy, or *h)* R^{13} is chloro and R^{15} is cyano, or *i)* R^{13} is cyano and R^{15} is trifluoromethyl, or *j)* R^{13} is methoxy and R^{15} is (N-methyl-N-methylsulfonyl)amino, or R^{14}, $R^{14'}$ and R^{15} are H and both R^{13} and $R^{13'}$ are methoxy, or R^{13}, $R^{13'}$ and $R^{14'}$ are H and *a)* R^{14} forms together with R^{15} a phenyl moiety fused to the phenyl ring they are attached to, or *b)* both R^{14} and R^{15} are methoxy, or $R^{13'}$, $R^{14'}$ and R^{15} are H and R^{13} and R^{14} are *a)* both methoxy, or *b)* R^{13} is methyl and R^{14} is methylsulfonylamino, or c) R^{13} is methoxy and R^{14} is cyano, or *d)* R^{13} is methyl and R^{14} is amino, or $R^{13'}$, R^{14} and R^{15} are H and R^{13} and $R^{14'}$ are *a)* both methoxy, or *b)* R^{13} is methoxy and $R^{14'}$ is cyano, or c) R^{13} is methyl and $R^{14'}$ is cyano, or R^{13} and R^{14} are H and $R^{13'}$, $R^{14'}$ and R^{15} are methoxy, or R^{14} and R^{15} are H and R^{13}, $R^{13'}$ and $R^{14'}$ are methoxy, or R^{13} and R^{14} are methoxy and $R^{13'}$ and R^{15} are H and $R^{14'}$ is cyano, or R^{14} and R^{15} are methoxy and R^{13} and $R^{14'}$ are H and $R^{13'}$ is cyano, or R^{13} and $R^{13'}$ are H and R^{14}, $R^{14'}$ and R^{15} are methoxy.

[0042] Other preferred compounds of formula Ic-1g are those of formula Ic-1h':



Ic-1h'

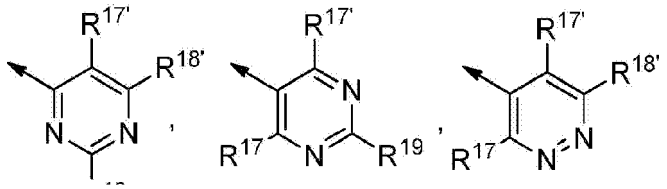
and pharmaceutically acceptable salts and solvates thereof, wherein

R is as defined above in respect to formula Ia-1b';

R^{8}, $R^{8'}$, R^{9}, $R^{9'}$ and R^{10} are as defined above in respect to formula Ic-1g;

R^{12} is as defined above in respect to formula Ic-1g, preferably R^{12} is H, fluoro, chloro, methyl, CF_3, or methoxy more preferably R^{12} is H or methoxy;

R^{16} is selected from the group of heteroaryl moieties consisting of:



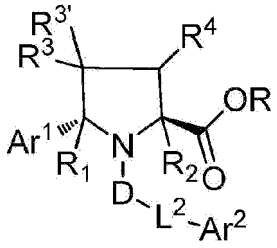
R^{18} ,

wherein the arrow marks the attachment point to the phenyl ring;

R^{17}, $R^{17'}$, R^{18}, $R^{18'}$ and **R^{19}** are independently selected from H, halo preferably chloro and fluoro, cyano, alkyl preferably methyl, ethyl, propyl, isopropyl, *tert-butyl,* haloalkyl preferably CF_3 or CHF_2, hydroxyl, hydroxyalkyl, alkoxy preferably methoxy, ethoxy, isopropyloxy, haloalkoxy preferably OCF_3, $OCHF_2$, or 1,1,1-trifluoroethyloxy, alkoxyalkoxy, cycloalkyloxy, alkoxyalkyl preferably methoxymethyl, cycloalkylalkyloxy preferably cyclopropylmethyloxy, aralkyloxy preferably benzyloxy, amino, alkylamino, alkylcarbonylamino, haloalkylcarbonylamino, carbamoyl, hydroxycarbamoyl, alkylcarbamoyl, carbamoylamino, alkylcarbamoylamino, carbamimidoyl, hydroxycarbamimidoyl, alkylsulfonyl preferably methylsulfonyl, haloalkylsulfonyl, sulfamoyl, alkylsulfamoyl, alkylsulfonylamino preferably methylsulfonylamino, (N-methyl-N-methylsulfonyl)amino, haloalkylsulfonylamino, preferably **R^{17}, $R^{17'}$, $R^{18'}$** and **R^{19}** are independently selected from H, halo preferably chloro and fluoro, cyano, alkyl preferably methyl, ethyl, propyl, isopropyl, *tert-butyl,* haloalkyl preferably CF_3, alkoxy preferably methoxy, ethoxy, isopropyloxy, haloalkoxy preferably OCF_3, $OCHF_2$, or 1,1,1-trifluoroethyloxy, alkoxyalkyl preferably methoxymethyl, aralkyloxy preferably benzyloxy, amino, alkylcarbonylamino, carbamoyl, carbamimidoyl, hydroxycarbamimidoyl, alkylsulfonyl preferably methylsulfonyl, alkylsulfonylamino preferably methylsulfonylamino, (N-methyl-N-methylsulfonyl)amino, more preferably **R^{17}, $R^{17'}$, $R^{18'}$** and **R^{19}** are independently selected from H, halo preferably chloro, alkoxy preferably methoxy, even more preferably **R^{17}, $R^{17'}$, $R^{18'}$** and **R^{19}** are independently selected from H, halo preferably chloro, alkoxy preferably methoxy;

Preferred compounds of formula Ic-1h' are those wherein **R^{16}** is selected from 2-2-methoxypyrimidin-4-yl, 2,4-dibenzyloxypyrimidin-5-yl, 2,4-dimethoxypyrimidin-5-yl, 3,6-dimethoxypyridazin-5-yl, 2-methoxypyrimidin-5-yl, 2-methoxypyrimidin-3-yl.

[0043] Other preferred compounds are those of formula Id-1b':



Id-1b'

and pharmaceutically acceptable salts and solvates thereof, wherein

R^2 and **R** are as defined above in respect of formula Ia-1b';

R^1 is H;

D is C=O;

L^2 is single bond;

Ar^1 is a 5- to 6-membered aryl or heteroaryl group, 3- to 6-membered cycloalkyl group, or a linear or branched C_3-C_6 alkyl group, each of which being optionally substituted by one or more group(s) selected from halo, cyano, alkyl, haloalkyl, cycloalkyl, aryl, heteroaryl, hydroxyl, alkoxy, haloalkoxy, amino, alkylamino, carboxy, alkoxycarbonyl, alkylcarbonyloxy, alkylcarbonylamino, haloalkylcarbonylamino, carbamoyl, hydroxycarbamoyl, alkylcarbamoyl, carbamoylamino, alkylcarbamoylamino, alkylsulfonyl, haloalkylsulfonyl, sulfamoyl, alkylsulfamoyl, alkylsulfonylamino, or two substituents form an alkylenedioxy group or a haloalkylenedioxy group, each of said aryl or heteroaryl substituents being optionally substituted by one or more further substituents selected from halo, cyano, alkyl, haloalkyl, hydroxyl, alkoxy, haloalkoxy, preferably Ar^1 is a 5- to 6-membered aryl preferably phenyl, 5- to 6-membered heteroaryl group preferably pyridin-2-yl, pyridin-3-yl, cyclohexyl, cyclopentyl, isopropyl, isobutyl or isopentyl each of said phenyl, pyridin-2-yl, pyridin-3-yl, cyclohexyl or cyclopentyl group being optionally substituted by one or more group(s) selected from halo preferably bromo, chloro or fluoro, cyano, C_1-C_4 alkyl preferably methyl, C_1-C_4 alkoxy preferably methoxy, aryl preferably phenyl, still more preferably Ar^1 is aryl preferably phenyl, cyclohexyl, isobutyl or isopentyl, said phenyl group being optionally substituted by one or more halo group preferably bromo, chloro or fluoro, cyano, methyl, phenyl or methoxy, further more preferably Ar^1 is phenyl, cyclohexyl, isobutyl, 2-chlorophenyl, 2-tolyl, 2-methoxyphenyl, 3-chlorophenyl, 4-chlorophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2,6-difluorophenyl, 2,4-difluorophenyl, 2,4-dichlorophenyl, 2-bromophenyl, 2-cyanophenyl, 3,5-difluorophenyl, 3,4-difluorophenyl, 2,3-difluorophenyl, 2,5-difluorophenyl, 1,1'-biphenyl-2-yl, 4-cyanophenyl, even more preferably Ar^1 is isobutyl, cyclohexyl, phenyl , 2-chlorophenyl, 2-tolyl, 2-methoxyphenyl, 3-chlorophenyl, 4-chlorophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2,4-difluorophenyl, 2,4-dichlorophenyl, 2-bromophenyl, 2,3-difluorophenyl, 2,5-difluorophenyl, still even more preferably Ar^1 is isobutyl, 2-chlorophenyl, 2-tolyl, 2-methoxyphenyl, 2-fluorophenyl, 2,4-difluorophenyl, 2-bromophenyl, 2,3-difluorophenyl, 2,5-difluorophenyl;

Ar^2 is an aryl or heteroaryl, cycloalkyl, monocyclic heterocyclyl or C_2-C_6 alkyl group, each of which being optionally substituted by one or more group(s) selected from halo, cyano, nitro, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, heteroalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, benzoxazol-2-yl heteroarylalkyl, hydroxyl, hydroxyalkyl, alkoxy, haloalkoxy, alkoxyalkoxy, cycloalkyloxy, cycloalkylalkyloxy, heterocyclyloxy, aryloxy, heteroaryloxy, alkoxyalkyl, haloalkoxyalkyl, arylalkyloxy, heteroarylalkyloxy, aryloxyalkyl, heteroaryloxyalkyl, amino, alkylamino, arylcarbonyl, carboxy, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, alkylcarbonyloxy, arylcarbonyloxy, heteroarylcarbonyloxy, alkylcarbonylamino, carbamoyl, hydroxycarbamoyl, alkylcarbamoyl, arylcarbamoyl, heteroarylcarbamoyl, carbamoylamino, alkylcarbamoylamino, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, heteroarylsulfamoyl, alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, oxo, or two substituents form

an alkylenedioxy group or a haloalkylenedioxy group, or fused to the aryl, heteroaryl, cycloalkyl or heterocyclyl group may be one or more aryl or heteroaryl moiety, each of said substituents being optionally substituted by one or more further substituents selected from halo, cyano, nitro, alkyl, hydroxyalkyl, haloalkyl, cyanomethyl, cycloalkyl, heterocyclyl, aryl optionally substituted by a chloro or methyl group, heteroaryl, heteroalkyl, hydroxyl, alkoxy, alkoxyalkyl, alkoxyalkoxy, haloalkoxy, cycloalkyloxy, cycloalkylalkyloxy, aryloxy, aralkyloxy optionally substituted by a fluoro group, carboxy, alkoxycarbonyl, alkylcarbonyloxy, amino, alkylamino, alkylcarbonylamino, haloalkylcarbonylamino, carbamoyl, hydroxycarbamoyl, alkylcarbamoyl, carbamoylalkyloxy, carbamoylamino, alkylcarbamoylamino, carbamimidoyl, hydroxycarbamimidoyl, alkylsulfonyl, haloalkylsulfonyl, cycloalkylsulfonyl, heterocyclylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, alkylsulfonylamino, haloalkylsulfonylamino, oxo, and haloalkoxyalkyl; preferably **Ar^2** is an aryl or heteroaryl preferably pyridyl, pyrazinyl, cycloalkyl, monocyclic heterocyclyl or C_2-C_6 alkyl group, each of each of said aryl, heteroaryl, cycloalkyl and heterocyclyl groups being optionally substituted by one or more group(s) selected from halo preferably chloro and fluoro, cyano, nitro, alkyl, haloalkyl preferably CF_3 or CHF_2, heterocyclyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, hydroxyl, alkoxy, haloalkoxy preferably OCF_3 or $OCHF_2$, alkoxyalkoxy, aryloxy, alkoxyalkyl, arylalkyloxy, heteroarylalkyloxy, cycloalkylalkyloxy, aryloxyalkyl, heteroaryloxyalkyl, arylcarbonyl, or two substituents form an alkylenedioxy group or a haloalkylenedioxy group, or fused to the cycloalkyl or heterocycloalkyl group may be one aryl moiety, each of said substituents being optionally substituted by one or more further substituents selected from halo preferably chloro or fluoro, cyano, nitro, alkyl preferably methyl, ethyl, propyl, isopropyl, *tert-butyl,* haloalkyl preferably CF_3, cyanomethyl, alkoxy preferably methoxy, ethoxy, isopropoxy, alkoxyalkyl, alkoxyalkoxy, cycloalkylalkyloxy, aryloxy, aralkyloxy optionally substituted by one fluoro, amino, alkylcarbonylamino, carbamoyl, hydroxycarbamimidoyl, alkylsulfonyl, alkylsulfonylamino, still more preferably **Ar^2** is an aryl preferably phenyl, heteroaryl preferably pyridyl, monocyclic heterocyclyl preferably piperidinyl, C_2-C_6 alkyl group preferably isobutyl, each of said aryl, heteroaryl and heterocyclyl groups being optionally substituted by one or more group(s) selected from halo preferably chloro and fluoro, cyano, nitro, alkyl, preferably methyl, heterocyclyl preferably pyrrolidin-1-yl, 4-methylpiperidin-1-yl, aryl preferably phenyl, heteroaryl preferably pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, alkoxy preferably methoxy, ethoxy or isopropyloxy, alkoxyalkyl, cycloalkylalkyloxy, arylalkyloxy preferably benzyloxy, phenethyloxy or 3,3-diphenylpropan-1-oxy, heteroarylalkyloxy preferably pyridylmethyloxy or pyridylethyloxy, aryloxyalkyl preferably phenoxymethyl, heteroaryloxyalkyl preferably pyridinyloxymethyl, arylcarbonyl preferably phenylacetyl, or two substituents form an haloalkylenedioxy group each of said substituents being optionally substituted by one or more further substituents selected from halo preferably chloro or fluoro, more preferably fluoro, cyano, nitro, alkyl preferably methyl, cycloalkyl, alkoxy preferably methoxy, isopropyloxy, isobutyloxy, cycloalkylalkyloxy preferably cyclopropylmethyloxy, alkoxyalkyl preferably methoxymethyl, alkoxyalkoxy preferably 2-methoxyethoxy, aryloxy preferably phenoxy, aralkyloxy optionally substituted by one fluoro, preferably benzyloxy or 4-fluorobenzyloxy, amino, alkylcarbonylamino preferably acetylamino, alkylsulfonyl preferably methylsulfonylalkylsulfonylamino preferably methylsulfonylamino, (N-methyl-N-methylsulfonyl)amino, further more preferably **Ar^2** is a biaryl consisting of two 6-

membered aryl moieties preferably biphenyl, more preferably a biphenyl linked to **L^2** at position 4' and monosubstituted at position 2, or **Ar^2** is a heterobiaryl consisting of one 6-membered aryl moiety and one 6-membered heteroaryl moiety or two 6-membered heteroaryl moieties, said heterobiaryl being linked to **L^2** either on the aryl or on the heteroaryl moiety and being preferably phenylpyridyl, pyrimidinylphenyl, pyridazinylphenyl, pyrazinylphenyl, or **Ar^2** is an aryl or heteroaryl optionally substituted by one group selected from arylalkyloxy, aryloxyalkyl, arylcarbonyl, each of said biaryl, heterobiaryl, aryl and heteroaryl groups being optionally substituted by one or more group(s) selected from halo preferably chloro or fluoro, cyano, nitro, alkyl preferably methyl, ethyl, propyl, isopropyl, *tert*-butyl, alkoxy preferably methoxy, isopropyloxy, isobutyloxy, cycloalkylalkyloxy, aryloxy preferably phenoxy, aralkyloxy optionally substituted by one fluoro preferably benzyloxy or 4-fluorobenzyloxy, amino, alkylcarbonylamino preferably acetylamino, alkylsulfonylamino preferably methylsulfonylamino, (N-methyl-N-methylsulfonyl)amino, or **Ar^2** is a piperidinyl ring linked to **L^2** at position 4 and N substituted with a phenyl, 4-(4-chlorophenyl)thiazol-2-yl or benzoxazol-2-yl moiety, said phenyl moiety being further substituted by one or more substituents selected from halo preferably chloro and fluoro, cyano, nitro, alkyl preferably methyl, haloalkyl preferably CF_3, alkoxy preferably methoxy, heterocyclylsulfonyl preferably (piperidin-1-yl)sulfonyl, (morpholin-4-yl)sulfonyl, alksulfamoyl preferably methylsulfonylamino, diethylaminosulfonyl, even more preferably **Ar^2** is 4'-(2-methoxy-1,1'-biphenyl), 4'-(2-methyl-1,1'-biphenyl), 4'-(2-fluoro-1,1'-biphenyl), 4'-(4-chloro-1,1'-biphenyl), 4'-(2-chloro-1,1'-biphenyl), 4'-(2-chloro-2'-methoxy-1,1'-biphenyl), 4'-(2-(2-methoxyethoxy)-1,1'-biphenyl), 4'-(2-(methoxymethyl)-1,1'-biphenyl), 4'-(4-methoxy-1,1'-biphenyl), 4'-(4-cyano-1,1'-biphenyl), 4'-(3-chloro-1,1'-biphenyl), 4'-(2-chloro-1,1'-biphenyl), 4'-(4-methylsulfonylamino-1,1'-biphenyl), 4'-(2-trifluoromethoxy-1,1'-biphenyl), 4'-(2-isopropoxy-1,1'-biphenyl), 4'-(2-cyclopropylmethyloxy-1,1'-biphenyl), 4'-(2-cyano-1,1'-biphenyl), 4'-(2,6-dimethoxy-1,1'-biphenyl), 4'-(2,4-dichloro-1,1'-biphenyl), 4'-(2-trifluoromethyl-1,1'-biphenyl), 4'-(2-methoxy-4-chloro-1,1'-biphenyl), 4'-(2,4-dimethoxy-1,1'-biphenyl), 4-(2,2'-dimethoxy-1,1'-biphenyl), 4-(naphtalen-2-yl)phenyl, 5-(2-phenyl)pyridyl, 4-cyclohexylphenyl, 4-benzylphenyl, 4-(3-thienyl)phenyl, 4-(pyridin-3-yl)phenyl, 4-(2-methoxypyridin-3-yl)phenyl, 4-(2,6-dimethoxy-pyridin-3-yl)phenyl, 4-(2-(2-methoxyethoxy)-pyridin-3-yl)phenyl, 4-(pyrimidin-2-yl)phenyl, 4-(pyrimidin-5-yl)phenyl, 4-(2-methoxypyrimidin-5-yl)-3-methoxyphenyl, 4-(2,4-dimethoxypyrimidin-6-yl)phenyl, 4-(2,4-dimethoxypyrimidin-5-yl)phenyl, (4-benzyloxy)phenyl, 4-phenoxyphenyl, (3-phenethyloxy)phenyl, (4-phenethyloxy)phenyl, (4-phenoxymethyl)phenyl, optionally substituted by one or more group(s) selected from halo preferably chloro or fluoro, more preferably fluoro, alkyl preferably methyl, alkoxy preferably methoxy, or **Ar^2** is 4'-(2,4-difluoro-1,1'-biphenyl), 4'-(3'-methyl-1,1'-biphenyl), 4'-(3'-fluoro-1,1'-biphenyl), 4'-(2-fluoro-4-methoxy-1,1'-biphenyl), 4'-(4-fluoro-2-methoxy-1,1'-biphenyl), 4'-(2,3-dimethoxy-1,1'-biphenyl), 4'-(3,4-dimethoxy-1,1'-biphenyl), 4'-(2,3,4-trimethoxy-1,1'-biphenyl), 4'-(2,3,6-trimethoxy-1,1'-biphenyl), 4'-(3,5-dimethoxy-1,1'-biphenyl), 4'-(2,5-dimethoxy-1,1'-biphenyl), 4'-(2-isopropyl-1,1'-biphenyl), 4'-(2,2'-dimethoxy-1,1'-biphenyl), 4'-(2'-fluoro,2-dimethoxy-1,1'-biphenyl), 4'-(2-ethyl-1,1'-biphenyl), 4'-(4-propyl-1,1'-biphenyl), 4'-(4-*tert*-butyl-1,1'-biphenyl), 4'-(2-methoxy-4-methylsulfonylamino-1,1'-biphenyl), 4'-(2-methoxy-4-acetylamino-1,1'-biphenyl), 4'-(3-hydroxycarbamimidoyl-1,1'-biphenyl), 4'-(4-amino-2-methoxy-1,1'-biphenyl), 4'-(3-carbamoyl-

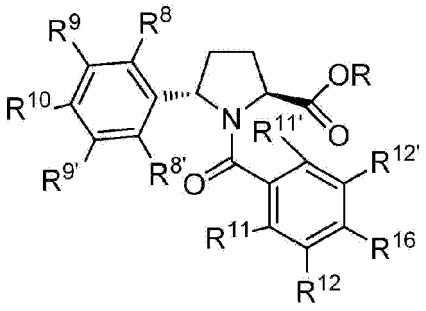
1,1'-biphenyl), 4'-(5-cyano-2,3-dimethoxy-1,1'-biphenyl), 4'-(2-cyano-4,5-dimethoxy-1,1'-biphenyl), 4'-(3,4,5-trimethoxy-1,1'-biphenyl), 4'-(2-cyanomethyl-4,5-dimethoxy-1,1'-biphenyl), 4'-(2-fluoro-5-cyano-1,1'-biphenyl), 4'-(2'-fluoro-3,4-dimethoxy-1,1'-biphenyl), 4'-(3-carbamoyl-4-cyano-1,1'-biphenyl), 4'-(2-cyano-4-methoxy-1,1'-biphenyl), 4'-(2'-fluoro-4-methylsulfonylamino-1,1'-biphenyl), 4'-(2'-fluoro-3-methylsulfonylamino-1,1'-biphenyl), 4'-(2-cyano-2'-fluoro-1,1'-biphenyl), 4'-(2-chloro-5-cyano-1,1'-biphenyl), 4'-(2-cyano-4-trifluoromethyl-1,1'-biphenyl), 4'-(2-methyl-3-(N-methyl-N-methylsulfonyl)amino-1,1'-biphenyl), 4'-(2-methyl-4-(N-methyl-N-methylsulfonyl)amino-1,1'-biphenyl), 4'-(4-methylsulfonyl-1,1'-biphenyl), 4'-(3-methylsulfonylamino-1,1'-biphenyl), 4'-(4-amino-2-methyl-1,1'-biphenyl), 4'-(5-cyano-2-methyl-1,1'-biphenyl), 4'-(5-cyano-2-methoxy-1,1'-biphenyl), 4'-(3-cyano-1,1'-biphenyl), 4'-(2-cyano-3-methoxy-1,1'-biphenyl), 4'-(2-methyl-3-methylsulfonylamino-1,1'-biphenyl), 4'-(2-methyl-3-acetylamino-1,1'-biphenyl), 4-(2-chloro-6-methoxypyrimidin-5-yl)phenyl, 4-(2-ethoxypyridin-5-yl)phenyl, 4-(2-isopropoxypyridin-5-yl)phenyl, 4-(2-methoxy-6-methylpyridin-5-yl)phenyl, 4-(2-methoxy-pyrimidin-4-yl)-3-chlorophenyl, 4-(2,6-dimethylpyridin-5-yl)phenyl, 4-(2,6-dimethoxy-pyrimidin-5-yl)-3-chlorophenyl, 4-(4-methoxy-pyridin-3-yl)-3-methoxyphenyl, 4-(6-methoxy-pyridin-3-yl)-3-methoxyphenyl, 4-(6-methoxy-pyridin-3-yl)-3-chlorophenyl, 4-(4,6-dimethoxy-pyridin-3-yl)phenyl, 4-(3,6-dimethoxypyridazin-5-yl)phenyl, 4-(2,6-dimethoxy-pyridin-3-yl)phenyl, 4-(5-methoxy-pyridin-3-yl)-3-methoxyphenyl, 4-(2,6-dimethoxy-pyridin-3-yl)-3-fluorophenyl, 4-(6-methoxypyridin-3-yl)-3-fluorophenyl, 4-(3,6-dimethoxy-pyridazin-5-yl)-3-fluorophenyl, 4-(4,6-dimethoxy-pyrimidin-5-yl)phenyl, 4-(2-methoxy-pyrimidin-5-yl)-3-methoxyphenyl, 4-(3-methoxy-pyridin-4-yl)phenyl, 4-(4-methoxy-pyridin-3-yl)phenyl, 4-(2-methoxypyrimidin-3-yl)phenyl, 3-methoxy-2-(2-methoxyphenyl)pyridin-5-yl, 3-methoxy-2-(5-cyano-2-methoxyphenyl)pyridin-5-yl, 3-methoxy-2-(2,4-dimethoxyphenyl)pyridin-5-yl, 2-(2,4-dimethoxyphenyl)pyridin-5-yl, 1-(2-cyano-4-trifluoromethyl)piperidin-4-yl, 1-(2-nitro-4-trifluoromethyl)piperidin-4-yl, 1-(2-methoxy-4-trifluoromethyl)piperidin-4-yl;

R^3 is H, cyano, alkyl, hydroxyalkyl, aralkyl, alkoxyalkyl, acetyl, arylsulfonyl;

$R^{3'}$ is H or C_1-C_4 alkyl;

R^4 is H, cyano, C_1-C_4 alkyl.

[0044] Preferred compounds of formula Id-1b' are those of formula Id-1g:



Id-1g

and pharmaceutically acceptable salts and solvates thereof, wherein

R is as defined above in respect of formula Ia-1b';

R^8, $R^{8'}$, R^9, $R^{9'}$ and **R^{10}** are independently selected from H, halo preferably fluoro, chloro, bromo, cyano, alkyl, hydroxyalkyl, haloalkyl preferably CF_3 or CHF_2, cycloalkyl, cycloalkylalkyl, heteroalkyl, heterocyclyl, heterocyclylalkyl, aryl preferably phenyl, aralkyl, heteroaryl, heteroarylalkyl, hydroxyl, haloalkoxy preferably OCF_3 or $OCHF_2$, heterocyclyloxy, alkylamino, alkoxycarbonyl, cycloalkyloxycarbonyl, heterocyclyloxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, alkylcarbonyloxy, cycloalkylcarbonyloxy, heterocyclylcarbonyloxy, arylcarbonyloxy, heteroarylcarbonyloxy, arylalkyloxy, alkylcarbonylamino, haloalkylcarbonylamino, cycloalkylcarbonylamino, heterocyclylcarbonylamino arylcarbonylamino, heteroarylcarbonylamino, alkylcarbonylaminoalkyl, carbamoyl, hydroxycarbamoyl, alkylcarbamoyl, arylcarbamoyl, heteroarylcarbamoyl, carbamoylalkyl, carbamoylamino, alkylcarbamoylamino, alkylsulfonyl, haloalkylsulfonyl, cycloalkylsulfonyl, heterocyclylsulfonyl, arylsulfonyl, heteroarylsulfonyl sulfamoyl, alkylsulfamoyl, arylsulfamoyl, heteroarylsulfamoyl, alkylsulfonylamino, cycloalkylsulfonylamino, heterocyclylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, or one or more of **R^8** and **R^9,** or **R^9** and **R^{10},** or **R^{10}** and **$R^{9'}$,** or **$R^{9'}$** and **$R^{8'}$** form an alkylenedioxy group or a haloalkylenedioxy group together with the phenyl group they are attached to, or one or more of **R^8** and **R^9,** or **R^9** and **R^{10},** or **R^{10}** and **$R^{9'}$,** or **$R^{9'}$** and **$R^{8'}$** form together a cycloalkyl, aryl, heterocycloalyl or heteroaryl moiety fused to the phenyl group they are attached to, each of said substituents being optionally substituted by one or more further substituents selected from halo, cyano, alkyl, hydroxyalkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, heteroalkyl, hydroxyl, alkoxy, haloalkoxy, cycloalkyloxy, alkylamino, carboxy, alkoxycarbonyl, alkylcarbonyloxy, cycloalkylcarbonyloxy, alkylcarbonylamino, haloalkylcarbonylamino, cycloalkylcarbonylamino, alkylcarbonylaminoalkyl, carbamoyl, hydroxycarbamoyl, alkylcarbamoyl, carbamoylalkyl, carbamoylamino, alkylcarbamoylamino, alkylsulfonyl, haloalkylsulfonyl, cycloalkylsulfonyl, sulfamoyl, alkylsulfamoyl, alkylsulfonylamino, cycloalkylsulfonylamino or oxo, preferably **R^8, $R^{8'}$, R^9, $R^{9'}$** and **R^{10}** are independently selected from H, halo preferably fluoro, chloro, bromo, cyano, alkyl, haloalkyl preferably CF_3 or CHF_2, cycloalkyl, aryl preferably phenyl, heteroaryl, hydroxyl, haloalkoxy preferably OCF_3 or $OCHF_2$, alkylamino, alkoxycarbonyl, alkylcarbonyloxy, alkylcarbonylamino, haloalkylcarbonylamino, carbamoyl, hydroxycarbamoyl, alkylcarbamoyl, carbamoylamino, alkylcarbamoylamino, alkylsulfonyl, haloalkylsulfonyl, sulfamoyl, alkylsulfamoyl, alkylsulfonylamino, or one or more of **R^8** and **R^9,** or **R^9** and **R^{10},** or **R^{10}** and **$R^{9'}$,** or **$R^{9'}$** and **$R^{8'}$** form an alkylenedioxy group or a haloalkylenedioxy group together with the phenyl group they are attached to, each of said substituents being optionally substituted by one or more further substituents selected from halo, cyano, alkyl, haloalkyl, hydroxyl, alkoxy, haloalkoxy, more preferably **R^8, $R^{8'}$, R^9, $R^{9'}$** and **R^{10}** are independently selected from H, halo preferably bromo, fluoro or chloro, cyano, C_1-C_4 alkyl preferably methyl, aryl preferably phenyl, alkoxy preferably methoxy, still more preferably **R^8, $R^{8'}$, R^9, $R^{9'}$** and **R^{10}** are independently selected from H, halo preferably bromo, fluoro or

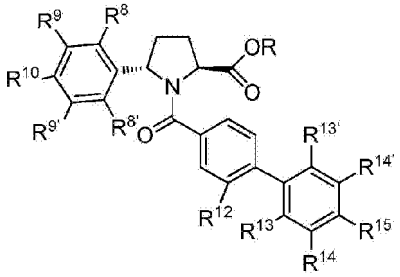
chloro, alkyl preferably methyl, still more preferably R^8 is Br, Cl or F, preferably Cl and $R^{8'}$, R^9, $R^{9'}$ and R^{10} are independently selected from H or F, or R^9 is Cl or F and R^8, $R^{8'}$, $R^{9'}$ and R^{10} are H, or R^9 and $R^{9'}$ are F and R^8, $R^{8'}$ and R^{10} are H, or R^{10} is Cl or F and R^8, $R^{8'}$, R^9 and $R^{9'}$ are H, even more preferably R^8 is Br, Cl or F and $R^{8'}$, R^9, $R^{9'}$ and R^{10} are H, or R^8 and R^9 are F and $R^{8'}$, $R^{9'}$ and R^{10} are H, or R^8 and R^{10} are F and $R^{8'}$, R^9 and $R^{9'}$ are H;

R^{11}, $R^{11'}$, R^{12}, $R^{12'}$ and R^{16} are independently selected from H, halo preferably chloro and fluoro more preferably chloro, cyano, nitro, alkyl, haloalkyl preferably CF_3 or CHF_2, cycloalkyl, cycloalkylalkyl, heteroalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, hydroxyl, hydroxyalkyl, alkoxy, haloalkoxy preferably -OCF_3 or -$OCHF_2$, alkoxyalkoxy, cycloalkyloxy, heterocyclyloxy, aryloxy, heteroaryloxy, alkoxyalkyl, haloalkoxyalkyl, cycloalkylalkyloxy, arylalkyloxy, heteroarylalkyloxy, aryloxyalkyl, heteroaryloxyalkyl, arylcarbonyl, alkyloxycarbonyl, aminoalkylalkoxycarbonyl, cycloalkyloxycarbonyl, heterocyclyloxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, alkylcarbonyloxy, cycloalkylcarbonyloxy, heterocyclylcarbonyloxy, arylcarbonyloxy, heteroarylcarbonyloxy, alkylcarbonylamino, haloalkylcarbonylamino, cycloalkylcarbonylamino, heterocyclylcarbonylamino arylcarbonylamino, heteroarylcarbonylamino, alkylcarbonylaminoalkyl, carbamoyl, hydroxycarbamoyl, alkylcarbamoyl, arylcarbamoyl, heteroarylcarbamoyl, carbamoylalkyl, carbamoylamino, alkylcarbamoylamino, alkylsulfonyl, haloalkylsulfonyl, cycloalkylsulfonyl, heterocyclylsulfonyl, arylsulfonyl, heteroarylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, heteroarylsulfamoyl, alkylsulfonylamino, cycloalkylsulfonylamino, heterocyclylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, haloalkylsulfonylamino, or one or more of R^{11} and R^{12}, or R^{12} and R^{16}, or R^{16} and $R^{12'}$, or $R^{12'}$ and $R^{11'}$ form an alkylenedioxy group or a haloalkylenedioxy group together with the phenyl group they are attached to, or one or more of R^{11} and R^{12}, or R^{12} and R^{16}, or R^{16} and $R^{12'}$, or $R^{12'}$ and $R^{11'}$ form together a cycloalkyl, aryl, heterocycloalkyl or heteroaryl moiety fused to the phenyl group they are attached to, each of said substituents being optionally substituted by one or more further substituents selected from halo preferably chloro or fluoro, cyano, alkyl, hydroxyalkyl, alkoxyalkyl, haloalkyl, cyanomethyl, cycloalkyl, heterocyclyl, aryl optionally substituted by one a chloro or methyl group, heteroaryl, cycloalkylalkyl, aralkyl, heteroarylalkyl, heteroalkyl, hydroxyl, alkoxy, alkoxyalkoxy, haloalkoxy preferably trifluoromethoxt, 1,1,1-trifluoroethyloxy, haloalkoxyalkyl, cycloalkyloxy, cycloalkylalkyloxy preferably cyclopropylmethyloxy, aryloxy, aralkyloxy optionally substituted by one fluoro, amino, alkylamino, carboxy, alkoxycarbonyl, alkylcarbonyloxy, alkylcarbonylamino, haloalkylcarbonylamino, cycloalkylcarbonylamino, alkylcarbonylaminoalkyl, carbamoyl, hydroxycarbamoyl, alkylcarbamoyl, carbamoylalkyl, carbamoylalkyloxy preferably carbamoylmethyloxy carbamoylamino, alkylcarbamoylamino, carbamimidoyl, hydroxycarbamimidoyl, alkylsulfonyl, haloalkylsulfonyl, cycloalkylsulfonyl, arylsulfonyl preferably phenylsulfonyl, sulfamoyl, alkylsulfamoyl, alkylsulfonylamino, cycloalkylsulfonylamino, haloalkylsulfonylamino and oxo, preferably R^{11}, $R^{11'}$, R^{12}, $R^{12'}$ and R^{16} are independently selected from H, halo preferably chloro and fluoro more preferably chloro, cyano, nitro, alkyl,

haloalkyl preferably CF_3 or CHF_2, cycloalkyl, cycloalkylalkyl, heteroalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, hydroxyl, hydroxyalkyl, alkoxy, haloalkoxy preferably -OCF_3 or -$OCHF_2$, alkoxyalkoxy, cycloalkyloxy, heterocyclyloxy, aryloxy, heteroaryloxy, alkoxyalkyl, haloalkoxyalkyl, cycloalkylalkyloxy, arylalkyloxy, heteroarylalkyloxy, aryloxyalkyl, heteroaryloxyalkyl, arylcarbonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, alkylcarbonyloxy, arylcarbonyloxy, heteroarylcarbonyloxy, alkylcarbonylamino, carbamoyl, hydroxycarbamoyl, alkylcarbamoyl, arylcarbamoyl, heteroarylcarbamoyl, carbamoylamino, alkylcarbamoylamino, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, heteroarylsulfamoyl, alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, or one or more of **R^{11}** and **R^{12},** or **R^{12}** and **R^{16},** or **R^{16}** and **$R^{12'}$,** or **$R^{12'}$** and **$R^{11'}$** form an alkylenedioxy group or a haloalkylenedioxy group together with the phenyl group they are attached to, or one or more of **R^{11}** and **R^{12},** or **R^{12}** and **R^{16},** or **R^{16}** and **$R^{12'}$,** or **$R^{12'}$** and **$R^{11'}$** form together an aryl or heteroaryl moiety fused to the phenyl group they are attached to, each of said substituents being optionally substituted by one or more further substituents selected from halo preferably chloro or fluoro, cyano, alkyl, hydroxyalkyl, alkoxyalkyl, haloalkyl, cyanomethyl, cycloalkyl, heterocyclyl, aryl optionally substituted by one a chloro or methyl group, heteroaryl, heteroalkyl, hydroxyl, alkoxy, alkoxyalkoxy, haloalkoxy preferably 1,1,1-trifluoroethyloxy, cycloalkyloxy, cycloalkylalkyloxy preferably cyclopropylmethyloxy, aryloxy, aralkyloxy optionally substituted by one fluoro, amino, alkylamino, carboxy, alkoxycarbonyl, alkylcarbonyloxy, alkylcarbonylamino, haloalkylcarbonylamino, carbamoyl, hydroxycarbamoyl, alkylcarbamoyl, carbamoylalkyloxy preferably carbamoylmethyloxy carbamoylamino, alkylcarbamoylamino, carbamimidoyl, hydroxycarbamimidoyl, alkylsulfonyl, haloalkylsulfonyl, cycloalkylsulfonyl, arylsulfonyl preferably phenylsulfonyl, sulfamoyl, alkylsulfamoyl, alkylsulfonylamino, haloalkylsulfonylamino and oxo, more preferably **R^{11}, $R^{11'}$, R^{12}, $R^{12'}$** and **R^{16}** are independently selected from H, halo preferably chloro and fluoro, cyano, nitro, alkyl, haloalkyl preferably CF_3 or CHF_2, heterocyclyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, hydroxyl, alkoxy, haloalkoxy preferably OCF_3 or $OCHF_2$, alkoxyalkoxy, aryloxy, cycloalkylalkyloxy, arylalkyloxy, heteroarylalkyloxy, alkoxyalkyl, aryloxyalkyl, heteroaryloxyalkyl, arylcarbonyl, or one or more of **R^{11}** and **R^{12},** or **R^{12}** and **R^{16},** or **R^{16}** and **$R^{12'}$,** or **$R^{12'}$** and **$R^{11'}$** form an alkylenedioxy group or a haloalkylenedioxy group together with the phenyl group they are attached to, or one or more of **R^{11}** and **R^{12},** or **R^{12}** and **R^{16},** or **R^{16}** and **$R^{12'}$, or $R^{12'}$** and **$R^{11'}$** form together an aryl, or heteroaryl moiety fused to the phenyl group they are attached to, each of said substituents being optionally substituted by one or more further substituents selected from halo preferably chloro or fluoro, cyano, alkyl preferably methyl, ethyl, propyl, isopropyl, *tert-butyl,* cyanomethyl, cycloalkyl, heterocyclyl, alkoxy preferably methoxy, ethoxy, isopropoxy, alkoxyalkyl, alkoxyalkoxy, cycloalkylalkyloxy, aryloxy, aralkyloxy optionally substituted by one fluoro, amino, alkylamino, alkylcarbonylamino, carbamoyl, hydroxycarbamimidoyl, alkylsulfonyl, alkylsulfonylamino, still more preferably **R^{11}, $R^{11'}$, R^{12}, $R^{12'}$** and **R^{16}** are independently selected from H, halo preferably chloro and fluoro, cyano, nitro, alkyl preferably methyl, ethyl, isopropyl or isobutyl, haloalkyl preferably CF_3 or CHF_2, cycloalkyl preferably cyclohexyl, heterocyclyl preferably pyrrolidin-1-yl, 4-methylpiperidin-1-yl, aryl preferably phenyl, heteroaryl preferably

thiophenyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, aralkyl preferably benzyl, alkoxy preferably methoxy, ethoxy or isopropyloxy, cycloalkylalkyloxy, arylalkyloxy preferably benzyloxy, phenethyloxy or 3,3-diphenylpropan-1-oxy, heteroarylalkyloxy preferably pyridylmethyloxy or pyridylethyloxy, aryloxyalkyl preferably phenoxymethyl, heteroaryloxyalkyl preferably pyridyloxymethyl, or two substituents form an haloalkylenedioxy group each of said substituents being optionally substituted by one or more further substituents selected from halo preferably chloro or fluoro, cyano, alkyl preferably methyl, haloalkyl preferably trifluoromethyl, alkoxy preferably methoxy, isopropyloxy, isobutyloxy, alkoxyalkyl preferably methoxymethyl, alkoxyalkoxy preferably 2-methoxyethoxy, cycloalkylalkyloxy preferably cyclopropylmethyloxy, aryloxy preferably phenoxy, aralkyloxy optionally substituted by one fluoro, preferably benzyloxy, 4-fluorobenzyloxy, amino, alkylcarbonylamino preferably acetylamino, alkylsulfonyl preferably methylsulfonyl, alkylsulfonylamino preferably methylsulfonylamino, (N-methyl-N-methylsulfonyl)amino.

[0045] Preferred compounds of formula Id-1g are those of formula Id-1h1:



Id-1h1

and pharmaceutically acceptable salts and solvates thereof, wherein

R is as defined above in respect to formula Ia-1b';

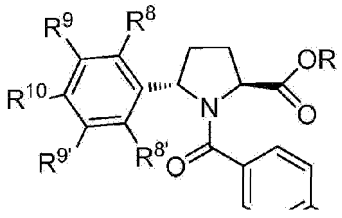
$\mathbf{R^8}$, $\mathbf{R^{8'}}$, $\mathbf{R^9}$, $\mathbf{R^{9'}}$ and $\mathbf{R^{10}}$ are as defined above in respect to formula Id-1g;

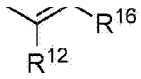
$\mathbf{R^{12}}$ is as defined above in respect to formula Id-1g, preferably $\mathbf{R^{12}}$ is H, fluoro, chloro, methyl, CF_3, nitro, cyano, methoxy or cyclopropylmethyloxy;

$\mathbf{R^{13}}$, $\mathbf{R^{13}}$, $\mathbf{R^{14}}$, $\mathbf{R^{14'}}$ and $\mathbf{R^{15}}$ are as defined above in respect to formula Id-1g, preferably $\mathbf{R^{13'}}$, $\mathbf{R^{14}}$, $\mathbf{R^{14'}}$ and $\mathbf{R^{15}}$ are H and $\mathbf{R^{13}}$ is chloro, cyano, hydroxyl, methyl, trifluoromethyl, cyanomethyl, methoxy, isopropoxy, isobutyloxy, OCF_3, cyclopropylmethyloxy, phenoxy, cyclopropylmethyloxy, benzyloxy, (4-fluorobenzyl)oxy, methoxymethyl, 2-methoxyethoxy, carbamoylmethyloxy, or $\mathbf{R^{13}}$, $\mathbf{R^{13'}}$, $\mathbf{R^{14'}}$ and $\mathbf{R^{15}}$ are H and $\mathbf{R^{14}}$ is chloro, methylsulfonylamino, or $\mathbf{R^{13}}$, $\mathbf{R^{13'}}$, $\mathbf{R^{14}}$ and $\mathbf{R^{14'}}$ are H and $\mathbf{R^{15}}$ is chloro, methylsulfonylamino, $\mathbf{R^{13'}}$, $\mathbf{R^{14}}$ and $\mathbf{R^{14'}}$ are H and $\mathbf{R^{13}}$ and $\mathbf{R^{15}}$ are *a)* independently selected from chloro or methoxy, or *b)* both F, or *c)* $\mathbf{R^{13}}$ is F and $\mathbf{R^{15}}$ is methoxy, or *d)* $\mathbf{R^{13}}$ is methoxy and $\mathbf{R^{15}}$ is F, or *e)* $\mathbf{R^{13}}$ is methoxy and $\mathbf{R^{15}}$ is acetylamino, or *f)* $\mathbf{R^{13}}$ is methoxy and $\mathbf{R^{15}}$ is amino, or *g)* $\mathbf{R^{13}}$ is cyano and $\mathbf{R^{15}}$ is methoxy, or

h) **R^{13}** is chloro and **R^{15}** is cyano, or *i)* **R^{13}** is cyano and **R^{15}** is trifluoromethyl, or *j)* **R^{13}** is methoxy and **R^{15}** is (N-methyl-N-methylsulfonyl)amino, or **R^{14}, R$^{14'}$** and **R^{15}** are H and both **R^{13}** and **R$^{13'}$** are methoxy, or **R^{13}, R$^{13'}$** and **R^{15}** are H and both **R^{14}** and **R$^{14'}$** are fluoro, methoxy, or **R^{13}, R$^{13'}$** and **R$^{14'}$** are H and *a)* **R^{14}** forms together with **R^{15}** a phenyl moiety fused to the phenyl ring they are attached to, or *b)* both **R^{14}** and **R^{15}** are methoxy, or **R$^{13'}$, R$^{14'}$** and **R^{15}** are H and **R^{13}** and **R^{14}** are *a)* both methoxy, or *b)* **R^{13}** is methyl and **R^{14}** is methylsulfonylamino, or *c)* **R^{13}** is methoxy and **R^{14}** is cyano, or *d)* **R^{13}** is methyl and **R^{14}** is amino, or **R$^{13'}$, R^{14}** and **R^{15}** are H and **R^{13}** and **R$^{14'}$** are *a)* both methoxy, or *b)* **R^{13}** is methoxy and **R$^{14'}$** is cyano, or c) **R^{13}** is methyl and **R$^{14'}$** is cyano, or **R^{13}** and **R^{14}** are H and **R$^{13'}$, R$^{14'}$** and **R^{15}** are methoxy, or **R^{14}** and **R^{15}** are H and **R^{13}, R$^{13'}$** and **R$^{14'}$** are methoxy, or **R^{13}** and **R^{14}** are methoxy and **R$^{13'}$** and **R^{15}** are H and **R$^{14'}$** is cyano, or **R^{14}** and **R^{15}** are methoxy and **R^{13}** and **R$^{14'}$** are H and **R$^{13'}$** is cyano, or **R^{13}** and **R$^{13'}$** are H and **R^{14}, R$^{14'}$** and **R^{15}** are methoxy, more preferably **R$^{13'}$, R^{14}, R$^{14'}$** and **R^{15}** are H and **R^{13}** is chloro, cyano, trifluoromethyl, methoxy, isopropoxy, cyclopropylmethyloxy, or **R^{13}, R$^{13'}$, R$^{14'}$** and **R^{15}** are H and **R^{14}** is chloro, or **R^{13}, R$^{13'}$, R^{14}** and **R$^{14'}$** are H and **R^{15}** is chloro, methylsulfonylamino, or **R$^{13'}$, R^{14}** and **R$^{14'}$** are H and **R^{13}** and **R^{15}** are *a)* independently selected from chloro or methoxy, or *b)* both F, or *c)* **R^{13}** is F and **R^{15}** is methoxy, or *d)* **R^{13}** is methoxy and **R^{15}** is F, or *e)* **R^{13}** is methoxy and **R^{15}** is acetylamino, or *f)* **R^{13}** is methoxy and **R^{15}** is amino, or *g)* **R^{13}** is cyano and **R^{15}** is methoxy, or *h)* **R^{13}** is chloro and **R^{15}** is cyano, or *i)* **R^{13}** is cyano and **R^{15}** is trifluoromethyl, or *j)* **R^{13}** is methoxy and **R^{15}** is (N-methyl-N-methylsulfonyl)amino, or **R^{14}, R$^{14'}$** and **R^{15}** are H and both **R^{13}** and **R$^{13'}$** are methoxy, or **R^{13}, R$^{13'}$** and **R$^{14'}$** are H and *a)* **R^{14}** forms together with **R^{15}** a phenyl moiety fused to the phenyl ring they are attached to, or *b)* both **R^{14}** and **R^{15}** are methoxy, or **R$^{13'}$, R$^{14'}$** and **R^{15}** are H and **R^{13}** and **R^{14}** are *a)* both methoxy, or *b)* **R^{13}** is methyl and **R^{14}** is methylsulfonylamino, or c) **R^{13}** is methoxy and **R^{14}** is cyano, or *d)* **R^{13}** is methyl and **R^{14}** is amino, or **R$^{13'}$, R^{14}** and **R^{15}** are H and **R^{13}** and **R$^{14'}$** are *a)* both methoxy, or *b)* **R^{13}** is methoxy and **R$^{14'}$** is cyano, or *c)* **R^{13}** is methyl and **R$^{14'}$** is cyano, or **R^{13}** and **R^{14}** are H and **R$^{13'}$, R$^{14'}$** and **R^{15}** are methoxy, or **R^{14}** and **R^{15}** are H and **R^{13}, R$^{13'}$** and **R$^{14'}$** are methoxy, or **R^{13}** and **R^{14}** are methoxy and **R$^{13'}$** and **R^{15}** are H and **R$^{14'}$** is cyano, or **R^{14}** and **R^{15}** are methoxy and **R^{13}** and **R$^{14'}$** are H and **R$^{13'}$** is cyano, or **R^{13}** and **R$^{13'}$** are H and **R^{14}, R$^{14'}$** and **R^{15}** are methoxy.

[0046] Other preferred compounds of formula Id-Ig are those of formula Id-1h':





Id-1h'

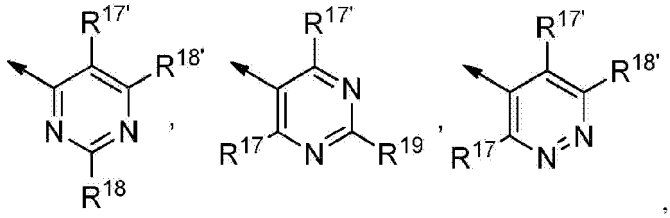
and pharmaceutically acceptable salts and solvates thereof, wherein

R is as defined above in respect to formula Ia-1b';

R^8, $R^{8'}$, R^9, $R^{9'}$ and **R^{10}** are as defined above in respect to formula Id-1g;

R^{12} is as defined above in respect to formula Id-1g, preferably **R^{12}** is H, fluoro, chloro, methyl, CF_3, or methoxy more preferably **R^{12}** is H or methoxy;

R^{16} is selected from the group of heteroaryl moieties consisting of:



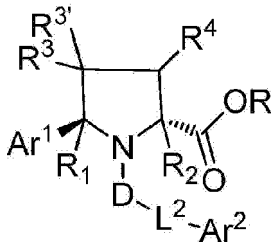
wherein the arrow marks the attachment point to the phenyl ring;

R^{17}, $R^{17'}$, R^{18}, $R^{18'}$ and **R^{19}** are independently selected from H, halo preferably chloro and fluoro, cyano, alkyl preferably methyl, ethyl, propyl, isopropyl, *tert-butyl,* haloalkyl preferably CF_3 or CHF_2, hydroxyl, hydroxyalkyl, alkoxy preferably methoxy, ethoxy, isopropyloxy, haloalkoxy preferably OCF_3, $OCHF_2$, or 1,1,1-trifluoroethyloxy, alkoxyalkoxy, cycloalkyloxy, alkoxyalkyl preferably methoxymethyl, cycloalkylalkyloxy preferably cyclopropylmethyloxy, aralkyloxy preferably benzyloxy, amino, alkylamino, alkylcarbonylamino, haloalkylcarbonylamino, carbamoyl, hydroxycarbamoyl, alkylcarbamoyl, carbamoylamino, alkylcarbamoylamino, carbamimidoyl, hydroxycarbamimidoyl, alkylsulfonyl preferably methylsulfonyl, haloalkylsulfonyl, sulfamoyl, alkylsulfamoyl, alkylsulfonylamino preferably methylsulfonylamino, (N-methyl-N-methylsulfonyl)amino, haloalkylsulfonylamino, preferably **R^{17}, $R^{17'}$, $R^{18'}$** and **R^{19}** are independently selected from H, halo preferably chloro and fluoro, cyano, alkyl preferably methyl, ethyl, propyl, isopropyl, *tert-butyl,* haloalkyl preferably CF_3, alkoxy preferably methoxy, ethoxy, isopropyloxy, haloalkoxy preferably OCF_3, $OCHF_2$, or 1,1,1-trifluoroethyloxy, alkoxyalkyl preferably methoxymethyl, aralkyloxy preferably benzyloxy, amino, alkylcarbonylamino, carbamoyl, carbamimidoyl, hydroxycarbamimidoyl, alkylsulfonyl preferably methylsulfonyl, alkylsulfonylamino preferably methylsulfonylamino, (N-methyl-N-methylsulfonyl)amino, more preferably **R^{17}, $R^{17'}$, $R^{18'}$** and **R^{19}** are independently selected from H, halo preferably chloro, alkoxy preferably methoxy, even more preferably **R^{17}, $R^{17'}$, $R^{18'}$** and **R^{19}** are independently selected from H, halo preferably chloro, alkoxy preferably methoxy;

Preferred compounds of formula Id-Ih' are those wherein **R^{16}** is selected from 2-2-methoxypyrimidin-4-yl, 2,4-dibenzyloxypyrimidin-5-yl, 2,4-dimethoxypyrimidin-5-yl, 3,6-

dimethoxypyridazin-5-yl, 2-methoxypyrimidin-5-yl, 2-methoxypyrimidin-3-yl.

[0047] Other preferred compounds are those of formula Ie-1b':



Ie-1b'

and pharmaceutically acceptable salts and solvates thereof, wherein

R^2 and **R** are as defined above in respect of formula Ia-1b';

R^1 is H;

D is C=O;

L^2 is single bond;

Ar^1 is a 5- to 6-membered aryl or heteroaryl group, 3- to 6-membered cycloalkyl group, or a linear or branched C_3-C_6 alkyl group, each of which being optionally substituted by one or more group(s) selected from halo, cyano, alkyl, haloalkyl, cycloalkyl, aryl, heteroaryl, hydroxyl, alkoxy, haloalkoxy, amino, alkylamino, carboxy, alkoxycarbonyl, alkylcarbonyloxy, alkylcarbonylamino, haloalkylcarbonylamino, carbamoyl, hydroxycarbamoyl, alkylcarbamoyl, carbamoylamino, alkylcarbamoylamino, alkylsulfonyl, haloalkylsulfonyl, sulfamoyl, alkylsulfamoyl, alkylsulfonylamino, or two substituents form an alkylenedioxy group or a haloalkylenedioxy group, each of said aryl or heteroaryl substituents being optionally substituted by one or more further substituents selected from halo, cyano, alkyl, haloalkyl, hydroxyl, alkoxy, haloalkoxy, preferably **Ar^1** is a 5- to 6-membered aryl preferably phenyl, 5- to 6-membered heteroaryl group preferably pyridin-2-yl, pyridin-3-yl, cyclohexyl, cyclopentyl, isopropyl, isobutyl or isopentyl each of said phenyl, pyridin-2-yl, pyridin-3-yl, cyclohexyl or cyclopentyl group being optionally substituted by one or more group(s) selected from halo preferably bromo, chloro or fluoro, cyano, C_1-C_4 alkyl preferably methyl, C_1-C_4 alkoxy preferably methoxy, aryl preferably phenyl, still more preferably **Ar^1** is aryl preferably phenyl, cyclohexyl, isobutyl or isopentyl, said phenyl group being optionally substituted by one or more halo group preferably bromo, chloro or fluoro, cyano, methyl, phenyl or methoxy, further more preferably **Ar^1** is phenyl, cyclohexyl, isobutyl, 2-chlorophenyl, 2-tolyl, 2-methoxyphenyl, 3-chlorophenyl, 4-chlorophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2,6-difluorophenyl, 2,4-difluorophenyl, 2,4-dichlorophenyl, 2-bromophenyl, 2-cyanophenyl, 3,5-difluorophenyl, 3,4-difluorophenyl, 2,3-difluorophenyl, 2,5-difluorophenyl, 1,1'-biphenyl-2-yl, 4-cyanophenyl, even more preferably **Ar^1** is isobutyl, cyclohexyl, phenyl , 2-chlorophenyl, 2-tolyl, 2-methoxyphenyl, 3-chlorophenyl, 4-chlorophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-

fluorophenyl, 2,4-difluorophenyl, 2,4-dichlorophenyl, 2-bromophenyl, 2,3-difluorophenyl, 2,5-difluorophenyl, still even more preferably **Ar^1** is isobutyl, 2-chlorophenyl, 2-tolyl, 2-methoxyphenyl, 2-fluorophenyl, 2,4-difluorophenyl, 2-bromophenyl, 2,3-difluorophenyl, 2,5-difluorophenyl;

Ar^2 is an aryl or heteroaryl, cycloalkyl, monocyclic heterocyclyl or C_2-C_6 alkyl group, each of which being optionally substituted by one or more group(s) selected from halo, cyano, nitro, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, heteroalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, benzoxazol-2-yl heteroarylalkyl, hydroxyl, hydroxyalkyl, alkoxy, haloalkoxy, alkoxyalkoxy, cycloalkyloxy, cycloalkylalkyloxy, heterocyclyloxy, aryloxy, heteroaryloxy, alkoxyalkyl, haloalkoxyalkyl, arylalkyloxy, heteroarylalkyloxy, aryloxyalkyl, heteroaryloxyalkyl, amino, alkylamino, arylcarbonyl, carboxy, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, alkylcarbonyloxy, arylcarbonyloxy, heteroarylcarbonyloxy, alkylcarbonylamino, carbamoyl, hydroxycarbamoyl, alkylcarbamoyl, arylcarbamoyl, heteroarylcarbamoyl, carbamoylamino, alkylcarbamoylamino, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, heteroarylsulfamoyl, alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, oxo, or two substituents form an alkylenedioxy group or a haloalkylenedioxy group, or fused to the aryl, heteroaryl, cycloalkyl or heterocyclyl group may be one or more aryl or heteroaryl moiety, each of said substituents being optionally substituted by one or more further substituents selected from halo, cyano, nitro, alkyl, hydroxyalkyl, haloalkyl, cyanomethyl, cycloalkyl, heterocyclyl, aryl optionally substituted by a chloro or methyl group, heteroaryl, heteroalkyl, hydroxyl, alkoxy, alkoxyalkyl, alkoxyalkoxy, haloalkoxy, cycloalkyloxy, cycloalkylalkyloxy, aryloxy, aralkyloxy optionally substituted by a fluoro group, carboxy, alkoxycarbonyl, alkylcarbonyloxy, amino, alkylamino, alkylcarbonylamino, haloalkylcarbonylamino, carbamoyl, hydroxycarbamoyl, alkylcarbamoyl, carbamoylalkyloxy, carbamoylamino, alkylcarbamoylamino, carbamimidoyl, hydroxycarbamimidoyl, alkylsulfonyl, haloalkylsulfonyl, cycloalkylsulfonyl, heterocyclylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, alkylsulfonylamino, haloalkylsulfonylamino, oxo, and haloalkoxyalkyl; preferably **Ar^2** is an aryl or heteroaryl preferably pyridyl, pyrazinyl, cycloalkyl, monocyclic heterocyclyl or C_2-C_6 alkyl group, each of each of said aryl, heteroaryl, cycloalkyl and heterocyclyl groups being optionally substituted by one or more group(s) selected from halo preferably chloro and fluoro, cyano, nitro, alkyl, haloalkyl preferably CF_3 or CHF_2, heterocyclyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, hydroxyl, alkoxy, haloalkoxy preferably OCF_3 or $OCHF_2$, alkoxyalkoxy, aryloxy, alkoxyalkyl, arylalkyloxy, heteroarylalkyloxy, cycloalkylalkyloxy, aryloxyalkyl, heteroaryloxyalkyl, arylcarbonyl, or two substituents form an alkylenedioxy group or a haloalkylenedioxy group, or fused to the cycloalkyl or heterocycloalkyl group may be one aryl moiety, each of said substituents being optionally substituted by one or more further substituents selected from halo preferably chloro or fluoro, cyano, nitro, alkyl preferably methyl, ethyl, propyl, isopropyl, *tert-butyl,* haloalkyl preferably CF_3, cyanomethyl, alkoxy preferably methoxy, ethoxy, isopropoxy, alkoxyalkyl, alkoxyalkoxy, cycloalkylalkyloxy, aryloxy, aralkyloxy optionally substituted by one fluoro, amino, alkylcarbonylamino, carbamoyl, hydroxycarbamimidoyl, alkylsulfonyl, alkylsulfonylamino, still more preferably **Ar^2** is an aryl preferably phenyl, heteroaryl preferably pyridyl, monocyclic heterocyclyl preferably piperidinyl,

C_2-C_6 alkyl group preferably isobutyl, each of said aryl, heteroaryl and heterocyclyl groups being optionally substituted by one or more group(s) selected from halo preferably chloro and fluoro, cyano, nitro, alkyl, preferably methyl, heterocyclyl preferably pyrrolidin-1-yl, 4-methylpiperidin-1-yl, aryl preferably phenyl, heteroaryl preferably pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, alkoxy preferably methoxy, ethoxy or isopropyloxy, alkoxyalkyl, cycloalkylalkyloxy, arylalkyloxy preferably benzyloxy, phenethyloxy or 3,3-diphenylpropan-1-oxy, heteroarylalkyloxy preferably pyridylmethyloxy or pyridylethyloxy, aryloxyalkyl preferably phenoxymethyl, heteroaryloxyalkyl preferably pyridinyloxymethyl, arylcarbonyl preferably phenylacetyl, or two substituents form an haloalkylenedioxy group each of said substituents being optionally substituted by one or more further substituents selected from halo preferably chloro or fluoro, more preferably fluoro, cyano, nitro, alkyl preferably methyl, cycloalkyl, alkoxy preferably methoxy, isopropyloxy, isobutyloxy, cycloalkylalkyloxy preferably cyclopropylmethyloxy, alkoxyalkyl preferably methoxymethyl, alkoxyalkoxy preferably 2-methoxyethoxy, aryloxy preferably phenoxy, aralkyloxy optionally substituted by one fluoro, preferably benzyloxy or 4-fluorobenzyloxy, amino, alkylcarbonylamino preferably acetylamino, alkylsulfonyl preferably methylsulfonylalkylsulfonylamino preferably methylsulfonylamino, (N-methyl-N-methylsulfonyl)amino, further more preferably **Ar^2** is a biaryl consisting of two 6-membered aryl moieties preferably biphenyl, more preferably a biphenyl linked to **L^2** at position 4' and monosubstituted at position 2, or **Ar^2** is a heterobiaryl consisting of one 6-membered aryl moiety and one 6-membered heteroaryl moiety or two 6-membered heteroaryl moieties, said heterobiaryl being linked to **L^2** either on the aryl or on the heteroaryl moiety and being preferably phenylpyridyl, pyrimidinylphenyl, pyridazinylphenyl, pyrazinylphenyl, or **Ar^2** is an aryl or heteroaryl optionally substituted by one group selected from arylalkyloxy, aryloxyalkyl, arylcarbonyl, each of said biaryl, heterobiaryl, aryl and heteroaryl groups being optionally substituted by one or more group(s) selected from halo preferably chloro or fluoro, cyano, nitro, alkyl preferably methyl, ethyl, propyl, isopropyl, *tert*-butyl, alkoxy preferably methoxy, isopropyloxy, isobutyloxy, cycloalkylalkyloxy, aryloxy preferably phenoxy, aralkyloxy optionally substituted by one fluoro preferably benzyloxy or 4-fluorobenzyloxy, amino, alkylcarbonylamino preferably acetylamino, alkylsulfonylamino preferably methylsulfonylamino, (N-methyl-N-methylsulfonyl)amino, or **Ar^2** is a piperidinyl ring linked to **L^2** at position 4 and N substituted with a phenyl, 4-(4-chlorophenyl)thiazol-2-yl or benzoxazol-2-yl moiety, said phenyl moiety being further substituted by one or more substituents selected from halo preferably chloro and fluoro, cyano, nitro, alkyl preferably methyl, haloalkyl preferably CF_3, alkoxy preferably methoxy, heterocyclylsulfonyl preferably (piperidin-1-yl)sulfonyl, (morpholin-4-yl)sulfonyl, alksulfamoyl preferably methylsulfonylamino, diethylaminosulfonyl, even more preferably **Ar^2** is 4'-(2-methoxy-1,1'-biphenyl), 4'-(2-methyl-1,1'-biphenyl), 4'-(2-fluoro-1,1'-biphenyl), 4'-(4-chloro-1,1'-biphenyl), 4'-(2-chloro-1,1'-biphenyl), 4'-(2-chloro-2'-methoxy-1,1'-biphenyl), 4'-(2-(2-methoxyethoxy)-1,1'-biphenyl), 4'-(2-(methoxymethyl)-1,1'-biphenyl), 4'-(4-methoxy-1,1'-biphenyl), 4'-(4-cyano-1,1'-biphenyl), 4'-(3-chloro-1,1'-biphenyl), 4'-(2-chloro-1,1'-biphenyl), 4'-(4-methylsulfonylamino-1,1'-biphenyl), 4'-(2-trifluoromethoxy-1,1'-biphenyl), 4'-(2-isopropoxy-1,1'-biphenyl), 4'-(2-cyclopropylmethyloxy-1,1'-biphenyl), 4'-(2-cyano-1,1'-biphenyl), 4'-(2,6-dimethoxy-1,1'-biphenyl), 4'-(2,4-dichloro-1,1'-biphenyl), 4'-(2-trifluoromethyl-1,1'-biphenyl), 4'-

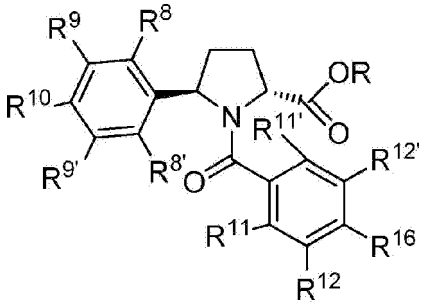
(2-methoxy-4-chloro-1,1'-biphenyl), 4'-(2,4-dimethoxy-1,1'-biphenyl), 4-(2,2'-dimethoxy-1,1'-biphenyl), 4-(naphtalen-2-yl)phenyl, 5-(2-phenyl)pyridyl, 4-cyclohexylphenyl, 4-benzylphenyl, 4-(3-thienyl)phenyl, 4-(pyridin-3-yl)phenyl, 4-(2-methoxypyridin-3-yl)phenyl, 4-(2,6-dimethoxy-pyridin-3-yl)phenyl, 4-(2-(2-methoxyethoxy)-pyridin-3-yl)phenyl, 4-(pyrimidin-2-yl)phenyl, 4-(pyrimidin-5-yl)phenyl, 4-(2-methoxypyrimidin-5-yl)-3-methoxyphenyl, 4-(2,4-dimethoxypyrimidin-6-yl)phenyl, 4-(2,4-dimethoxypyrimidin-5-yl)phenyl, (4-benzyloxy)phenyl, 4-phenoxyphenyl, (3-phenethyloxy)phenyl, (4-phenethyloxy)phenyl, (4-phenoxymethyl)phenyl, optionally substituted by one or more group(s) selected from halo preferably chloro or fluoro, more preferably fluoro, alkyl preferably methyl, alkoxy preferably methoxy, or Ar^2 is 4'-(2,4-difluoro-1,1'-biphenyl), 4'-(3'-methyl-1,1'-biphenyl), 4'-(3'-fluoro-1,1'-biphenyl), 4'-(2-fluoro-4-methoxy-1,1'-biphenyl), 4'-(4-fluoro-2-methoxy-1,1'-biphenyl), 4'-(2,3-dimethoxy-1,1'-biphenyl), 4'-(3,4-dimethoxy-1,1'-biphenyl), 4'-(2,3,4-trimethoxy-1,1'-biphenyl), 4'-(2,3,6-trimethoxy-1,1'-biphenyl), 4'-(3,5-dimethoxy-1,1'-biphenyl), 4'-(2,5-dimethoxy-1,1'-biphenyl), 4'-(2-isopropyl-1,1'-biphenyl), 4'-(2,2'-dimethoxy-1,1'-biphenyl), 4'-(2'-fluoro,2-dimethoxy-1,1'-biphenyl), 4'-(2-ethyl-1,1'-biphenyl), 4'-(4-propyl-1,1'-biphenyl), 4'-(4-tert-butyl-1,1'-biphenyl), 4'-(2-methoxy-4-methylsulfonylamino-1,1'-biphenyl), 4'-(2-methoxy-4-acetylamino-1,1'-biphenyl), 4'-(3-hydroxycarbamimidoyl-1,1'-biphenyl), 4'-(4-amino-2-methoxy-1,1'-biphenyl), 4'-(3-carbamoyl-1,1'-biphenyl), 4'-(5-cyano-2,3-dimethoxy-1,1'-biphenyl), 4'-(2-cyano-4,5-dimethoxy-1,1'-biphenyl), 4'-(3,4,5-trimethoxy-1,1'-biphenyl), 4'-(2-cyanomethyl-4,5-dimethoxy-1,1'-biphenyl), 4'-(2-fluoro-5-cyano-1,1'-biphenyl), 4'-(2'-fluoro-3,4-dimethoxy-1,1'-biphenyl), 4'-(3-carbamoyl-4-cyano-1,1'-biphenyl), 4'-(2-cyano-4-methoxy-1,1'-biphenyl), 4'-(2'-fluoro-4-methylsulfonylamino-1,1'-biphenyl), 4'-(2'-fluoro-3-methylsulfonylamino-1,1'-biphenyl), 4'-(2-cyano-2'-fluoro-1,1'-biphenyl), 4'-(2-chloro-5-cyano-1,1'-biphenyl), 4'-(2-cyano-4-trifluoromethyl-1,1'-biphenyl), 4'-(2-methyl-3-(N-methyl-N-methylsulfonyl)amino-1,1'-biphenyl), 4'-(2-methyl-4-(N-methyl-N-methylsulfonyl)amino-1,1'-biphenyl), 4'-(4-methylsulfonyl-1,1'-biphenyl), 4'-(3-methylsulfonylamino-1,1'-biphenyl), 4'-(4-amino-2-methyl-1,1'-biphenyl), 4'-(5-cyano-2-methyl-1,1'-biphenyl), 4'-(5-cyano-2-methoxy-1,1'-biphenyl), 4'-(3-cyano-1,1'-biphenyl), 4'-(2-cyano-3-methoxy-1,1'-biphenyl), 4'-(2-methyl-3-methylsulfonylamino-1,1'-biphenyl), 4'-(2-methyl-3-acetylamino-1,1'-biphenyl), 4-(2-chloro-6-methoxypyrimidin-5-yl)phenyl, 4-(2-ethoxypyridin-5-yl)phenyl, 4-(2-isopropoxypyridin-5-yl)phenyl, 4-(2-methoxy-6-methylpyridin-5-yl)phenyl, 4-(2-methoxy-pyrimidin-4-yl)-3-chlorophenyl, 4-(2,6-dimethylpyridin-5-yl)phenyl, 4-(2,6-dimethoxy-pyrimidin-5-yl)-3-chlorophenyl, 4-(4-methoxy-pyridin-3-yl)-3-methoxyphenyl, 4-(6-methoxy-pyridin-3-yl)-3-methoxyphenyl, 4-(6-methoxy-pyridin-3-yl)-3-chlorophenyl, 4-(4,6-dimethoxy-pyridin-3-yl)phenyl, 4-(3,6-dimethoxypyridazin-5-yl)phenyl, 4-(2,6-dimethoxy-pyridin-3-yl)phenyl, 4-(5-methoxy-pyridin-3-yl)-3-methoxyphenyl, 4-(2,6-dimethoxy-pyridin-3-yl)-3-fluorophenyl, 4-(6-methoxypyridin-3-yl)-3-fluorophenyl, 4-(3,6-dimethoxy-pyridazin-5-yl)-3-fluorophenyl, 4-(4,6-dimethoxy-pyrimidin-5-yl)phenyl, 4-(2-methoxy-pyrimidin-5-yl)-3-methoxyphenyl, 4-(3-methoxy-pyridin-4-yl)phenyl, 4-(4-methoxy-pyridin-3-yl)phenyl, 4-(2-methoxypyrimidin-3-yl)phenyl, 3-methoxy-2-(2-methoxyphenyl)pyridin-5-yl, 3-methoxy-2-(5-cyano-2-methoxyphenyl)pyridin-5-yl, 3-methoxy-2-(2,4-dimethoxyphenyl)pyridin-5-yl, 2-(2,4-dimethoxyphenyl)pyridin-5-yl, 1-(2-cyano-4-trifluoromethyl)piperidin-4-yl, 1-(2-nitro-4-trifluoromethyl)piperidin-4-yl, 1-(2-methoxy-4-trifluoromethyl)piperidin-4-yl;

R^3 is H, cyano, alkyl, hydroxyalkyl, aralkyl, alkoxyalkyl, acetyl, arylsulfonyl;

$R^{3'}$ is H or C_1-C_4 alkyl;

R^4 is H, cyano, C_1-C_4 alkyl.

[0048] Preferred compounds of formula Ie-Ib' are those of formula Ie-1g:



Ie-1g

and pharmaceutically acceptable salts and solvates thereof, wherein

R is as defined above in respect of formula Ia-1b';

R^8, $R^{8'}$, R^9, $R^{9'}$ and R^{10} are independently selected from H, halo preferably fluoro, chloro, bromo, cyano, alkyl, hydroxyalkyl, haloalkyl preferably CF_3 or CHF_2, cycloalkyl, cycloalkylalkyl, heteroalkyl, heterocyclyl, heterocyclylalkyl, aryl preferably phenyl, aralkyl, heteroaryl, heteroarylalkyl, hydroxyl, haloalkoxy preferably OCF_3 or $OCHF_2$, heterocyclyloxy, alkylamino, alkoxycarbonyl, cycloalkyloxycarbonyl, heterocyclyloxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, alkylcarbonyloxy, cycloalkylcarbonyloxy, heterocyclylcarbonyloxy, arylcarbonyloxy, heteroarylcarbonyloxy, arylalkyloxy, alkylcarbonylamino, haloalkylcarbonylamino, cycloalkylcarbonylamino, heterocyclylcarbonylamino arylcarbonylamino, heteroarylcarbonylamino, alkylcarbonylaminoalkyl, carbamoyl, hydroxycarbamoyl, alkylcarbamoyl, arylcarbamoyl, heteroarylcarbamoyl, carbamoylalkyl, carbamoylamino, alkylcarbamoylamino, alkylsulfonyl, haloalkylsulfonyl, cycloalkylsulfonyl, heterocyclylsulfonyl, arylsulfonyl, heteroarylsulfonyl sulfamoyl, alkylsulfamoyl, arylsulfamoyl, heteroarylsulfamoyl, alkylsulfonylamino, cycloalkylsulfonylamino, heterocyclylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, or one or more of R^8 and R^9, or R^9 and R^{10}, or R^{10} and $R^{9'}$, or $R^{9'}$ and $R^{8'}$ form an alkylenedioxy group or a haloalkylenedioxy group together with the phenyl group they are attached to, or one or more of R^8 and R^9, or R^9 and R^{10}, or R^{10} and $R^{9'}$, or $R^{9'}$ and $R^{8'}$ form together a cycloalkyl, aryl, heterocycloalyl or heteroaryl moiety fused to the phenyl group they are attached to, each of said substituents being optionally substituted by one or more further substituents selected from halo, cyano, alkyl, hydroxyalkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, heteroalkyl, hydroxyl, alkoxy, haloalkoxy, cycloalkyloxy, alkylamino, carboxy, alkoxycarbonyl, alkylcarbonyloxy, cycloalkylcarbonyloxy, alkylcarbonylamino,

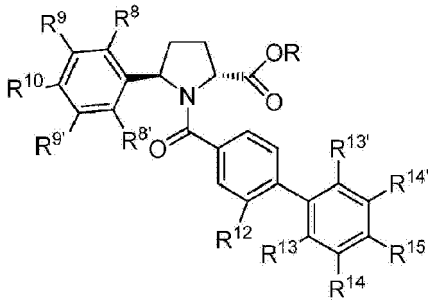
haloalkylcarbonylamino, cycloalkylcarbonylamino, alkylcarbonylaminoalkyl, carbamoyl, hydroxycarbamoyl, alkylcarbamoyl, carbamoylalkyl, carbamoylamino, alkylcarbamoylamino, alkylsulfonyl, haloalkylsulfonyl, cycloalkylsulfonyl, sulfamoyl, alkylsulfamoyl, alkylsulfonylamino, cycloalkylsulfonylamino or oxo, preferably **R^8, $R^{8'}$, R^9, $R^{9'}$** and **R^{10}** are independently selected from H, halo preferably fluoro, chloro, bromo, cyano, alkyl, haloalkyl preferably CF_3 or CHF_2, cycloalkyl, aryl preferably phenyl, heteroaryl, hydroxyl, haloalkoxy preferably OCF_3 or $OCHF_2$, alkylamino, alkoxycarbonyl, alkylcarbonyloxy, alkylcarbonylamino, haloalkylcarbonylamino, carbamoyl, hydroxycarbamoyl, alkylcarbamoyl, carbamoylamino, alkylcarbamoylamino, alkylsulfonyl, haloalkylsulfonyl, sulfamoyl, alkylsulfamoyl, alkylsulfonylamino, or one or more of **R^8** and **R^9,** or **R^9** and **R^{10},** or **R^{10}** and **$R^{9'}$,** or **$R^{9'}$** and **$R^{8'}$** form an alkylenedioxy group or a haloalkylenedioxy group together with the phenyl group they are attached to, each of said substituents being optionally substituted by one or more further substituents selected from halo, cyano, alkyl, haloalkyl, hydroxyl, alkoxy, haloalkoxy, more preferably **R^8, $R^{8'}$, R^9, $R^{9'}$** and **R^{10}** are independently selected from H, halo preferably bromo, fluoro or chloro, cyano, C_1-C_4 alkyl preferably methyl, aryl preferably phenyl, alkoxy preferably methoxy, still more preferably **R^8, $R^{8'}$, R^9, $R^{9'}$** and **R^{10}** are independently selected from H, halo preferably bromo, fluoro or chloro, alkyl preferably methyl, still more preferably **R^8** is Br, Cl or F, preferably Cl and **$R^{8'}$, R^9, $R^{9'}$** and **R^{10}** are independently selected from H or F, or **R^9** is Cl or F and **R^8, $R^{8'}$, $R^{9'}$** and **R^{10}** are H, or **R^9** and **$R^{9'}$** are F and **R^8, $R^{8'}$** and **R^{10}** are H, or **R^{10}** is Cl or F and **R^8, $R^{8'}$, R^9** and **$R^{9'}$** are H, even more preferably **R^8** is Br, Cl or F and **$R^{8'}$, R^9, $R^{9'}$** and **R^{10}** are H, or **R^8** and **R^9** are F and **$R^{8'}$, $R^{9'}$** and **R^{10}** are H, or **R^8** and **R^{10}** are F and **$R^{8'}$, R^9** and **$R^{9'}$** are H;

R^{11}, $R^{11'}$, R^{12}, $R^{12'}$ and **R^{16}** are independently selected from H, halo preferably chloro and fluoro more preferably chloro, cyano, nitro, alkyl, haloalkyl preferably CF_3 or CHF_2, cycloalkyl, cycloalkylalkyl, heteroalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, hydroxyl, hydroxyalkyl, alkoxy, haloalkoxy preferably -OCF_3 or -$OCHF_2$, alkoxyalkoxy, cycloalkyloxy, heterocyclyloxy, aryloxy, heteroaryloxy, alkoxyalkyl, haloalkoxyalkyl, cycloalkylalkyloxy, arylalkyloxy, heteroarylalkyloxy, aryloxyalkyl, heteroaryloxyalkyl, arylcarbonyl, alkyloxycarbonyl, aminoalkylalkoxycarbonyl, cycloalkyloxycarbonyl, heterocyclyloxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, alkylcarbonyloxy, cycloalkylcarbonyloxy, heterocyclylcarbonyloxy, arylcarbonyloxy, heteroarylcarbonyloxy, alkylcarbonylamino, haloalkylcarbonylamino, cycloalkylcarbonylamino, heterocyclylcarbonylamino arylcarbonylamino, heteroarylcarbonylamino, alkylcarbonylaminoalkyl, carbamoyl, hydroxycarbamoyl, alkylcarbamoyl, arylcarbamoyl, heteroarylcarbamoyl, carbamoylalkyl, carbamoylamino, alkylcarbamoylamino, alkylsulfonyl, haloalkylsulfonyl, cycloalkylsulfonyl, heterocyclylsulfonyl, arylsulfonyl, heteroarylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, heteroarylsulfamoyl, alkylsulfonylamino, cycloalkylsulfonylamino, heterocyclylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, haloalkylsulfonylamino, or one or more of **R^{11}** and **R^{12},** or **R^{12}** and **R^{16},** or **R^{16}** and **$R^{12'}$,** or **$R^{12'}$** and **$R^{11'}$** form an alkylenedioxy group or a haloalkylenedioxy group together with the phenyl

group they are attached to, or one or more of R^{11} and R^{12}, or R^{12} and R^{16}, or R^{16} and $R^{12'}$, or $R^{12'}$ and $R^{11'}$ form together a cycloalkyl, aryl, heterocycloalkyl or heteroaryl moiety fused to the phenyl group they are attached to, each of said substituents being optionally substituted by one or more further substituents selected from halo preferably chloro or fluoro, cyano, alkyl, hydroxyalkyl, alkoxyalkyl, haloalkyl, cyanomethyl, cycloalkyl, heterocyclyl, aryl optionally substituted by one a chloro or methyl group, heteroaryl, cycloalkylalkyl, aralkyl, heteroarylalkyl, heteroalkyl, hydroxyl, alkoxy, alkoxyalkoxy, haloalkoxy preferably trifluoromethoxt, 1,1,1-trifluoroethyloxy, haloalkoxyalkyl, cycloalkyloxy, cycloalkylalkyloxy preferably cyclopropylmethyloxy, aryloxy, aralkyloxy optionally substituted by one fluoro, amino, alkylamino, carboxy, alkoxycarbonyl, alkylcarbonyloxy, alkylcarbonylamino, haloalkylcarbonylamino, cycloalkylcarbonylamino, alkylcarbonylaminoalkyl, carbamoyl, hydroxycarbamoyl, alkylcarbamoyl, carbamoylalkyl, carbamoylalkyloxy preferably carbamoylmethyloxy carbamoylamino, alkylcarbamoylamino, carbamimidoyl, hydroxycarbamimidoyl, alkylsulfonyl, haloalkylsulfonyl, cycloalkylsulfonyl, arylsulfonyl preferably phenylsulfonyl, sulfamoyl, alkylsulfamoyl, alkylsulfonylamino, cycloalkylsulfonylamino, haloalkylsulfonylamino and oxo, preferably R^{11}, $R^{11'}$, R^{12}, $R^{12'}$ and R^{16} are independently selected from H, halo preferably chloro and fluoro more preferably chloro, cyano, nitro, alkyl, haloalkyl preferably CF_3 or CHF_2, cycloalkyl, cycloalkylalkyl, heteroalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, hydroxyl, hydroxyalkyl, alkoxy, haloalkoxy preferably -OCF_3 or -$OCHF_2$, alkoxyalkoxy, cycloalkyloxy, heterocyclyloxy, aryloxy, heteroaryloxy, alkoxyalkyl, haloalkoxyalkyl, cycloalkylalkyloxy, arylalkyloxy, heteroarylalkyloxy, aryloxyalkyl, heteroaryloxyalkyl, arylcarbonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, alkylcarbonyloxy, arylcarbonyloxy, heteroarylcarbonyloxy, alkylcarbonylamino, carbamoyl, hydroxycarbamoyl, alkylcarbamoyl, arylcarbamoyl, heteroarylcarbamoyl, carbamoylamino, alkylcarbamoylamino, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, heteroarylsulfamoyl, alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, or one or more of R^{11} and R^{12}, or R^{12} and R^{16}, or R^{16} and $R^{12'}$, or $R^{12'}$ and $R^{11'}$ form an alkylenedioxy group or a haloalkylenedioxy group together with the phenyl group they are attached to, or one or more of R^{11} and R^{12}, or R^{12} and R^{16}, or R^{16} and $R^{12'}$, or $R^{12'}$ and $R^{11'}$ form together an aryl or heteroaryl moiety fused to the phenyl group they are attached to, each of said substituents being optionally substituted by one or more further substituents selected from halo preferably chloro or fluoro, cyano, alkyl, hydroxyalkyl, alkoxyalkyl, haloalkyl, cyanomethyl, cycloalkyl, heterocyclyl, aryl optionally substituted by one a chloro or methyl group, heteroaryl, heteroalkyl, hydroxyl, alkoxy, alkoxyalkoxy, haloalkoxy preferably 1,1,1-trifluoroethyloxy, cycloalkyloxy, cycloalkylalkyloxy preferably cyclopropylmethyloxy, aryloxy, aralkyloxy optionally substituted by one fluoro, amino, alkylamino, carboxy, alkoxycarbonyl, alkylcarbonyloxy, alkylcarbonylamino, haloalkylcarbonylamino, carbamoyl, hydroxycarbamoyl, alkylcarbamoyl, carbamoylalkyloxy preferably carbamoylmethyloxy carbamoylamino, alkylcarbamoylamino, carbamimidoyl, hydroxycarbamimidoyl, alkylsulfonyl, haloalkylsulfonyl, cycloalkylsulfonyl, arylsulfonyl preferably phenylsulfonyl, sulfamoyl, alkylsulfamoyl, alkylsulfonylamino, haloalkylsulfonylamino and oxo, more preferably R^{11}, $R^{11'}$, R^{12}, $R^{12'}$ and R^{16} are independently

selected from H, halo preferably chloro and fluoro, cyano, nitro, alkyl, haloalkyl preferably CF_3 or CHF_2, heterocyclyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, hydroxyl, alkoxy, haloalkoxy preferably OCF_3 or $OCHF_2$, alkoxyalkoxy, aryloxy, cycloalkylalkyloxy, arylalkyloxy, heteroarylalkyloxy, alkoxyalkyl, aryloxyalkyl, heteroaryloxyalkyl, arylcarbonyl, or one or more of **R^{11}** and **R^{12}**, or **R^{12}** and **R^{16}**, or **R^{16}** and **$R^{12'}$**, or **$R^{12'}$** and **$R^{11'}$** form an alkylenedioxy group or a haloalkylenedioxy group together with the phenyl group they are attached to, or one or more of **R^{11}** and **R^{12}**, or **R^{12}** and **R^{16}**, or **R^{16}** and **$R^{12'}$**, or **$R^{12'}$** and **$R^{11'}$** form together an aryl, or heteroaryl moiety fused to the phenyl group they are attached to, each of said substituents being optionally substituted by one or more further substituents selected from halo preferably chloro or fluoro, cyano, alkyl preferably methyl, ethyl, propyl, isopropyl, *tert-butyl,* cyanomethyl, cycloalkyl, heterocyclyl, alkoxy preferably methoxy, ethoxy, isopropoxy, alkoxyalkyl, alkoxyalkoxy, cycloalkylalkyloxy, aryloxy, aralkyloxy optionally substituted by one fluoro, amino, alkylamino, alkylcarbonylamino, carbamoyl, hydroxycarbamimidoyl, alkylsulfonyl, alkylsulfonylamino, still more preferably **R^{11}**, **$R^{11'}$**, **R^{12}**, **$R^{12'}$** and **R^{16}** are independently selected from H, halo preferably chloro and fluoro, cyano, nitro, alkyl preferably methyl, ethyl, isopropyl or isobutyl, haloalkyl preferably CF_3 or CHF_2, cycloalkyl preferably cyclohexyl, heterocyclyl preferably pyrrolidin-1-yl, 4-methylpiperidin-1-yl, aryl preferably phenyl, heteroaryl preferably thiophenyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, aralkyl preferably benzyl, alkoxy preferably methoxy, ethoxy or isopropyloxy, cycloalkylalkyloxy, arylalkyloxy preferably benzyloxy, phenethyloxy or 3,3-diphenylpropan-1-oxy, heteroarylalkyloxy preferably pyridylmethyloxy or pyridylethyloxy, aryloxyalkyl preferably phenoxymethyl, heteroaryloxyalkyl preferably pyridyloxymethyl, or two substituents form an haloalkylenedioxy group each of said substituents being optionally substituted by one or more further substituents selected from halo preferably chloro or fluoro, cyano, alkyl preferably methyl, haloalkyl preferably trifluoromethyl, alkoxy preferably methoxy, isopropyloxy, isobutyloxy, alkoxyalkyl preferably methoxymethyl, alkoxyalkoxy preferably 2-methoxyethoxy, cycloalkylalkyloxy preferably cyclopropylmethyloxy, aryloxy preferably phenoxy, aralkyloxy optionally substituted by one fluoro, preferably benzyloxy, 4-fluorobenzyloxy, amino, alkylcarbonylamino preferably acetylamino, alkylsulfonyl preferably methylsulfonyl, alkylsulfonylamino preferably methylsulfonylamino, (N-methyl-N-methylsulfonyl)amino.

[0049] Preferred compounds of formula Ie-Ig are those of formula Ie-1h1:



Ie-1h1

and pharmaceutically acceptable salts and solvates thereof, wherein

R is as defined above in respect to formula Ia-1b';

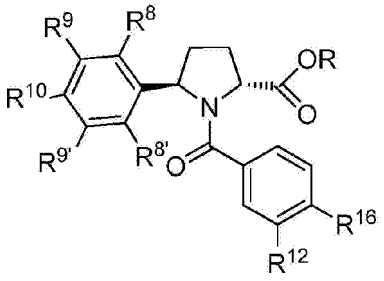
R^8, $R^{8'}$, R^9, $R^{9'}$ and R^{10} are as defined above in respect to formula Ie-1g;

R^{12} is as defined above in respect to formula Ie-1g, preferably R^{12} is H, fluoro, chloro, methyl, CF_3, nitro, cyano, methoxy or cyclopropylmethyloxy;

R^{13}, $R^{13'}$, R^{14}, $R^{14'}$ and R^{15} are as defined above in respect to formula Ie-1g, preferably $R^{13'}$, R^{14}, $R^{14'}$ and R^{15} are H and R^{13} is chloro, cyano, hydroxyl, methyl, trifluoromethyl, cyanomethyl, methoxy, isopropoxy, isobutyloxy, OCF_3, cyclopropylmethyloxy, phenoxy, cyclopropylmethyloxy, benzyloxy, (4-fluorobenzyl)oxy, methoxymethyl, 2-methoxyethoxy, carbamoylmethyloxy, or R^{13}, $R^{13'}$, $R^{14'}$ and R^{15} are H and R^{14} is chloro, methylsulfonylamino, or R^{13}, $R^{13'}$, R^{14} and $R^{14'}$ are H and R^{15} is chloro, methylsulfonylamino, $R^{13'}$, R^{14} and $R^{14'}$ are H and R^{13} and R^{15} are *a)* independently selected from chloro or methoxy, or *b)* both F, or *c)* R^{13} is F and R^{15} is methoxy, or *d)* R^{13} is methoxy and R^{15} is F, or *e)* R^{13} is methoxy and R^{15} is acetylamino, or *f)* R^{13} is methoxy and R^{15} is amino, or *g)* R^{13} is cyano and R^{15} is methoxy, or *h)* R^{13} is chloro and R^{15} is cyano, or *i)* R^{13} is cyano and R^{15} is trifluoromethyl, or *j)* R^{13} is methoxy and R^{15} is (N-methyl-N-methylsulfonyl)amino, or R^{14}, $R^{14'}$ and R^{15} are H and both R^{13} and $R^{13'}$ are methoxy, or R^{13}, $R^{13'}$ and R^{15} are H and both R^{14} and $R^{14'}$ are fluoro, methoxy, or R^{13}, $R^{13'}$ and $R^{14'}$ are H and *a)* R^{14} forms together with R^{15} a phenyl moiety fused to the phenyl ring they are attached to, or *b)* both R^{14} and R^{15} are methoxy, or $R^{13'}$, $R^{14'}$ and R^{15} are H and R^{13} and R^{14} are *a)* both methoxy, or *b)* R^{13} is methyl and R^{14} is methylsulfonylamino, or *c)* R^{13} is methoxy and R^{14} is cyano, or *d)* R^{13} is methyl and R^{14} is amino, or $R^{13'}$, R^{14} and R^{15} are H and R^{13} and $R^{14'}$ are *a)* both methoxy, or *b)* R^{13} is methoxy and $R^{14'}$ is cyano, or *c)* R^{13} is methyl and $R^{14'}$ is cyano, or R^{13} and R^{14} are H and $R^{13'}$, $R^{14'}$ and R^{15} are methoxy, or R^{14} and R^{15} are H and R^{13}, $R^{13'}$ and $R^{14'}$ are methoxy, or R^{13} and R^{14} are methoxy and $R^{13'}$ and R^{15} are H and $R^{14'}$ is cyano, or R^{14} and R^{15} are methoxy and R^{13} and $R^{14'}$ are H and $R^{13'}$ is cyano, or R^{13} and $R^{13'}$ are H and R^{14}, $R^{14'}$ and R^{15} are methoxy, more preferably $R^{13'}$, R^{14}, $R^{14'}$ and R^{15} are H and R^{13} is chloro, cyano, trifluoromethyl, methoxy, isopropoxy, cyclopropylmethyloxy, or R^{13}, $R^{13'}$, $R^{14'}$ and R^{15} are H and R^{14} is chloro, or R^{13}, $R^{13'}$, R^{14} and $R^{14'}$ are H and R^{15} is chloro, methylsulfonylamino, or $R^{13'}$, R^{14} and $R^{14'}$ are H and R^{13} and R^{15} are *a)* independently selected from chloro or methoxy, or *b)* both F, or *c)* R^{13} is F and R^{15} is methoxy, or *d)* R^{13} is methoxy and R^{15} is F, or *e)* R^{13} is methoxy and R^{15} is acetylamino, or *f)* R^{13} is methoxy and R^{15} is amino, or *g)* R^{13} is cyano and R^{15} is methoxy, or *h)* R^{13} is chloro and R^{15} is cyano, or *i)* R^{13} is cyano and R^{15} is trifluoromethyl, or *j)* R^{13} is methoxy and R^{15} is (N-methyl-N-methylsulfonyl)amino, or R^{14}, $R^{14'}$ and R^{15} are H and both R^{13} and $R^{13'}$ are methoxy,

or **R13**, **R13'** and **R14'** are H and *a)* **R14** forms together with **R15** a phenyl moiety fused to the phenyl ring they are attached to, or *b)* both **R14** and **R15** are methoxy, or **R13'**, **R14'** and **R15** are H and **R13** and **R14** are *a)* both methoxy, or *b)* **R13** is methyl and **R14** is methylsulfonylamino, or c) **R13** is methoxy and **R14** is cyano, or *d)* **R13** is methyl and **R14** is amino, or **R13'**, **R14** and **R15** are H and **R13** and **R14'** are *a)* both methoxy, or *b)* **R13** is methoxy and **R14'** is cyano, or *c)* **R13** is methyl and **R14'** is cyano, or **R13** and **R14** are H and **R13'**, **R14'** and **R15** are methoxy, or **R14** and **R15** are H and **R13**, **R13'** and **R14'** are methoxy, or **R13** and **R14** are methoxy and **R13'** and **R15** are H and **R14'** is cyano, or **R14** and **R15** are methoxy and **R13** and **R14'** are H and **R13'** is cyano, or **R13** and **R13'** are H and **R14**, **R14'** and **R15** are methoxy.

[0050] Other preferred compounds of formula Ie-1g are those of formula Ie-1h':



Ie-1h'

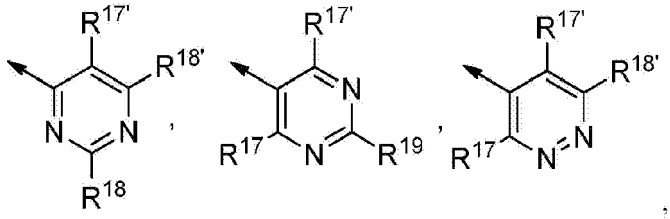
and pharmaceutically acceptable salts and solvates thereof, wherein

R is as defined above in respect to formula Ia-1b';

R8, **R8'**, **R9**, **R9'** and **R10** are as defined above in respect to formula Ie-1g;

R12 is as defined above in respect to formula Ie-1g, preferably **R12** is H, fluoro, chloro, methyl, CF_3, or methoxy more preferably **R12** is H or methoxy;

R16 is selected from the group of heteroaryl moieties consisting of:



wherein the arrow marks the attachment point to the phenyl ring;

R17, **R17'**, **R18**, **R18'** and **R19** are independently selected from H, halo preferably chloro and fluoro, cyano, alkyl preferably methyl, ethyl, propyl, isopropyl, *tert*-butyl, haloalkyl preferably CF_3 or CHF_2, hydroxyl, hydroxyalkyl, alkoxy preferably methoxy, ethoxy, isopropyloxy, haloalkoxy preferably OCF_3, $OCHF_2$, or 1,1,1-trifluoroethyloxy, alkoxyalkoxy, cycloalkyloxy,

alkoxyalkyl preferably methoxymethyl, cycloalkylalkyloxy preferably cyclopropylmethyloxy, aralkyloxy preferably benzyloxy, amino, alkylamino, alkylcarbonylamino, haloalkylcarbonylamino, carbamoyl, hydroxycarbamoyl, alkylcarbamoyl, carbamoylamino, alkylcarbamoylamino, carbamimidoyl, hydroxycarbamimidoyl, alkylsulfonyl preferably methylsulfonyl, haloalkylsulfonyl, sulfamoyl, alkylsulfamoyl, alkylsulfonylamino preferably methylsulfonylamino, (N-methyl-N-methylsulfonyl)amino, haloalkylsulfonylamino, preferably R^{17}, $R^{17'}$, $R^{18'}$ and R^{19} are independently selected from H, halo preferably chloro and fluoro, cyano, alkyl preferably methyl, ethyl, propyl, isopropyl, *tert*-butyl, haloalkyl preferably CF_3, alkoxy preferably methoxy, ethoxy, isopropyloxy, haloalkoxy preferably OCF_3, $OCHF_2$, or 1,1,1-trifluoroethyloxy, alkoxyalkyl preferably methoxymethyl, aralkyloxy preferably benzyloxy, amino, alkylcarbonylamino, carbamoyl, carbamimidoyl, hydroxycarbamimidoyl, alkylsulfonyl preferably methylsulfonyl, alkylsulfonylamino preferably methylsulfonylamino, (N-methyl-N-methylsulfonyl)amino, more preferably R^{17}, $R^{17'}$, $R^{18'}$ and R^{19} are independently selected from H, halo preferably chloro, alkoxy preferably methoxy, even more preferably R^{17}, $R^{17'}$, $R^{18'}$ and R^{19} are independently selected from H, halo preferably chloro, alkoxy preferably methoxy.

[0051] Preferred compounds of formula Ie-Ih' are those wherein R^{16} is selected from 2-2-methoxypyrimidin-4-yl, 2,4-dibenzyloxypyrimidin-5-yl, 2,4-dimethoxypyrimidin-5-yl, 3,6-dimethoxypyridazin-5-yl, 2-methoxypyrimidin-5-yl, 2-methoxypyrimidin-3-yl.

[0052] Particularly preferred compounds of the invention are those listed in Table 1 hereafter:

Table 1:

Compound No.	Compound name	$(M+H)^+$
1	(2S,5R)-5-(2-chlorophenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	436.9
2	(2S,5R)-5-(2-chlorophenyl)-1-(2'-methyl-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	420.9
3	(2S,5R)-1-(3-((4-chlorobenzyl)oxy)-5-methoxybenzoyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid	501.4
4	(2S,5R)-5-(2-chlorophenyl)-1-(2'-fluoro-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	424.9
5	(2S,5R)-5-(2-chlorophenyl)-1-(4'-methyl-[1,1'-biphenyl] -4-carbonyl)pyrrolidine-2-carboxylic acid	420.9
6	(2S,5R)-5-(2-chlorophenyl)-1-(3-methoxy-5-phenethoxybenzoyl)pyrrolidine-2-carboxylic acid	481.0
8	(2S,5R)-1-([1,1'-biphenyl]-4-carbonyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid	406.9
9	(2S,5R)-5-(2-chlorophenyl)-1-(3-(3,3-diphenylpropoxy)-5-methoxybenzoyl)pyrrolidine-2-carboxylic acid	571.1

Compound No.	Compound name	$(M+H)^+$
10	(2S,5R)-5-(2-chlorophenyl)-1-(3'-fluoro-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	424.9
11	(2S,5R)-5-(2-chlorophenyl)-1-(3'-methyl-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	420.9
12	(2S,5R)-5-(2-chlorophenyl)-1-(3-methoxy-5-((4-(methylsulfonyl)benzyl)oxy)benzoyl)pyrrolidine-2-carboxylic acid	545.0
13	(2S,5R)-5-(2-chlorophenyl)-1-(3'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	436.9
14	(2S,5R)-5-(2-chlorophenyl)-1-(3,5-dimethoxybenzoyl)pyrrolidine-2-carboxylic acid	390.8
15	(2S,5R)-5-(2-chlorophenyl)-1-(4-(phenoxymethyl)benzoyl)pyrrolidine-2-carboxylic acid	436.9
16	(2S,5R)-5-(2-chlorophenyl)-1-(4-((2-fluorobenzyl)oxy)benzoyl)pyrrolidine-2-carboxylic acid	454.9
17	(2S,5R)-1-(3-chloro-5-methoxybenzoyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid	395.2
18	(2S,5R)-5-(2-chlorophenyl)-1-(4'-fluoro-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	424.9
19	(2S,5R)-5-(2-chlorophenyl)-1-(4-phenethoxybenzoyl)pyrrolidine-2-carboxylic acid	450.9
21	(2S,5R)-5-(2-chlorophenyl)-1-(3,5-diethoxybenzoyl)pyrrolidine-2-carboxylic acid	418.9
23	(2S,5R)-5-(2-chlorophenyl)-1-(3-phenethoxybenzoyl)pyrrolidine-2-carboxylic acid	450.9
24	(2S)-1-([1,1'-biphenyl]-4-carbonyl)-4-benzyl-5-phenylpyrrolidine-2-carboxylic acid	462.6
25	(2S,5R)-5-(2-chlorophenyl)-1-(1,2,3,4-tetrahydronaphthalene-2-carbonyl)pyrrolidine-2-carboxylic acid	384.9
26	(2S,5R)-5-(2-chlorophenyl)-1-(4-isobutylbenzoyl)pyrrolidine-2-carboxylic acid	386.9
27	(2S,5R)-5-(2-chlorophenyl)-1-(2,2-difluorobenzo[d][1,3]dioxole-6-carbonyl)pyrrolidine-2-carboxylic acid	410.8
28	(2S,5R)-1-([1,1'-biphenyl]-4-carbonyl)-5-phenylpyrrolidine-2-carboxylic acid	372.4
29	(2S,5R)-5-(2-chlorophenyl)-1-(3-fluoro-5-methoxybenzoyl)pyrrolidine-2-carboxylic acid	378.8
30	(2S,5R)-5-(2-chlorophenyl)-1-(6-phenylnicotinoyl)pyrrolidine-2-carboxylic acid	407.9

Compound No.	Compound name	$(M+H)^+$
31	(2S,5R)-5-(2-chlorophenyl)-1-(3-methoxy-5-(2-methoxyethoxy)benzoyl)pyrrolidine-2-carboxylic acid	434.9
32	(2S,5R)-5-(2-chlorophenyl)-1-(3'-methoxy-[1,1'-biphenyl]-3-carbonyl)pyrrolidine-2-carboxylic acid	436.9
33	(2S,5R)-5-(2-chlorophenyl)-1-(3-methoxy-5-(trifluoromethyl)benzoyl)pyrrolidine-2-carboxylic acid	428.8
34	(2S,5R)-5-(2-chlorophenyl)-1-(1-(4-methoxyphenyl)-5-phenyl-1H-pyrazole-3-carbonyl)pyrrolidine-2-carboxylic acid	503.0
35	(2S,5R)-5-(2-chlorophenyl)-1-(4-isopropoxybenzoyl)pyrrolidine-2-carboxylic acid	388.9
36	(2S,5R)-5-(2-chlorophenyl)-1-(3-((3,5-dimethylisoxazol-4-yl)methoxy)-5-methoxybenzoyl)pyrrolidine-2-carboxylic acid	485.9
37	(2S,5R)-5-(2-chlorophenyl)-1-(2,3-dihydro-1H-indene-2-carbonyl)pyrrolidine-2-carboxylic acid	370.8
38	(2S,5R)-5-(2-chlorophenyl)-1-(3-methyl-5-(trifluoromethoxy)benzoyl)pyrrolidine-2-carboxylic acid	428.8
39	(2S,5R)-1-(3-(benzyloxy)benzoyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid	436.9
40	(2S,5R)-5-(2-chlorophenyl)-1-(3-methoxybenzoyl)pyrrolidine-2-carboxylic acid	360.8
41	(2S,5R)-5-(2-chlorophenyl)-1-(2-phenylpyrimidine-5-carbonyl)pyrrolidine-2-carboxylic acid	408.9
42	(2S,5R)-5-(2-chlorophenyl)-1-(4-(trifluoromethoxy)benzoyl)pyrrolidine-2-carboxylic acid	414.8
43	(2S,5R)-5-(2-chlorophenyl)-1-(4-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)benzoyl)pyrrolidine-2-carboxylic acid	438.9
44	4-((2S,5R)-2-carboxy-5-(2-chlorophenyl)pyrrolidine-1-carbonyl)-2,6-dimethoxypyrimidin-1-ium formate	438.8
45	(2S,5R)-5-(2-chlorophenyl)-1-(4-phenylbutanoyl)pyrrolidine-2-carboxylic acid	372.9
46	(2S,5R)-5-(2-chlorophenyl)-1-(3-methyl-5-(trifluoromethyl)benzoyl)pyrrolidine-2-carboxylic acid	412.8
47	(2S,5R)-1-([1,1'-biphenyl]-4-carbonyl)-5-(3-chloropyridin-2-yl)pyrrolidine-2-carboxylic acid	407.9
48	(2S,5R)-5-(2-chlorophenyl)-1-(3-hydroxy-5-(trifluoromethyl)benzoyl)pyrrolidine-2-carboxylic acid	414.8
49	(2S,5S)-5-(2-chlorophenyl)-1-(3-methoxybenzoyl)pyrrolidine-2-carboxylic acid	360.8
50	(2S,5R)-1-(3,5-dimethoxybenzoyl)-5-phenylpyrrolidine-2-carboxylic acid	356.4

Compound No.	Compound name	$(M+H)^+$
51	(S)-5-([1,1'-biphenyl]-3-yl)-1-(3-methoxybenzoyl)pyrrolidine-2-carboxylic acid	402.5
52	(2S,5R)-5-(2-chlorophenyl)-1-(3-phenylpropanoyl)pyrrolidine-2-carboxylic acid	358.8
53	(2S,5S)-5-(2-chlorophenyl)-1-(2'-methoxy-[1,1'-biphenyl] -4-carbonyl)pyrrolidine-2-carboxylic acid	436.9
54	(2S,5R)-1-([1,1'-bipbenyl]-4-carbonyl)-5-(pyridin-2-yl)pyrrolidine-2-carboxylic acid	373.4
55	(2S,5R)-5-(2-chlorophenyl)-1-(5-phenylpicolinoyl)pyrrolidine-2-carboxylic acid	407.9
57	(2S,5R)-5-(2-fluorophenyl)-1-(3-methoxybenzoyl)pyrrolidine-2-carboxylic acid	344.3
59	(2R,5S)-1-([1,1'-biphenyl]-4-carbonyl)-5-phenylpyrrolidine-2-carboxylic acid	372.4
62	(2S,5R)-1-(3-methoxybenzoyl)-5-(2-methoxyphenyl)pyrrolidine-2-carboxylic acid	356.4
63	(2R,5S)-5-(2-chlorophenyl)-1-(3-methoxybenzoyl)pyrrolidine-2-carboxylic acid	360.8
64	(2R,5R)-5-(2-chlorophenyl)-1-(3-methoxybenzoyl)pyrrolidine-2-carboxylic acid	360.8
65	(2S)-5-(4-chlorophenyl)-1-(3-methoxybenzoyl)pyrrolidine-2-carboxylic acid	360.8
66	(2S)-5-([1,1'-biphenyl]-4-yl)-1-(3-methoxybenzoyl)pyrrolidine-2-carboxylic acid	402.5
67	(2S,5R)-methyl 5-(2-chlorophenyl)-1-3-methoxybenzoyl)pyrrolidine-2-carboxylate	374.8
69	(2S)-5-cyclohexyl-1-(3-methoxybenzoyl)pyrrolidine-2-carboxylic acid	332.4
71	(2S,5S)-5-(2-chlorophenyl)-1-(3,5-dimethoxybenzoyl)pyrrolidine-2-carboxylic acid	390.8
72	(2S,5R)-5-([1,1'-biphenyl]-2-yl)-1-(3-methoxybenzoyl)pyrrolidine-2-carboxylic acid	402.5
75	(2S,5R)-5-(2-chlorophenyl)-1-(6-phenylpyrimidine-4-carbonyl)pyrrolidine-2-carboxylic acid	408.9
76	(2S,5R)-5-(2-chlorophenyl)-1-(6-(2-fluorophenyl)nicotinoyl)pyrrolidine-2-carboxylic acid	425.9
77	(2S,5R)-5-(2-chlorophenyl)-1-(6-(2-chlorophenyl)nicotinoyl)pyrrolidine-2-carboxylic acid	442.3
78	(2S,5R)-5-(2-chlorophenyl)-1-(6-(2-methoxyphenyl)nicotinoyl)pyrrolidine-2-carboxylic acid	437.9

Compound No.	Compound name	$(M+H)^+$
79	(2S,5R)-5-(2-chlorophenyl)-1-(6-(3-fluorophenyl)nicotinoyl)pyrrolidine-2-carboxylic acid	425.9
80	(2S,5R)-5-(2-chlorophenyl)-1-(6-(3-methoxyphenyl)nicotinoyl)pyrrolidine-2-carboxylic acid	437.9
81	(2S,5R)-5-(2-chlorophenyl)-1-(6-(4-methoxyphenyl)nicotinoyl)pyrrolidine-2-carboxylic acid	437.9
82	(2S,5R)-5-(2-chlorophenyl)-1-(6-(4-fluorophenyl)nicotinoyl)pyrrolidine-2-carboxylic acid	425.9
83	(2S,5R)-5-(2-chlorophenyl)-1-(2-(2-chlorophenyl)pyrimidine-5-carbonyl)pyrrolidine-2-carboxylic acid	443.3
84	(2S,5R)-5-(2-chlorophenyl)-1-(2-methyl-6-phenylnicotinoyl)pyrrolidine-2-carboxylic acid	421.9
85	(2S,5R)-1-(4-chloro-2-(pyridin-3-yl)pyrimidine-5-carbonyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid	444.3
86	(2S,5R)-1-(4-chloro-2-(pyridin-2-yl)pyrimidine-5-carbonyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid	444.3
87	(2S,5R)-1-(4-chloro-2-(pyridin-4-yl)pyrimidine-5-carbonyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid	444.3
88	(2S,5R)-5-(2-chlorophenyl)-1-(4-(pyridin-2-yl)benzoyl)pyrrolidine-2-carboxylic acid	407.9
89	(2S,5R)-1-(4-((4-chlorophenoxy)methyl)benzoyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid	471.3
90	(2S,5R)-5-(2-chlorophenyl)-1-(4-((4-fluorophenoxy)methyl)benzoyl)pyrrolidine-2-carboxylic acid	454.9
91	(2S,5R)-5-(2-chlorophenyl)-1-(4-((4-methoxyphenoxy)methyl)benzoyl)pyrrolidine-2-carboxylic acid	466.9
92	(2S,5R)-1-(4-((2-chlorophenoxy)methyl)benzoyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid	471.3
93	(2S,5R)-5-(2-chlorophenyl)-1-(4-((2-methoxyphenoxy)methyl)benzoyl)pyrrolidine-2-carboxylic acid	466.9
94	(2S,5R)-5-(2-chlorophenyl)-1-(4-((3-methoxyphenoxy)methyl)benzoyl)pyrrolidine-2-carboxylic acid	466.9
95	(2S,5R)-1-(4-((3-chlorophenoxy)methyl)benzoyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid	471.3
96	(2S,5R)-5-(2-chlorophenyl)-1-(4-((p-tolyloxy)methyl)benzoyl)pyrrolidine-2-carboxylic acid	450.9
97	(2S,5R)-5-(2-chlorophenyl)-1-(4-((3-methoxybenzyl)oxy)benzoyl)pyrrolidine-2-carboxylic acid	466.9

Compound No.	Compound name	$(M+H)^+$
98	(2S,5R)-1-(4-((3-chlorobenzyl)oxy)benzoyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid	471.3
99	(2S,5R)-5-(2-chlorophenyl)-1-(4-((3,5-dimethylisoxazol-4-yl)methoxy)benzoyl)pyrrolidine-2-carboxylic acid	455.9
100	(2S,5R)-5-(2-chlorophenyl)-1-(4-((3,5-dimethyl-1H-pyrazol-1-yl)methoxy)benzoyl)pyrrolidine-2-carboxylic acid	454.9
101	(2S,5R)-5-(2-chlorophenyl)-1-(4-(pyridin-2-ylmethoxy)benzoyl)pyrrolidine-2-carboxylic acid	437.9
102	(2S,5R)-5-(2-chlorophenyl)-1-(4-(pyridin-4-ylmethoxy)benzoyl)pyrrolidine-2-carboxylic acid	437.9
103	(2S,5R)-5-(2-chlorophenyl)-1-(4-(pyridin-3-ylmethoxy)benzoyl)pyrrolidine-2-carboxylic acid	437.9
104	(2S,5R)-5-(2-chlorophenyl)-1-(4-(5-methyl-1H-pyrazol-1-yl)benzoyl)pyrrolidine-2-carboxylic acid	410.9
105	(2S,5R)-5-(2-chlorophenyl)-1-(4-(isoxazol-5-yl)benzoyl)pyrrolidine-2-carboxylic acid	397.8
106	(2S,5R)-1-(4-(4H-1,2,4-triazol-4-yl)benzoyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid	397.8
107	(2S,5R)-5-(2-chlorophenyl)-1-(4-(5-(p-tolyl)-1H-1,2,3-triazol-1-yl)benzoyl)pyrrolidine-2-carboxylic acid	488.0
108	(2S,5R)-5-(2-chlorophenyl)-1-(4-(5-oxo-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl)benzoyl)pyrrolidine-2-carboxylic acid	488.9
109	(2S,5R)-5-(2-chlorophenyl)-1-(4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzoyl)pyrrolidine-2-carboxylic acid	478.9
110	(2S,5R)-1-(4-(1H-pyrazol-1-yl)benzoyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid	396.8
111	(2S,5R)-5-(2-chlorophenyl)-1-(4-(oxazol-5-yl)benzoyl)pyrrolidine-2-carboxylic acid	397.8
112	(2S,5R)-5-(2-chlorophenyl)-1-(4-(3,5-dimethyl-1H-pyrazol-1-yl)benzoyl)pyrrolidine-2-carboxylic acid	424.9
113	(2S,5R)-5-(2-chlorophenyl)-1-(2',5'-dichloro-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	475.8
114	(2S,5R)-5-(2-chlorophenyl)-1-(4-(pyrimidin-5-yl)benzoyl)pyrrolidine-2-carboxylic acid	408.9
115	(2S,5R)-5-(2-chlorophenyl)-1-(4-(furan-3-yl)benzoyl)pyrrolidine-2-carboxylic acid	396.8
116	(2S,5R)-5-(2-chlorophenyl)-1-(4-(6-methoxypyridin-3-yl)benzoyl)pyrrolidine-2-carboxylic acid	437.9

Compound No.	Compound name	$(M+H)^+$
117	(2S,5R)-5-(2-chlorophenyl)-1-(4-(3-fluoropyridin-4-yl)benzoyl)pyrrolidine-2-carboxylic acid	425.9
118	(2S,5R)-5-(2-chlorophenyl)-1-(4-(pyridin-3-yl)benzoyl)pyrrolidine-2-carboxylic acid	407.9
119	(2S,5R)-5-(2-chlorophenyl)-1-(4-(6-(dimethylamino)pyridin-3-yl)benzoyl)pyrrolidine-2-carboxylic acid	450.9
120	(2S,5R)-5-(2-chlorophenyl)-1-(4-(pyridin-4-yl)benzoyl)pyrrolidine-2-carboxylic acid	407.9
121	(2S,5R)-5-(2-chlorophenyl)-1-(4-(6-methylpyridin-3-yl)benzoyl)pyrrolidine-2-carboxylic acid	421.9
122	(2S,5R)-5-(2-chlorophenyl)-1-(4-(2-methoxypyridin-3-yl)benzoyl)pyrrolidine-2-carboxylic acid	437.9
123	(2S,5R)-5-(2-chlorophenyl)-1-(4'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	436.9
124	(2S,5R)-5-(2-chlorophenyl)-1-(4'-cyano-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	431.9
125	(2S,5R)-5-(2-chlorophenyl)-1-(4-(4-methoxypyridin-3-yl)benzoyl)pyrrolidine-2-carboxylic acid	437.9
126	(2S,5R)-1-(4'-chloro-[1,1'-biphenyl]-4-carbonyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid	441.3
127	(2S,5R)-1-(3'-chloro-[1,1'-biphenyl]-4-carbonyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid	441.3
128	(2S,5R)-1-(2'-chloro-[1,1'-biphenyl]-4-carbonyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid	441.3
129	(2S,5R)-5-(2-chlorophenyl)-1-(4'-(methylsulfonamido)-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	500.0
130	(2S,5R)-5-(2-chlorophenyl)-1-(3'-(methylsulfonamido)-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	500.0
131	(2S,5R)-5-(2-chlorophenyl)-1-(2'-(methylsulfonamido)-[1,1'-biphenyl] -4-carbonyl)pyrrolidine-2-carboxylic acid	500.0
132	(2S,5R)-5-(2-chlorophenyl)-1-(4-(naphthalen-2-yl)benzoyl)pyrrolidine-2-carboxylic acid	456.9
133	(2S,5R)-5-(2-chlorophenyl)-1-(3',5'-difluoro-[1,1'-biphenyl] -4-carbonyl)pyrrolidine-2-carboxylic acid	442.9
134	(2S,5R)-5-(2-chlorophenyl)-1-(2'-hydroxy-[1,1'-biphenyl] -4-carbonyl)pyrrolidine-2-carboxylic acid	422.9
135	(2S,5R)-5-(2-chlorophenyl)-1-(2'-(trifluoromethoxy)-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	490.9
136	(2S,5R)-1-(2'-(benzyloxy)-[1,1'-bipbenyl]-4-carbonyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid	513.0

Compound No.	Compound name	$(M+H)^+$
137	(2S,5R)-5-(2-chlorophenyl)-1-(2'-phenoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	499.0
138	(2S,5R)-5-(2-chlorophenyl)-1-(2'-isopropoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	465.0
139	(2S,5R)-5-(2-chlorophenyl)-1-(2'-isobutoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	479.0
140	(2S,5R)-5-(2-chlorophenyl)-1-(2'-(cyclopropylmethoxy)-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	477.0
141	(2S,5R)-5-(2-chlorophenyl)-1-(2'-((4-fluorobenzyl)oxy)-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	531.0
142	(2S,5R)-5-(2-chlorophenyl)-1-(4-(6-chloropyridin-3-yl)benzoyl)pyrrolidine-2-carboxylic acid	442.3
143	(2S,5R)-5-(2-chlorophenyl)-1-(4-(6-fluoropyridin-3-yl)benzoyl)pyrrolidine-2-carboxylic acid	425.9
144	(2S,5R)-5-(2-chlorophenyl)-1-(4-(2-chloropyridin-4-yl)benzoyl)pyrrolidine-2-carboxylic acid	442.3
145	(2S,5R)-1-(4-(2-chloro-3-fluoropyridin-4-yl)benzoyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid	460.3
146	(2S,5R)-5-(2-chlorophenyl)-1-(4-(2-chloropyridin-3-yl)benzoyl)pyrrolidine-2-carboxylic acid	442.3
147	(2S,5R)-1-(4-(6-(benzyloxy)pyridin-3-yl)benzoyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid	514.0
148	(2S,5R)-1-(4-(1H-pyrazol-4-yl)benzoyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid	396.8
149	(2S,5R)-5-(2-chlorophenyl)-1-(4-(thiophen-3-yl)benzoyl)pyrrolidine-2-carboxylic acid	412.9
150	(2S,5R)-5-(2-chlorophenyl)-1-(4-cyclohexylbenzoyl)pyrrolidine-2-carboxylic acid	412.9
151	(2S,5R)-5-(2-chlorophenyl)-1-(4'-(methylsulfonyl)-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	485.0
152	(2S,5R)-5-(2-chlorophenyl)-1-(9-oxo-9H-fluorene-2-carbonyl)pyrrolidine-2-carboxylic acid	432.9
153	(2S,5R)-5-(2-chlorophenyl)-1-(2'-(methylsulfonyl)-[1,1'-biphenyl] -4-carbonyl)pyrrolidine-2-carboxylic acid	485.0
154	(2S,5R)-5-(2-chlorophenyl)-1-(4-(tetrahydro-2H-pyran-4-yl)benzoyl)pyrrolidine-2-carboxylic acid	414.9
156	(2S,5R)-5-(2-chlorophenyl)-1-(4-phenoxybenzoyl)pyrrolidine-2-carboxylic acid	422.9
157	(2S,5R)-1-(4-benzylbenzoyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid	420.9

Compound No.	Compound name	$(M+H)^+$
158	(2S,5R)-1-(4-benzoylbenzoyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid	434.9
159	(2S,5R)-5-(2-chlorophenyl)-1-(4-(pyrimidin-2-yl)benzoyl)pyrrolidine-2-carboxylic acid	408.9
160	(2S,5R)-5-(2-chlorophenyl)-1-(4-(4,6-dimethoxypyrimidin-2-yl)benzoyl)pyrrolidine-2-carboxylic acid	468.9
161	(2S,5R)-5-(2-chlorophenyl)-1-(4-(2,4-dimethoxypyrimidin-5-yl)benzoyl)pyrrolidine-2-carboxylic acid	468.9
162	(2S,5R)-5-(2-chlorophenyl)-1-(4-(2-methoxypyrimidin-5-yl)benzoyl)pyrrolidine-2-carboxylic acid	438.9
163	(2S,5R)-5-(2-chlorophenyl)-1-(4-(2-(dimethylamino)pyrimidin-5-yl)benzoyl)pyrrolidine-2-carboxylic acid	451.9
164	(2S,5R)-5-(2-chlorophenyl)-1-(4-(2-morpholinopyrimidin-5-yl)benzoyl)pyrrolidine-2-carboxylic acid	494.0
165	(2S,5R)-5-(2-chlorophenyl)-1-(4-(2-(piperidin-1-yl)pyrimidin-5-yl)benzoyl)pyrrolidine-2-carboxylic acid	492.0
168	(2S,5R)-5-(2-chlorophenyl)-1-(cyclohexanecarbonyl)pyrrolidine-2-carboxylic acid	336.8
169	(2S,5R)-5-(2-chlorophenyl)-1-(4-methylpentanoyl)pyrrolidine-2-carboxylic acid	324.8
172	(2S,5R)-5-(2-chlorophenyl)-1-(4-(4-methylpiperidin-1-yl)-3-nitrobenzoyl)pyrrolidine-2-carboxylic acid	472.9
173	(2S,5R)-5-(2-chlorophenyl)-1-(4-(2-oxopiperidin-1-yl)benzoyl)pyrrolidine-2-carboxylic acid	427.9
174	(2S,5R)-5-(2-chlorophenyl)-1-(3-methyl-4-morpholinobenzoyl)pyrrolidine-2-carboxylic acid	429.9
175	(2S,5R)-5-(2-chlorophenyl)-1-(4-(piperidin-1-yl)benzoyl)pyrrolidine-2-carboxylic acid	413.9
176	(2S,5R)-5-(2-chlorophenyl)-1-(4-morpholinobenzoyl)pyrrolidine-2-carboxylic acid	415.9
177	(2S,5R)-5-(2-chlorophenyl)-1-(1-(2-cyanophenyl)piperidine-4-carbonyl)pyrrolidine-2-carboxylic acid	438.9
178	(2S,5R)-5-(2-chlorophenyl)-1-(4-(4-chlorophenyl)cyclohexanecarbonyl)pyrrolidine-2-carboxylic acid	447.4
179	(2S,5R)-5-(2-chlorophenyl)-1-(4-phenylcyclohexanecarbonyl)pyrrolidine-2-carboxylic acid	412.9
184	(2R,5S)-5-(2-chlorophenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	436.9

Compound No.	Compound name	$(M+H)^+$
189	(2S,5R)-5-(2-chlorophenyl)-1-(6-(2-fluorophenyl)nicotinoyl)pyrrolidine-2-carboxylic acid	425.9
191	(2S,5R)-5-(2-chlorophenyl)-1-(5-methoxy-6-phenylnicotinoyl)pyrrolidine-2-carboxylic acid	437.9
192	(2S,5R)-5-(2-chlorophenyl)-1-(4-(2-methoxyphenoxy)benzoyl)pyrrolidine-2-carboxylic acid	452.9
193	(2S,5R)-5-(2-chlorophenyl)-1-(4-(3-methoxypyridin-4-yl)benzoyl)pyrrolidine-2-carboxylic acid	437.9
194	(2S)-5-(2-chlorophenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)-4,4-dimethylpyrrolidine-2-carboxylic acid	465.0
195	(2S)-5-(2-chlorophenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)-4-methylpyrrolidine-2-carboxylic acid	450.9
196	(2S,5R)-5-(2-chlorophenyl)-1-(2-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	436.9
197	(2S,5R)-5-(2-chlorophenyl)-1-(2'-cyano-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	431.9
198	(2S,5R)-5-(2-chlorophenyl)-1-(2',6'-dimethoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	466.9
199	(2S,5R)-5-(2-chlorophenyl)-1-(2',4'-dichloro-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	475.8
200	(2S,5R)-5-(2-chlorophenyl)-1-(2'-(trifluoromethyl)-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	474.9
201	(2S,5R)-5-(2-chlorophenyl)-1-(2,2'-dimethoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	466.9
202	(2S,5R)-1-(4'-chloro-2'-methoxy-[1,1'-biphenyl]-4-carbonyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid	471.3
203	(2S,5R)-5-(2-chlorophenyl)-1-(4-(4-methoxypyrimidin-5-yl)benzoyl)pyrrolidine-2-carboxylic acid	438.9
204	(2S,5R)-5-(2-chlorophenyl)-1-(2',4'-dimethoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	466.9
205	(2S,5R)-1-([1,1'-biphenyl]-4-carbonyl)-5-(pyridin-3-yl)pyrrolidine-2-carboxylic acid	373.4
206	(2R,5R)-5-(2-chlorophenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	436.9
207	(2S,5R)-5-(2-chlorophenyl)-1-(1-phenyl-1H-benzo[d]imidazole-5-carbonyl)pyrrolidine-2-carboxylic acid	446.9
208	(2S,5R)-methyl 5-(2-chlorophenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylate	450.9
211	(2S,4S,5R)-5-(2-chlorophenyl)-4-(hydroxymethyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic	466.9

Compound No.	Compound name	$(M+H)^+$
	acid	
217	(2S,4S,5S)-5-(2-chlorophenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)-4-(phenylsulfonyl)pyrrolidine-2-carboxylic acid	577.1
220	(2S,5R)-5-(2-chlorophenyl)-4-cyano-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	461.9
221	(2S,3R,5R)-5-(2-chlorophenyl)-3-cyano-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	461.9
224	(2S,5R)-1-(2-chloro-[1,1'-biphenyl]-4-carbonyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid	441.3
225	(2S,5R)-1-(2'-chloro-2-methoxy-[1,1'-biphenyl]-4-carbonyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid	471.3
226	(2S,5R)-5-(2-chlorophenyl)-1-(2'-(2-methoxyethoxy)-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	481.0
227	(2S,5R)-5-(2-chlorophenyl)-1-(4-(2-methylthiophen-3-yl)benzoyl)pyrrolidine-2-carboxylic acid	426.9
228	(2S,5R)-5-(2-chlorophenyl)-1-(2',6'-dichloro-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	475.8
229	(2S,5R)-1-(2'-chloro-4'-methoxy-[1,1'-biphenyl]-4-carbonyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid	471.3
230	(2S,5R)-5-(2-chlorophenyl)-1-(3-methoxy-4-(pyrimidin-5-yl)benzoyl)pyrrolidine-2-carboxylic acid	438.9
231	(2S,5R)-1-(2'-carbamimidoyl-[1,1'-biphenyl]-4-carbonyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid	448.9
232	(2S,5R)-5-(2-fluorophenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	420.4
233	(2S,5R)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)-5-(o-tolyl)pyrrolidine-2-carboxylic acid	416.5
234	(2S,5R)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)-5-(2-methoxyphenyl)pyrrolidine-2-carboxylic acid	432.5
235	(2S,5R)-5-(2-chlorophenyl)-1-(2'-(methoxymethyl)-[1,1'-biphenyl] -4-carbonyl)pyrrolidine-2-carboxylic acid	450.9
236	(2S,5R)-5-(2-chlorophenyl)-1-(4-(2,6-dimethoxypyridin-3-yl)benzoyl)pyrrolidine-2-carboxylic acid	467.9
237	(2S,5R)-5-(2-chlorophenyl)-1-(3-methoxy-4-(2-methoxypyrimidin-5-yl)benzoyl)pyrrolidine-2-carboxylic acid	468.9
238	(2S,5R)-5-(2-chlorophenyl)-1-(4-(5-methoxypyrazin-2-yl)benzoyl)pyrrolidine-2-carboxylic acid	438.9
239	(2S,5R)-5-(2-chlorophenyl)-1-(4-(2-(2-methoxyethoxy)pyridin-3-yl)benzoyl)pyrrolidine-2-carboxylic	481.9

Compound No.	Compound name	$(M+H)^+$
	acid	
240	(2S,5R)-5-(2-chlorophenyl)-1-(4-(3-methoxypyrazin-2-yl)benzoyl)pyrrolidine-2-carboxylic acid	438.9
241	(2S,5R)-1-(4-(2-chloro-4-(dimethylamino)pyrimidin-5-yl)benzoyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid	486.4
242	(2S,5R)-5-(2-chlorophenyl)-1-(4-(2,6-dimethoxypyrimidin-4-yl)benzoyl)pyrrolidine-2-carboxylic acid	468.9
243	(2S,5R)-5-(2-chlorophenyl)-1-(2'-(dimethylamino)-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	449.9
244	(2S,5R)-5-(2-chlorophenyl)-1-(4-(2-methoxypyrimidin-4-yl)benzoyl)pyrrolidine-2-carboxylic acid	438.9
245	(2S,5R)-5-(2-chlorophenyl)-1-(3-methoxy-4-(2-methoxypyrimidin-4-yl)benzoyl)pyrrolidine-2-carboxylic acid	468.9
246	(2S,5R)-5-(2-fluorophenyl)-1-(4-(2-methoxypyridin-3-yl)benzoyl)pyrrolidine-2-carboxylic acid	421.4
247	(2S,5R)-1-(4-(2,4-dimethoxypyrimidin-5-yl)benzoyl)-5-(2-fluorophenyl)pyrrolidine-2-carboxylic acid	452.4
248	(2S,5R)-5-(2-chlorophenyl)-1-(2-methyl-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	420.9
249	(2S,5R)-5-(2-chlorophenyl)-1-(3-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	436.9
251	(2S,5R)-5-(2-chlorophenyl)-1-(5-phenylpyrazine-2-carbonyl)pyrrolidine-2-carboxylic acid	408.9
252	(2S,5R)-5-(2-chlorophenyl)-1-(5-methoxy-6-(2-methoxyphenyl)nicotinoyl)pyrrolidine-2-carboxylic acid	467.9
253	(2S,5R)-5-(2-chlorophenyl)-1-(4-(5-methoxypyrimidin-4-yl)benzoyl)pyrrolidine-2-carboxylic acid	438.9
254	(2S,5R)-5-(2-chlorophenyl)-1-(4-(pyridazin-4-yl)benzoyl)pyrrolidine-2-carboxylic acid	408.9
255	(2S,5R)-1-(4-(1H-1,2,3-triazol-1-yl)benzoyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid	397.8
256	(2S,5R)-5-(2-chlorophenyl)-1-(4-(4-(p-tolyl)-1H-1,2,3-triazol-1-yl)benzoyl)pyrrolidine-2-carboxylic acid	488.0
257	(2S,5R)-5-(2-chlorophenyl)-1-(1-(2-methoxyphenyl)piperidine-4-carbonyl)pyrrolidine-2-carboxylic acid	443.9
258	(2S,5R)-5-(2-chlorophenyl)-1-(4-(2-methoxyphenyl)piperazine-1-carbonyl)pyrrolidine-2-carboxylic acid	444.9

Compound No.	Compound name	$(M+H)^+$
259	(2S,5R)-5-(2-chlorophenyl)-1-(1-(4-methoxypyrimidin-5-yl)piperidine-4-carbonyl)pyrrolidine-2-carboxylic acid	445.9
260	(2S,5R)-5-(2-chlorophenyl)-1-(4-(4-methoxypyrimidin-5-yl)piperazine-1-carbonyl)pyrrolidine-2-carboxylic acid	446.9
261	(2S,5R)-5-(2-chlorophenyl)-1-(3-methoxy-4-(4-methylpiperidin-1-yl)benzoyl)pyrrolidine-2-carboxylic acid	458.0
262	(2S,5R)-5-(2-chlorophenyl)-1-(3-methoxy-4-(1-methylpiperidin-4-yl)benzoyl)pyrrolidine-2-carboxylic acid	458.0
263	(2S,5R)-5-(2-chlorophenyl)-1-(2-cyano-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	431.9
264	(2S,5R)-5-(2-chlorophenyl)-1-(2-isobutoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	479.0
265	(2S,5R)-5-(2-chlorophenyl)-1-(4-(2,4-dichloropyrimidin-5-yl)benzoyl)pyrrolidine-2-carboxylic acid	477.7
266	(2S,5R)-5-(2-chlorophenyl)-1-(4-(2,4-dimethoxypyrimidin-5-yl)-3-methoxybenzoyl)pyrrolidine-2-carboxylic acid	498.9
267	(2S,5R)-1-(4-(2-chloro-4-methoxypyrimidin-5-yl)benzoyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid	473.3
268	(2S,3S,5S)-5-(2-chlorophenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)-3-methylpyrrolidine-2-carboxylic acid	450.9
269	(2S,5R)-1-(4-(2,6-dimethoxypyridin-3-yl)benzoyl)-5-(2-fluorophenyl)pyrrolidine-2-carboxylic acid	451.5
270	(2S,5R)-1-(2'-(2-amino-2-oxoethoxy)-[1,1'-biphenyl]-4-carbonyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid	479,9
271	(2S,5R)-5-(2-chlorophenyl)-1-(2-(cyclopropylmethoxy)-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	477,0
272	(2S,5R)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)-5-phenylpyrrolidine-2-carboxylic acid	402,5
273	(2S,5R)-5-(3-chlorophenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	436,9
274	(2S,5R)-5-(4-chlorophenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	436,9
275	(2S,5R)-5-(3-fluorophenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	420,4
276	(2S,5R)-5-(4-fluorophenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	420,4
278	(2S,5R)-4-acetyl-5-(2-chlorophenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	478,9
279	(2S,4S,5R)-5-(2-chlorophenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)-4-(methoxymethyl)pyrrolidine-2-	481,0

Compound No.	Compound name	$(M+H)^+$
	carboxylic acid	
280	(2S,5R)-5-(2-chlorophenyl)-1-(4-(2-methoxypyrimidin-4-yl)benzoyl)pyrrolidine-2-carboxylic acid	438,9
281	(2S,5R)-5-cyclohexyl-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	408,5
283	(2S,5R)-1-(4-(2-chloro-4-methoxypyrimidin-5-yl)benzoyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid	473,3
284	(2S,5R)-5-(2-chlorophenyl)-1-(4-(3-methoxypyridin-2-yl)benzoyl)pyrrolidine-2-carboxylic acid	437,9
285	(2R,5R)-5-(2-fluorophenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	420,4
286	(2S,5S)-5-(2-fluorophenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	420,4
287	(2R,5S)-5-(2-fluorophenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	420,4
288	(2S,5R)-5-(2-chlorophenyl)-1-(2-(trifluoromethyl)-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	474,9
289	(2S,5R)-5-(2-chlorophenyl)-1-(2',4'-difluoro-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	442,9
290	(2S,5R)-5-(2-chlorophenyl)-1-(2-methyl-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	420,9
291	(2S,5R)-5-(2,6-difluorophenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	438,4
292	(2S,5R)-5-(2,4-difluorophenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	438,4
293	(2S,5R)-5-(2,4-dichlorophenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	471,3
294	(2S,5R)-5-isobutyl-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	382,5
295	(2S,5R)-5-isopropyl-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	368,4
296	(2S,5R)-1-(3-chloro-4-(pyrimidin-4-yl)benzoyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid	443,3
297	(2S,5R)-5-(2-chlorophenyl)-1-(2-fluoro-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	424,9
298	(2S,5R)-5-(2-chlorophenyl)-1-(2'-fluoro-4'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	454,9
299	(2S,5R)-5-(2-chlorophenyl)-1-(4'-fluoro-2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	454,9

Compound No.	Compound name	$(M+H)^+$
300	(2S,5R)-5-(2-chlorophenyl)-1-(4-(6-ethoxypyridin-3-yl)benzoyl)pyrrolidine-2-carboxylic acid	451,9
301	(2S,5R)-5-(2-chlorophenyl)-1-(4-(6-isopropoxypyridin-3-yl)benzoyl)pyrrolidine-2-carboxylic acid	465,9
302	(2S,5R)-5-(2-chlorophenyl)-1-(4-(6-methoxy-2-methylpyridin-3-yl)benzoyl)pyrrolidine-2-carboxylic acid	451,9
303	(2S,5R)-1-(3-chloro-4-(2-methoxypyrimidin-4-yl)benzoyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid	473,3
304	(2S,5R)-1-(3-chloro-4-(pyrimidin-5-yl)benzoyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid	443,3
305	(2S,5R)-5-(2-chlorophenyl)-4-cyano-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)-3-methylpyrrolidine-2-carboxylic acid	475,9
306	(2S,4S,5R)-5-(2-chlorophenyl)-4-cyano-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)-4-methylpyrrolidine-2-carboxylic acid	475,9
307	(2S,5R)-5-(2-chlorophenyl)-1-(2',3'-dimethoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	466,9
308	(2S,5R)-5-(2-chlorophenyl)-1-(3',4'-dimethoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	466,9
309	(2S,5R)-5-(2-chlorophenyl)-1-(2',3',4'-trimethoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	497,0
310	(2S,5R)-5-(2-chlorophenyl)-1-(2',3',6'-trimethoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	497,0
311	(2S,5R)-5-(2-chlorophenyl)-1-(3',5'-dimethoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	466,9
312	(2S,5R)-5-(2-chlorophenyl)-1-(2',5'-dimethoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	466,9
313	(2S,5R)-5-(2-chlorophenyl)-1-(2'-isopropyl-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	449,0
314	(2S,5R)-1-(2,2'-dimethoxy-[1,1'-biphenyl]-4-carbonyl)-5-(2-fluorophenyl)pyrrolidine-2-carboxylic acid	450,5
315	(2S,5R)-1-(2-fluoro-2'-methoxy-[1,1'-biphenyl]-4-carbonyl)-5-(2-fluorophenyl)pyrrolidine-2-carboxylic acid	438,4
316	(2S,5R)-5-(2-chlorophenyl)-1-(2-fluoro-2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	454,9
318	(2S,5R)-5-cyclopentyl-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	394,5
319	(2S,5R)-5-(2-chlorophenyl)-1-(2'-ethyl-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	434,9
320	(2S,5R)-5-(2-chlorophenyl)-1-(4-(2,6-dimethylpyridin-3-yl)benzoyl)pyrrolidine-2-carboxylic acid	435,9

Compound No.	Compound name	$(M+H)^+$
321	(2S,5R)-1-(4-(2,4-bis(benzyloxy)pyrimidin-5-yl)benzoyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid	621,1
322	(2S,5R)-1-([1,1':4',1"-terphenyl]-4-carbonyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid	483,0
323	(2S,5R)-5-(2-chlorophenyl)-1-(4'-propyl-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	449,0
324	(2S,5R)-1-(4'-(tert-butyl)-[1,1'-biphenyl]-4-carbonyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid	463,0
325	(2S,5R)-1-(3-chloro-4-(2,4-dimethoxypyrimidin-5-yl)benzoyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid	503,3
326	(2S,5R)-5-(2-chlorophenyl)-1-(5-(2-methoxyphenyl)pyrazine-2-carbonyl)pyrrolidine-2-carboxylic acid	438,9
327	(2S,5R)-5-(2-chlorophenyl)-1-(3-methoxy-4-(4-methoxypyridin-3-yl)benzoyl)pyrrolidine-2-carboxylic acid	467,9
328	(2S,5R)-5-(2-chlorophenyl)-1-(3-methoxy-4-(6-methoxypyridin-3-yl)benzoyl)pyrrolidine-2-carboxylic acid	467,9
329	(2S,5R)-1-(3-chloro-4-(2-methoxypyrimidin-5-yl)benzoyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid	473,3
330	(2S,5R)-1-(3-chloro-4-(6-methoxypyridin-3-yl)benzoyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid	472,3
331	(2S,SR)-5-(2-chlorophenyl)-1-(1-(4-(4-chlorophenyl)thiazol-2-yl)piperidine-4-carbonyl)pyrrolidine-2-carboxylic acid	531,5
332	(2S,5R)-5-(2-fluorophenyl)-1-(5-methoxy-6-(2-methoxyphenyl)nicotinoyl)pyrrolidine-2-carboxylic acid	451,5
333	(2S,5R)-1-(1-(benzo[d]oxazol-2-yl)piperidine-4-carbonyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid	454,9
334	(2S,5R)-5-(2-chlorophenyl)-1-(3-methoxy-4-(pyrrolidin-1-yl)benzoyl)pyrrolidine-2-carboxylic acid	429,9
335	(2S,5R)-5-(2-chlorophenyl)-1-(5-methoxy-6-(2-methoxyphenyl)nicotinoyl)pyrrolidine-2-carboxylic acid	467,9
336	(2S,5R)-5-(2-chlorophenyl)-1-(1-(2-methoxyphenyl)piperidine-4-carbonyl)pyrrolidine-2-carboxylic acid	443,9
337	(2S,5R)-5-(2-chlorophenyl)-1-(4-(2,4-dimethoxypyrimidin-5-yl)-3-methoxybenzoyl)pyrrolidine-2-carboxylic acid	498,9
338	(2S,5R)-5-(2-bromophenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	481,4
339	(2S,5R)-5-(2-chlorophenyl)-1-(3'-cyano-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	431,9

Compound No.	Compound name	$(M+H)^+$
340	(2S,5R)-5-(2-chlorophenyl)-1-(3'-cyano-2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	461,9
341	(2S,5R)-5-(2-chlorophenyl)-1-(3'-cyano-2',4'-bis(2,2,2-trifluoroethoxy)-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	627,9
342	(2S,5R)-1-(3'-amino-2'-methyl-[1,1'-biphenyl]-4-carbonyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid	435,9
343	(2S,5R)-5-(2-chlorophenyl)-1-(2'-methyl-3'-(methylsulfonamido)-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	514,0
344	(2S,5R)-1-(3'-acetamido-2'-methyl-[1,1'-biphenyl]-4-carbonyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid	478,0
345	(2S,5R)-5-(2-chlorophenyl)-1-(5'-cyano-2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	461,9
346	(2S,5R)-5-(2-chlorophenyl)-1-(5'-cyano-2'-methyl-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	445,9
347	(2S,5R)-5-(2-chlorophenyl)-1-(4-(4,6-dimethoxypyridin-3-yl)benzoyl)pyrrolidine-2-carboxylic acid	467,9
348	(2S,5R)-5-(2-chlorophenyl)-1-(4-(3,6-dimethoxypyridazin-4-yl)benzoyl)pyrrolidine-2-carboxylic acid	468,9
349	(2S,5S)-5-isopentyl-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	396,5
350	(2S,5R)-5-(2-chlorophenyl)-1-(2'-methoxy-4'-(methylsulfonamido)-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	530,0
351	(2S,5R)-1-(4'-acetamido-2'-methoxy-[1,1'-biphenyl]-4-carbonyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid	494,0
352	(2S,5R)-1-(3'-carbamimidoyl-[1,1'-biphenyl]-4-carbonyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid	448,9
353	(2S,5R)-5-(2-chlorophenyl)-1-(3'-((E)-N'-hydroxycarbamimidoyl)-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	464,9
354	(2S,5R)-5-(2-fluorophenyl)-1-(2'-methoxy-4'-(methylsulfonamido)-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	513,6
355	(2S,5R)-5-(2,4-difluorophenyl)-1-(4-(2,6-dimethoxypyridin-3-yl)benzoyl)pyrrolidine-2-carboxylic acid	469,4
356	(2S,5R)-5-(2-chlorophenyl)-1-(3-methoxy-4-(5-methoxypyridin-3-yl)benzoyl)pyrrolidine-2-carboxylic acid	467,9
357	(2S,5R)-1-(4'-amino-2'-methoxy-[1,1'-biphenyl]-4-carbonyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid	451,9

Compound No.	Compound name	$(M+H)^+$
358	(2S,5R)-5-(2-chlorophenyl)-1-(2',3,6'-trimethoxy-[2,3'-bipyridine]-5-carbonyl)pyrrolidine-2-carboxylic acid	498,9
359	(2S,5R)-1-(3'-carbamoyl-[1,1'-biphenyl]-4-carbonyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid	449,9
360	(2S,5R)-5-(2-chlorophenyl)-1-(5'-cyano-2',3'-dimethoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	491,9
361	(2S,5R)-5-(2-chlorophenyl)-1-(2'-cyano-4',5'-dimethoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	491,9
362	(2S,5R)-5-(2-chlorophenyl)-1-(3',4',5'-trimethoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	497,0
363	(2S,5R)-5-(2-chlorophenyl)-1-(2'-(cyanomethyl)-4',5'-dimethoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	506,0
364	(2S,5R)-5-(2-chlorophenyl)-1-(3',4'-dicyano-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	456,9
365	(2S,5R)-5-(2-chlorophenyl)-1-(5'-cyano-2'-fluoro-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	449,9
366	(2S,5R)-5-(2-chlorophenyl)-1-(2-fluoro-3',4'-dimethoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	484,9
367	(2S,5R)-5-(2-chlorophenyl)-1-(4-(2,6-dimethoxypyridin-3-yl)-3-fluorobenzoyl)pyrrolidine-2-carboxylic acid	485,9
368	(2S,5R)-5-(2-chlorophenyl)-1-(3-fluoro-4-(6-methoxypyridin-3-yl)benzoyl)pyrrolidine-2-carboxylic acid	455,9
369	(2S,5R)-5-(2-chlorophenyl)-1-(1-(2-cyano-4-(trifluoromethyl)phenyl)piperidine-4-carbonyl)pyrrolidine-2-carboxylic acid	506,9
370	(2S,5R)-1-(1-(2-chloro-4-(trifluoromethyl)phenyl)piperidine-4-carbonyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid	516,4
371	(2S,5R)-1-(5'-cyano-2'-methoxy-[1,1'-biphenyl]-4-carbonyl)-5-(2-fluorophenyl)pyrrolidine-2-carboxylic acid	445,5
372	(2S,5R)-1-(4-(2,6-dimethoxypyridin-3-yl)-3-fluorobenzoyl)-5-(2-fluorophenyl)pyrrolidine-2-carboxylic acid	469,4
373	(2S,5R)-1-(3-fluoro-4-(6-methoxypyridin-3-yl)benzoyl)-5-(2-fluorophenyl)pyrrolidine-2-carboxylic acid	439,4
374	(2S,5R)-1-(4-(3,6-dimethoxypyridazin-4-yl)benzoyl)-5-(2-fluorophenyl)pyrrolidine-2-carboxylic acid	452,4
375	(2S,5R)-1-(3'-carbamoyl-4'-cyano-[1,1'-biphenyl]-4-carbonyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid	474,9
376	(2S,5R)-5-(2-chlorophenyl)-1-(1-(2-nitro-4-(trifluoromethyl)phenyl)piperidine-4-carbonyl)pyrrolidine-2-carboxylic acid	526,9

Compound No.	Compound name	$(M+H)^+$
377	(2S,5R)-5-(2-chlorophenyl)-1-(1-(4-(morpholinosulfonyl)-2-nitrophenyl)piperidine-4-carbonyl)pyrrolidine-2-carboxylic acid	608,1
378	(2S,5R)-5-(2-chlorophenyl)-1-(1-(2-nitro-4-(piperidin-1-ylsulfonyl)phenyl)piperidine-4-carbonyl)pyrrolidine-2-carboxylic acid	606,1
379	(2S,5R)-5-(2-chlorophenyl)-1-(1-(4-(N,N-diethylsulfamoyl)-2-nitrophenyl)piperidine-4-carbonyl)pyrrolidine-2-carboxylic acid	594,1
380	(2S,5R)-5-(2-chlorophenyl)-1-(1-(4-methyl-2-nitrophenyl)piperidine-4-carbonyl)pyrrolidine-2-carboxylic acid	472,9
381	(2S,5R)-5-(2-chlorophenyl)-1-(1-(2-cyano-4-nitrophenyl)piperidine-4-carbonyl)pyrrolidine-2-carboxylic acid	483,9
382	(2S,5R)-5-(2-chlorophenyl)-1-(1-(4-nitrophenyl)piperidine-4-carbonyl)pyrrolidine-2-carboxylic acid	458,9
383	(2S,5R)-5-(2-chlorophenyl)-1-(1-(2-fluoro-4-nitrophenyl)piperidine-4-carbonyl)pyrrolidine-2-carboxylic acid	476,9
384	(2S,5R)-5-(2-chlorophenyl)-1-(1-(3-methoxy-4-nitrophenyl)piperidine-4-carbonyl)pyrrolidine-2-carboxylic acid	488,9
385	(2S,5R)-1-(1-(5-chloro-2-nitrophenyl)piperidine-4-carbonyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid	493,4
386	(2S,5R)-5-(2-cyanophenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	427,5
387	(2S,5R)-5-(2-chlorophenyl)-1-(2'-cyano-4'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	461,9
388	(2S,5R)-5-(2-chlorophenyl)-1-(2-fluoro-4'-(methylsulfonamido)-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	518,0
389	(2S,5R)-5-(2-chlorophenyl)-1-(2-fluoro-3'-(methylsulfonamido)-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	518,0
390	(2S,5R)-5-(2-chlorophenyl)-1-(2'-cyano-2-fluoro-[1,1'-biphenyl] -4-carbonyl)pyrrolidine-2-carboxylic acid	449,9
391	(2S,5R)-5-(2-chlorophenyl)-1-(1-(2-cyano-4-(methylsulfonamido)phenyl)piperidine-4-carbonyl)pyrrolidine-2-carboxylic acid	532,0
392	(2S,5R)-5-(2-chlorophenyl)-1-(1-(2-cyano-4-methoxyphenyl)piperidine-4-carbonyl)pyrrolidine-2-	468,9

Compound No.	Compound name	$(M+H)^+$
	carboxylic acid	
393	(2S,5R)-5-(2-chlorophenyl)-1-(1-(2-(methylsulfonamido)-4-(trifluoromethyl)phenyl)piperidine-4-carbonyl)pyrrolidine-2-carboxylic acid	575,0
394	(2S,5R)-5-(2-chlorophenyl)-1-(1-(2-nitrophenyl)piperidine-4-carbonyl)pyrrolidine-2-carboxylic acid	458,9
395	(2S,5R)-5-(2-chlorophenyl)-1-(1-(4-cyanophenyl)piperidine-4-carbonyl)pyrrolidine-2-carboxylic acid	438,9
396	(2S,5R)-5-(3,5-difluorophenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	438,4
397	(2S,5R)-5-(3,4-difluorophenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	438,4
398	(2S,5R)-5-(2,3-difluorophenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	438,4
399	(2S,5R)-5-(2,5-difluorophenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	438,4
400	(2S,5R)-5-([1,1'-biphenyl]-2-yl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	478,6
401	(2S,5R)-1-(2'-cyano-4'-methoxy-[1,1'-biphenyl]-4-carbonyl)-5-(2-fluorophenyl)pyrrolidine-2-carboxylic acid	445,5
402	(2S,5R)-5-(4-cyanophenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	427,5
403	(2S,5R)-5-(2-chlorophenyl)-1-(4-(5-methyl-4-(phenylsulfonyl)-1H-1,2,3-triazol-1-yl)benzoyl)pyrrolidine-2-carboxylic acid	552,0
404	(2S,5R)-5-(2-chlorophenyl)-1-(3'-cyano-4'-fluoro-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	449,9
405	(2S,5R)-1-(2'-chloro-5'-cyano-[1,1'-biphenyl]-4-carbonyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid	466,3
406	(2S,5R)-5-(2-chlorophenyl)-1-(2'-cyano-4'-(trifluoromethyl)-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	499,9
407	(2S,5R)-5-(2-chlorophenyl)-1-(1-(2-methoxy-4-(trifluoromethyl)phenyl)piperidine-4-carbonyl)pyrrolidine-2-carboxylic acid	511,9
408	(2S,5R)-5-(2-chlorophenyl)-1-(2'-methyl-3'-(N-methylmethylsulfonamido)-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	528,0
409	(2S,5R)-5-(2-chlorophenyl)-1-(2'-methoxy-4'-(N-methylmethylsulfonamido)-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	544,0
	(2S,5R)-5-(2-chlorophenyl)-1-(6-(5-cyano-2-	

Compound No.	Compound name	$(M+H)^+$
410	methoxyphenyl)-5-methoxynicotinoyl)pyrrolidine-2-carboxylic acid	492,9
411	(2S,5R)-5-(2-chlorophenyl)-1-(6-(2,4-dimethoxyphenyl)-5-methoxynicotinoyl)pyrrolidine-2-carboxylic acid	497,9
412	(2S,5R)-5-(2-chlorophenyl)-1-(6-(2,4-dimethoxyphenyl)nicotinoyl)pyrrolidine-2-carboxylic acid	467,9
413	(2S,5R)-1-(2'-cyano-4'-(trifluoromethyl)-[1,1'-biphenyl]-4-carbonyl)-5-(2-fluorophenyl)pyrrolidine-2-carboxylic acid	483,4
414	(2S,5R)-1-(3'-cyano-4'-fluoro-[1,1'-biphenyl]-4-carbonyl)-5-(2-fluorophenyl)pyrrolidine-2-carboxylic acid	433,4
415	(2S,5R)-1-(2'-chloro-5'-cyano-[1,1'-biphenyl]-4-carbonyl)-5-(2-fluorophenyl)pyrrolidine-2-carboxylic acid	449,9
416	(2S,5R)-5-(2-chlorophenyl)-1-(4-(3,6-dimethoxypyridazin-4-yl)-3-fluorobenzoyl)pyrrolidine-2-carboxylic acid	486,9
417	(2S,5R)-5-(2-fluorophenyl)-1-(2'-methyl-3'-(N-methylmethylsulfonamido)-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	511,6
418	(2S,5R)-5-(2-fluorophenyl)-1-(2'-methoxy-4'-(N-methylmethylsulfonamido)-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	527,6
419	(2S,5R)-5-(2-chlorophenyl)-1-(4-(4,6-dimethoxypyrimidin-5-yl)benzoyl)pyrrolidine-2-carboxylic acid	468,9
420	(2S,5R)-5-(2,3-difluorophenyl)-1-(4-(2,4-dimethoxypyrimidin-5-yl)benzoyl)pyrrolidine-2-carboxylic acid	470.4
421	(2S,5R)-1-(5'-cyano-2'-methyl-[1,1'-biphenyl]-4-carbonyl)-5-(2,3-difluorophenyl)pyrrolidine-2-carboxylic acid	447.4
422	(2S,5R)-5-(2,3-difluorophenyl)-1-(2'-methoxy-4'-(methylsulfonamido)-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	531.5
423	(2S,5R)-5-(2,3-difluorophenyl)-1-(2'-methyl-3'-(methylsulfonamido)-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	515.5
424	(2S,5R)-5-(2-fluorophenyl)-1-(2'-methyl-3'-(methylsulfonamido)-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid	497.6
425	(2S,5R)-5-(2,3-difluorophenyl)-1-(4-(2-methoxypyridin-3-yl)benzoyl)pyrrolidine-2-carboxylic acid	439.4
426	(2S,5R)-5-(2,3-difluorophenyl)-1-(3-methoxy-4-(2-methoxypyrimidin-5-yl)benzoyl)pyrrolidine-2-carboxylic acid	470.4
427	(2S,5R)-5-(2-fluorophenyl)-1-(3-methoxy-4-(2-methoxypyrimidin-5-yl)benzoyl)pyrrolidine-2-carboxylic acid	452.4

Compound No.	Compound name	$(M+H)^+$
428	(2S,5R)-5-(2,3-difluorophenyl)-1-(4-(3,6-dimethoxypyridazin-4-yl)benzoyl)pyrrolidine-2-carboxylic acid	470.4
429	(2S,5R)-1-(5'-cyano-2'-methoxy-[1,1'-biphenyl]-4-carbonyl)-5-(2,3-difluorophenyl)pyrrolidine-2-carboxylic acid	463.4
430	(2S,5R)-1-(5'-cyano-2'-methyl-[1,1'-biphenyl]-4-carbonyl)-5-(2-fluorophenyl)pyrrolidine-2-carboxylic acid	429.5
431	(2S,5R)-5-(2,3-difluorophenyl)-1-(4-(3,6-dimethoxypyridazin-4-yl)-3-fluorobenzoyl)pyrrolidine-2-carboxylic acid	488.4
432	(2S,5R)-1-(4-(3,6-dimethoxypyridazin-4-yl)-3-fluorobenzoyl)-5-(2-fluorophenyl)pyrrolidine-2-carboxylic acid	470.4

[0053] The compounds of table 1 were named using ChemDraw Ultra 12 purchased from CambridgeSoft (Cambridge, MA, USA).

[0054] The compounds of formula Ia-1b' can be prepared by different ways with reactions known by the person skilled in the art. Reaction schemes as described in the example section illustrate by way of example different possible approaches.

APPLICATIONS

[0055] The inflammatory disease may be, without being limited thereto, selected from the group consisting of rheumatoid arthritis; inflammatory bowel disease (IBD) including but not limited to Crohn's disease, ulcerative colitis and colitis; Pagets disease; osteoporosis; multiple myeloma; uveitis; acute and chronic myelogenous leukemia; pancreatic β cell destruction; rheumatoid spondylitis; osteoarthritis; gouty arthritis and other arthritis conditions; gout; adult respiratory distress syndrome (ARDS); chronic pulmonary inflammatory diseases; silicosis; pulmonary sarcoidosis; psoriasis; rhinitis; anaphylaxis; contact dermatitis; pancreatitis; asthma; muscle degeneration; cachexia such as cachexia secondary to infection or malignancy, cachexia secondary to acquired immune deficiency syndrome; Reiter's syndrome; type I diabetes; bone resorption disease; graft vs. host reaction; ischemia reperfusion injury; brain trauma; multiple sclerosis; cerebral malaria; sepsis; septic shock; toxic shock syndrome; endotoxic shock; gram negative sepsis; fever and myalgias due to infection such as influenza; pyrosis. More particularly, the inflammatory disease may be, without being limited thereto, selected from the group consisting of rheumatoid arthritis; inflammatory bowel disease (IBD) including but not limited to Crohn's disease, ulcerative colitis and colitis; Pagets disease; osteoporosis; multiple myeloma; uveitis; acute and chronic myelogenous leukemia; pancreatic β cell destruction; rheumatoid spondylitis, osteoarthritis; gouty arthritis and other arthritis conditions; gout; adult respiratory distress syndrome (ARDS); chronic pulmonary inflammatory diseases; silicosis; pulmonary sarcoidosis; psoriasis; rhinitis; anaphylaxis; contact dermatitis;

pancreatitis; asthma; muscle degeneration; cachexia such as cachexia secondary to infection or malignancy, cachexia secondary to acquired immune deficiency syndrome; Reiter's syndrome; bone resorption disease; graft vs. host reaction; ischemia reperfusion injury; brain trauma; multiple sclerosis; cerebral malaria; sepsis; septic shock; toxic shock syndrome; endotoxic shock; gram negative sepsis; fever and myalgias due to infection such as influenza; and pyrosis.

[0056] Even more particularly, the inflammatory disease may be, without being limited thereto, selected from the group consisting of rheumatoid arthritis; gouty arthritis and other arthritis conditions; inflammatory bowel disease (IBD) including but not limited to Crohn's disease, ulcerative colitis and colitis.

[0057] Still even more particularly, the inflammatory disease may be, without being limited thereto, selected from the group consisting of rheumatoid arthritis; inflammatory bowel disease (IBD) including but not limited to Crohn's disease, ulcerative colitis and colitis.

[0058] In one embodiment, the inflammatory diseases are TNF, IL-1, IL-6, and/or IL-8 mediated diseases or disease states.

[0059] The patient receiving the treatment/medicament according to the invention is preferably a warm-blooded animal, more preferably a human.

[0060] The invention also provides compounds for use in a method for delaying in a patient the onset of an inflammatory disease, comprising the administration of a pharmaceutically effective amount of a compound of formula (I) or pharmaceutically acceptable salt or solvate thereof to a patient in need thereof. The inflammatory disease, selected from the group consisting of rheumatoid arthritis; inflammatory bowel disease (IBD) including but not limited to Crohn's disease, ulcerative colitis and colitis; Pagets disease; osteoporosis; multiple myeloma; uveitis; acute and chronic myelogenous leukemia; pancreatic β cell destruction; rheumatoid spondylitis; osteoarthritis; gouty arthritis and other arthritis conditions; gout; adult respiratory distress syndrome (ARDS); chronic pulmonary inflammatory diseases; silicosis; pulmonary sarcoidosis; psoriasis; rhinitis; anaphylaxis; contact dermatitis; pancreatitis; asthma; muscle degeneration; cachexia such as cachexia secondary to infection or malignancy, cachexia secondary to acquired immune deficiency syndrome; Reiter's syndrome; type I diabetes; bone resorption disease; graft vs. host reaction; ischemia reperfusion injury; brain trauma; multiple sclerosis; cerebral malaria; sepsis; septic shock; toxic shock syndrome; endotoxic shock; gram negative sepsis; fever and myalgias due to infection such as influenza; pyrosis, comprising the administration of a pharmaceutically effective amount of a compound of formula (I) or pharmaceutically acceptable salts or solvates thereof to a patient in need thereof. More particularly, the inflammatory disease may be, without being limited thereto, selected from the group consisting of rheumatoid arthritis; inflammatory bowel disease (IBD) including but not limited to Crohn's disease, ulcerative colitis and colitis; Pagets disease; osteoporosis; multiple myeloma; uveitis; acute and chronic myelogenous leukemia; pancreatic β cell destruction; rheumatoid spondylitis, osteoarthritis; gouty arthritis and other arthritis conditions; gout; adult

respiratory distress syndrome (ARDS); chronic pulmonary inflammatory diseases; silicosis; pulmonary sarcoidosis; psoriasis; rhinitis; anaphylaxis; contact dermatitis; pancreatitis; asthma; muscle degeneration; cachexia such as cachexia secondary to infection or malignancy, cachexia secondary to acquired immune deficiency syndrome; Reiter's syndrome; bone resorption disease; graft vs. host reaction; ischemia reperfusion injury; brain trauma; multiple sclerosis; cerebral malaria; sepsis; septic shock; toxic shock syndrome; endotoxic shock; gram negative sepsis; fever and myalgias due to infection such as influenza; and pyrosis.

[0061] Even more particularly, the inflammatory disease may be, without being limited thereto, selected from the group consisting of rheumatoid arthritis; gouty arthritis and other arthritis conditions; inflammatory bowel disease (IBD) including but not limited to Crohn's disease, ulcerative colitis and colitis.

[0062] Still even more particularly, the inflammatory disease may be, without being limited thereto, selected from the group consisting of rheumatoid arthritis; inflammatory bowel disease (IBD) including but not limited to Crohn's disease, ulcerative colitis and colitis.

[0063] In one embodiment, the inflammatory diseases are TNF, IL-1, IL-6, and/or IL-8 mediated diseases or disease states.

[0064] The patient receiving the treatment for delaying the onset of an inflammatory disease according to the invention is preferably a warm-blooded animal, more preferably a human.

[0065] The invention further provides a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof for use in delaying the onset of an inflammatory disease. The inflammatory disease may be, without being limited thereto, selected from the group consisting of rheumatoid arthritis; inflammatory bowel disease (IBD) including but not limited to Crohn's disease, ulcerative colitis and colitis; Pagets disease; osteoporosis; multiple myeloma; uveitis; acute and chronic myelogenous leukemia; pancreatic β cell destruction; rheumatoid spondylitis; osteoarthritis; gouty arthritis and other arthritis conditions; gout; adult respiratory distress syndrome (ARDS); chronic pulmonary inflammatory diseases; silicosis; pulmonary sarcoidosis; psoriasis; rhinitis; anaphylaxis; contact dermatitis; pancreatitis; asthma; muscle degeneration; cachexia such as cachexia secondary to infection or malignancy, cachexia secondary to acquired immune deficiency syndrome; Reiter's syndrome; type I diabetes; bone resorption disease; graft vs. host reaction; ischemia reperfusion injury; brain trauma; multiple sclerosis; cerebral malaria; sepsis; septic shock; toxic shock syndrome; endotoxic shock; gram negative sepsis; fever and myalgias due to infection such as influenza; pyrosis. More particularly, the inflammatory disease may be, without being limited thereto, selected from the group consisting of rheumatoid arthritis; inflammatory bowel disease (IBD) including but not limited to Crohn's disease, ulcerative colitis and colitis; Pagets disease; osteoporosis; multiple myeloma; uveitis; acute and chronic myelogenous leukemia; pancreatic β cell destruction; rheumatoid spondylitis, osteoarthritis; gouty arthritis and other arthritis conditions; gout; adult respiratory distress syndrome (ARDS); chronic pulmonary inflammatory diseases; silicosis; pulmonary sarcoidosis; psoriasis; rhinitis; anaphylaxis; contact dermatitis; pancreatitis; asthma;

muscle degeneration; cachexia such as cachexia secondary to infection or malignancy, cachexia secondary to acquired immune deficiency syndrome; Reiter's syndrome; bone resorption disease; graft vs. host reaction; ischemia reperfusion injury; brain trauma; multiple sclerosis; cerebral malaria; sepsis; septic shock; toxic shock syndrome; endotoxic shock; gram negative sepsis; fever and myalgias due to infection such as influenza; pyrosis.

[0066] Even more particularly, the inflammatory disease may be, without being limited thereto, selected from the group consisting of rheumatoid arthritis; gouty arthritis and other arthritis conditions; inflammatory bowel disease (IBD) including but not limited to Crohn's disease, ulcerative colitis and colitis.

[0067] Still even more particularly, the inflammatory disease may be, without being limited thereto, selected from the group consisting of rheumatoid arthritis; inflammatory bowel disease (IBD) including but not limited to Crohn's disease, ulcerative colitis and colitis.

[0068] In one embodiment, the inflammatory diseases are TNF, IL-1, IL-6, and/or IL-8 mediated diseases or disease states.

[0069] The patient receiving the medicament for delaying the onset of an inflammatory disease according to the invention is preferably a warm-blooded animal, more preferably a human.

[0070] According to a further feature of the present invention there is provided compounds for use in a method for modulating GPR43 receptor activity, in a patient having inflammatory disease(s), preferably a warm blooded animal, and even more preferably a human, in need of such treatment, which comprises administering to said patient an effective amount of compound of the present invention, or a pharmaceutically acceptable salt or solvate thereof.

[0071] According to one embodiment, the compounds of the invention, their pharmaceutical acceptable salts or solvates may be administered as part of a combination therapy. Thus, are included within the scope of the present invention embodiments comprising coadministration of, and compositions and medicaments which contain, in addition to a compound of the present invention, a pharmaceutically acceptable salt or solvate thereof as active ingredient, additional therapeutic agents and/or active ingredients. Such multiple drug regimens, often referred to as combination therapy, may be used in the treatment and/or prevention of any of the diseases or conditions mediated by or associated with GPR43 receptor modulation, particularly rheumatoid arthritis; inflammatory bowel disease (IBD) including but not limited to Crohn's disease, ulcerative colitis and colitis; Pagets disease; osteoporosis; multiple myeloma; uveitis; acute and chronic myelogenous leukemia; pancreatic β cell destruction; rheumatoid spondylitis; osteoarthritis; gouty arthritis and other arthritis conditions; gout; adult respiratory distress syndrome (ARDS); chronic pulmonary inflammatory diseases; silicosis; pulmonary sarcoidosis; psoriasis; rhinitis; anaphylaxis; contact dermatitis; pancreatitis; asthma; muscle degeneration; cachexia such as cachexia secondary to infection or malignancy, cachexia secondary to acquired immune deficiency syndrome; Reiter's syndrome; type I diabetes; bone resorption disease; graft vs. host reaction; ischemia reperfusion injury; brain trauma; multiple

sclerosis; cerebral malaria; sepsis; septic shock; toxic shock syndrome; endotoxic shock; gram negative sepsis; fever and myalgias due to infection such as influenza; pyrosis. The use of such combinations of therapeutic agents is especially pertinent with respect to the treatment of the above-mentioned list of diseases within a patient in need of treatment or one at risk of becoming such a patient.

[0072] In addition to the requirement of therapeutic efficacy, which may necessitate the use of active agents in addition to the GPR43 agonist or partial agonist compounds of Formula Ia-1b' or their pharmaceutical acceptable salts or solvates thereof, there may be additional rationales which compel or highly recommend the use of combinations of drugs involving active ingredients which represent adjunct therapy, i.e., which complement and supplement the function performed by the GPR43 receptor agonist or partial agonist compounds of the present invention. Suitable supplementary therapeutic agents used for the purpose of auxiliary treatment include drugs which, instead of directly treating or preventing a disease or condition mediated by or associated with GPR43 receptor modulation, treat diseases or conditions which directly result from or indirectly accompany the basic or underlying GPR43 receptor modulated disease or condition.

[0073] Thus, the pharmaceutical compositions of the present and the compounds of Formula Ia-1b' or their pharmaceutical acceptable salts or solvates thereof may be employed in the form of monotherapy, but said compounds and compositions may also be used in the form of multiple therapy in which one or more compounds of Formula Ia-1b' or their pharmaceutically acceptable salts or solvates are coadministered in combination with one or more other therapeutic agents such as those described in detail further herein.

[0074] Examples of other active ingredients that may be administered in combination with a compound of Formula Ia-1b' or a pharmaceutically acceptable salt or solvate thereof, and either administered separately or in the same pharmaceutical composition, include but are not limited to:

1. (i) anti-inflammatory agents including steroids (corticosteroids, such as glucocorticoids),
2. (ii) non-steroidal anti-inflammatory drugs (NSAIDS) (i.e. Asacol, Pentasa) and TNFα inhibitiors such as Remicaide, Enbrel and TNF specific monoclonal antibody such as Humira. Other example of NSAIDS are those mentioned below but no limited to:
    1. (a) salicylates (like aspirin, methyl salicylate, diflunisal, benorylate, faislamine, amoxiprin);
    2. (b) arylalkanoic acids (like diclofenac, indometacin, sulindac, 2-arylpropionic acids);
    3. (c) profens (like carprofen, fenoprofen, flurbiprofen, ibuprofen, ketoprofen, ketorolac, loxoprofen, naproxen, tiaprofenic acid);
    4. (d) N-arylanthranilic acids (like fenamic acids, mefenamic acid, meclofenamic acid);
    5. (e) Pyrazolidine derivatives (like phenylbutazone, oxyphenylbutazone);
    6. (f) Oxicams (like piroxicam, meloxicam);

7. (g) Coxibs (like celecoxib, rofecoxib, valdecoxib, parecoxib, etoricoxib); sulphonanilides (like nimesulide);
8. (h) Lipoxygenase inhibitors (like baicalein, caffeic acid, esculetin, gossypol, nordihydroguaiaretic acid, flubiprofen, nordihydroguaiaretic acid, eicosatriynoic acid, 5-hydroxyeicosatetraenoic (HETE) lactone, 5(S)-HETE, eicosatetraynoic acid);
9. (i) Macrolide derivatives (like-9-(S)-dihydroerythromycin derivatives);
10. (j) Anti-inflammatory peptide (antiflamins) (like peptides derived from seminal vesicle proteins, selectin-binding peptides, cationic peptides based on Bactericidal permeability increasing protein, IL-2 derived peptides);
11. (k) Anti-inflammatory cytokines (like IL-1 receptor antagonist, IL-4, IL-6, IL-10, IL-11, and IL-13);
12. (l) Pro-inflammatory cytokines inhibitors (like tumor necrosis factor-alpha, IL-18);
13. (m) Galectins (like galectin-1);
14. (n) Antibodies neutralizing pro-inflammatory signaling molecules/cytokines, like antibodies against TNF-alpha, IL-1 etc; and
15. (o) Statins.

[0075] The above combinations include combinations of a compound of the present invention or a pharmaceutically acceptable salt or solvate not only with one other active compound but also with two or more active compounds.

[0076] In the above-described embodiment combinations of the present invention; the compound of Formula Ia-1b', a pharmaceutically acceptable salt or solvate thereof and other therapeutic active agents may be administered in terms of dosage forms either separately or in conjunction with each other, and in terms of their time of administration, either serially or simultaneously. Thus, the administration of one component agent may be prior to, concurrent with, or subsequent to the administration of the other component agent(s).

[0077] The invention also provides pharmaceutical compositions for treating and/or preventing the development or for delaying the onset of an inflammatory disease, comprising a compound of formula Ia-1b' or a pharmaceutically acceptable salt or solvate thereof and at least one pharmaceutically acceptable carrier, diluent, excipient and/or adjuvant. As indicated above, the invention also covers pharmaceutical compositions which contain, in addition to a compound of the present invention, a pharmaceutically acceptable salt or solvate thereof as active ingredient, additional therapeutic agents and/or active ingredients.

[0078] As set forth above, the compounds of the invention, their pharmaceutically acceptable salts or solvates may be used in monotherapy or in combination therapy. Thus, according to one embodiment, the invention provides the use of a compound of the invention for the manufacture of a medicament for at least one of the purposes described above, wherein said medicament is administered to a patient in need thereof, preferably a warm-blooded animal,

and even more preferably a human, in combination with at least one additional therapeutic agent and/or active ingredient. The benefits and advantages of such a multiple drug regimen, possible administration regimens as well as suitable additional therapeutic agents and/or active ingredients are those described above.

[0079] Generally, the compounds of the invention may be formulated as a pharmaceutical preparation comprising at least one compound of the invention or a pharmaceutically acceptable salt or solvate thereof and at least one pharmaceutically acceptable carrier, diluent, excipient and/or adjuvant, and optionally one or more further pharmaceutically active compounds.

[0080] By means of non-limiting examples, such a formulation may be in a form suitable for oral administration, for parenteral administration (such as by intravenous, intramuscular or subcutaneous injection or intravenous infusion), for topical administration (including ocular), for administration by inhalation, by a skin patch, by an implant, by a suppository, etc. Such suitable administration forms - which may be solid, semi-solid or liquid, depending on the manner of administration - as well as methods and carriers, diluents and excipients for use in the preparation thereof, will be clear to the skilled person; reference is made to the latest edition of Remington's Pharmaceutical Sciences.

[0081] Some preferred, but non-limiting examples of such preparations include tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols, ointments, cremes, lotions, soft and hard gelatin capsules, suppositories, drops, sterile injectable solutions and sterile packaged powders (which are usually reconstituted prior to use) for administration as a bolus and/or for continuous administration, which may be formulated with carriers, excipients, and diluents that are suitable per se for such formulations, such as lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, polyethylene glycol, cellulose, (sterile) water, methylcellulose, methyl- and propylhydroxybenzoates, talc, magnesium stearate, edible oils, vegetable oils and mineral oils or suitable mixtures thereof. The formulations can optionally contain other substances that are commonly used in pharmaceutical formulations, such as lubricating agents, wetting agents, emulsifying and suspending agents, dispersing agents, desintegrants, bulking agents, fillers, preserving agents, sweetening agents, flavoring agents, flow regulators, release agents, etc.. The compositions may also be formulated so as to provide rapid, sustained or delayed release of the active compound(s) contained therein.

[0082] The pharmaceutical preparations of the invention are preferably in a unit dosage form, and may be suitably packaged, for example in a box, blister, vial, bottle, sachet, ampoule or in any other suitable single-dose or multi-dose holder or container (which may be properly labeled); optionally with one or more leaflets containing product information and/or instructions for use. Generally, such unit dosages will contain between 0,05 and 1000 mg, and usually between 1 and 500 mg, of the at least one compound of the invention, e.g. about 10, 25, 50, 100, 200, 300 or 400 mg per unit dosage.

[0083] Usually, depending on the condition to be prevented or treated and the route of administration, the active compound of the invention will usually be administered between 0.01 to 100 mg per kilogram, more often between 0.1 and 50 mg, such as between 1 and 25 mg, for example about 0.5, 1, 5, 10, 15, 20 or 25 mg, per kilogram body weight of the patient per day, which may be administered as a single daily dose, divided over one or more daily doses, or essentially continuously, e.g. using a drip infusion.

DEFINITIONS

[0084] The definitions and explanations below are for the terms as used throughout the entire application, including both the specification and the claims.

[0085] When describing the compounds of the invention, the terms used are to be construed in accordance with the following definitions, unless indicated otherwise.

[0086] Where groups may be substituted, such groups may be substituted with one or more substituents, and preferably with one, two or three substituents. Substituents may be selected from but not limited to, for example, the group comprising halogen, hydroxyl, oxo, cyano, nitro, amido, carboxy, amino, cyano haloalkoxy, and haloalkyl.

[0087] As used herein the terms such as "alkyl, aryl, or cycloalkyl, each being optionally substituted with..." or "alkyl, aryl, or cycloalkyl, optionally substituted with..." encompasses "alkyl optionally substituted with...", "aryl optionally substituted with..." and "cycloalkyl optionally substituted with...".

[0088] The term "halo" or "halogen" means fluoro, chloro, bromo, or iodo. Preferred halo groups are fluoro and chloro.

[0089] The term "alkyl" by itself or as part of another substituent refers to a hydrocarbyl radical of Formula C_nH_{2n+1} wherein n is a number greater than or equal to 1. Generally, alkyl groups of this invention comprise from 1 to 6 carbon atoms, preferably from 1 to 4 carbon atoms, more preferably from 1 to 3 carbon atoms, still more preferably 1 to 2 carbon atoms. Alkyl groups may be linear or branched and may be substituted as indicated herein. C_{x-y} -alkyl and Cx-Cy-alkyl refer to alkyl groups which comprise from x to y carbon atoms.

[0090] Suitable alkyl groups include methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl and *tert*-butyl, pentyl and its isomers (e.g. n-pentyl, iso-pentyl), and hexyl and its isomers (e.g. n-hexyl, iso-hexyl). Preferred alkyl groups include methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl and *tert*-butyl.

[0091] When the suffix "ene" ("alkylene") is used in conjunction with an alkyl group, this is intended to mean the alkyl group as defined herein having two single bonds as points of

attachment to other groups. The term "alkylene" includes methylene, ethylene, methylmethylene, propylene, ethylethylene, and 1,2-dimethylethylene.

[0092] The term "alkenyl" as used herein refers to an unsaturated hydrocarbyl group, which may be linear or branched, comprising one or more carbon-carbon double bonds. Suitable alkenyl groups comprise between 2 and 6 carbon atoms, preferably between 2 and 4 carbon atoms, still more preferably between 2 and 3 carbon atoms. Examples of alkenyl groups are ethenyl, 2-propenyl, 2-butenyl, 3-butenyl, 2-pentenyl and its isomers, 2-hexenyl and its isomers, 2,4-pentadienyl and the like.

[0093] The term "alkynyl" as used herein refers to a class of monovalent unsaturated hydrocarbyl groups, wherein the unsaturation arises from the presence of one or more carbon-carbon triple bonds. Alkynyl groups typically, and preferably, have the same number of carbon atoms as described above in relation to alkenyl groups. Non limiting examples of alkynyl groups are ethynyl, 2-propynyl, 2-butynyl, 3-butynyl, 2-pentynyl and its isomers, 2-hexynyl and its isomers-and the like. The terms "alkenylene" and "alkynylene" respectively mean an alkenyl group or an alkinyl group as defined above having two single bonds as points of attachment to other groups.

[0094] The term "haloalkyl" alone or in combination, refers to an alkyl radical having the meaning as defined above wherein one or more hydrogens are replaced with a halogen as defined above. Non-limiting examples of such haloalkyl radicals include chloromethyl, 1-bromoethyl, fluoromethyl, difluoromethyl, trifluoromethyl, 1,1,1-trifluoroethyl and the like.

[0095] The term "cycloalkyl" as used herein is a cyclic alkyl group, that is to say, a monovalent, saturated, or unsaturated hydrocarbyl group having 1 or 2 cyclic structures. Cycloalkyl includes monocyclic or bicyclic hydrocarbyl groups. Cycloalkyl groups may comprise 3 or more carbon atoms in the ring and generally, according to this invention comprise from 3 to 10, more preferably from 3 to 8 carbon atoms still more preferably from 3 to 6 carbon atoms. Examples of cycloalkyl groups include but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, with cyclopropyl being particularly preferred.

[0096] When the suffix "ene" is used in conjunction with a cyclic group, this is intended to mean the cyclic group as defined herein having two single bonds as points of attachment to other groups.

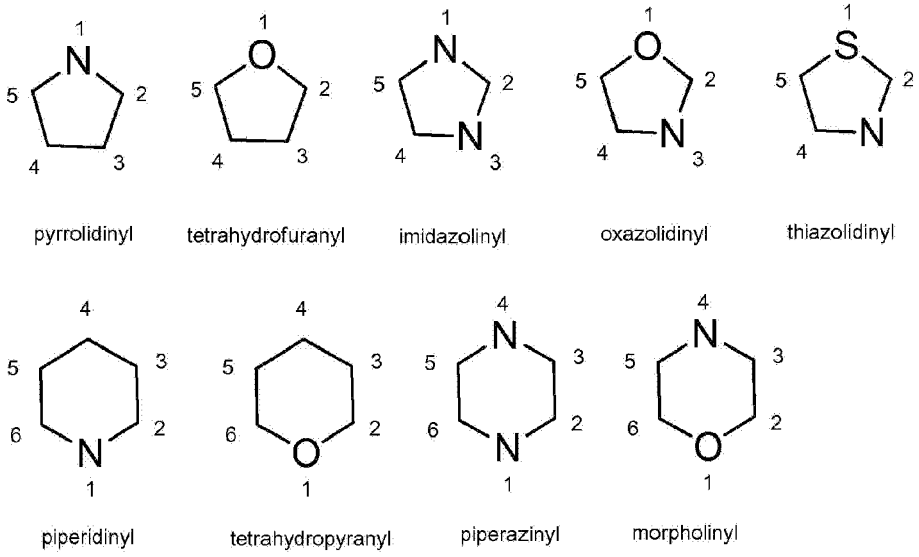
[0097] Therefore, "cycloalkylene" herein refers to a saturated homocyclic hydrocarbyl biradical of Formula C_nH_{2n-2}. Suitable cycloalkylene groups are C_{3-6} cycloalkylene group, preferably a C_{3-5} cycloalkylene (i.e. 1,2cyclopropylene, 1,1-cyclopropylene, 1,1-cyclobutylene, 1,2-cyclobutylene, 1,3-cyclobutylene, 1,3-cyclopentylene,or 1,1-cyclopentylene), more preferably a C_{3-4} cycloalkylene (i.e. 1,3-cyclopropylene, 1,1-cyclopropylene, 1,1-cyclobutylene, 1,2-cyclobutylene).

[0098] Where at least one carbon atom in a cycloalkyl group is replaced with a heteroatom, the

resultant ring is referred to herein as "heterocycloalkyl" or "heterocyclyl".

[0099] The terms "heterocyclyl", "heterocycloalkyl" or "heterocyclo" as used herein by itself or as part of another group refer to non-aromatic, fully saturated or partially unsaturated cyclic groups (for example, 3 to 7 member monocyclic, 7 to 11 member bicyclic, or containing a total of 3 to 10 ring atoms) which have at least one heteroatom in at least one carbon atom-containing ring. Each ring of the heterocyclic group containing a heteroatom may have 1, 2, 3 or 4 heteroatoms selected from nitrogen, oxygen and/or sulfur atoms, where the nitrogen and sulfur heteroatoms may optionally be oxidized and the nitrogen heteroatoms may optionally be quaternized. Any of the carbon atoms of the heterocyclic group may be substituted by oxo (for example piperidone, pyrrolidinone).The heterocyclic group may be attached at any heteroatom or carbon atom of the ring or ring system, where valence allows. The rings of multi-ring heterocycles may be fused, bridged and/or joined through one or more spiro atoms. Non limiting exemplary heterocyclic groups include oxetanyl, piperidinyl, azetidinyl, 2-imidazolinyl, pyrazolidinyl imidazolidinyl, isoxazolinyl, oxazolidinyl, isoxazolidinyl, thiazolidinyl, isothiazolidinyl, piperidinyl, 3H-indolyl, indolinyl, isoindolinyl, 2-oxopiperazinyl, piperazinyl, homopiperazinyl, 2-pyrazolinyl, 3-pyrazolinyl, tetrahydro-2H-pyranyl, 2H-pyranyl, 4H-pyranyl, 3,4-dihydro-2H-pyranyl, 3-dioxolanyl, 1,4-dioxanyl, 2,5-dioximidazolidinyl, 2-oxopiperidinyl, 2-oxopyrrolodinyl, indolinyl, tetrahydropyranyl, tetrahydrofuranyl, tetrahydroquinolinyl, tetrahydroisoquinolin-1-yl, tetrahydroisoquinolin-2-yl, tetrahydroisoquinolin-3-yl, tetrahydroisoquinolin-4-yl, thiomorpholin-4-yl, thiomorpholin-4-ylsulfoxide, thiomorpholin-4-ylsulfone, 1,3-dioxolanyl, 1,4-oxathianyl, 1H-pyrrolizinyl, tetrahydro-1,1-dioxothiophenyl, N-formylpiperazinyl, and morpholin-4-yl.

[0100] The ring atoms of heterocyclyl and heterocyclylene moieties are numbered based on scheme below



[0101] The term "aryl" as used herein refers to a polyunsaturated, aromatic hydrocarbyl group having a single ring (i.e. phenyl) or multiple aromatic rings fused together (e.g. naphtyl) or linked covalently, typically containing 5 to 12 atoms; preferably 6 to 10, wherein at least one

ring is aromatic. The aromatic ring may optionally include one to two additional rings (either cycloalkyl, heterocyclyl or heteroaryl) fused thereto. Aryl is also intended to include the partially hydrogenated derivatives of the carbocyclic systems enumerated herein. Non-limiting examples of aryl comprise phenyl, biphenylyl, biphenylenyl, 5- or 6-tetralinyl, naphthalen-1- or -2-yl, 4-, 5-, 6 or 7-indenyl, 1- 2-, 3-, 4- or 5-acenaphtylenyl, 3-, 4- or 5-acenaphtenyl, 1- or 2-pentalenyl, 4- or 5-indanyl, 5-, 6-, 7- or 8-tetrahydronaphthyl, 1,2,3,4-tetrahydronaphthyl, 1,4-dihydronaphthyl, 1-, 2-, 3-, 4- or 5-pyrenyl.

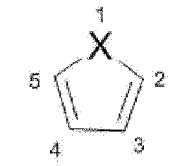
[0102] The term "arylene" as used herein is intended to include divalent carbocyclic aromatic ring systems such as phenylene, biphenylylene, naphthylene, indenylene, pentalenylene, azulenylene and the like. Arylene is also intended to include the partially hydrogenated derivatives of the carbocyclic systems enumerated above. Non-limiting examples of such partially hydrogenated derivatives are 1,2,3,4-tetrahydronaphthylene, 1,4-dihydronaphthylene and the like.

[0103] The term "arylalkyl" or "aralkyl" refers to a linear or branched alkyl group where one carbon is attached to an aryl ring. Non limiting examples of aralkyl comprise benzyl, phenethyl, (naphtalen-1-yl) or (naphtalen-2-yl)methyl. When an aralkyl group is substituted, the substituent(s) is/are attached either on the alkyl group or on the aryl ring. A "x-membered aralkyl" refers to a linear or branched alkyl group where one carbon is attached to a x-membered aryl ring. Where at least one carbon atom in an aryl group is replaced with a heteroatom, the resultant ring is referred to herein as a heteroaryl ring.

[0104] The term "heteroaryl" as used herein by itself or as part of another group refers but is not limited to 5 to 12 carbon-atom aromatic rings or ring systems containing 1 to 2 rings which are fused together or linked covalently, typically containing 5 to 6 atoms; at least one of which is aromatic, in which one or more carbon atoms in one or more of these rings is replaced by oxygen, nitrogen and/or sulfur atoms where the nitrogen and sulfur heteroatoms may optionally be oxidized and the nitrogen heteroatoms may optionally be quaternized. Such rings may be fused to an aryl, cycloalkyl, heteroaryl or heterocyclyl ring. Non-limiting examples of such heteroaryl, include: furanyl, thiophenyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, oxatriazolyl, thiatriazolyl, pyridinyl, pyrimidyl, pyrazinyl, pyridazinyl, oxazinyl, dioxinyl, thiazinyl, triazinyl, imidazo[2,1-b][1,3]thiazolyl, thieno[3,2-b]furanyl, thieno[3,2-b]thiophenyl, thieno[2,3-d][1,3]thiazolyl, thieno[2,3-d]imidazolyl, tetrazolo[1,5-a]pyridinyl, indolyl, indolizinyl, isoindolyl, benzofuranyl, isobenzofuranyl, benzothiophenyl, isobenzothiophenyl, indazolyl, benzimidazolyl, 1,3-benzoxazolyl, 1,2-benzisoxazolyl, 2,1-benzisoxazolyl, 1,3-benzothiazolyl, 1,2-benzoisothiazolyl, 2,1-benzoisothiazolyl, benzotriazolyl, 1,2,3-benzoxadiazolyl, 2,1,3-benzoxadiazolyl, 1,2,3-benzothiadiazolyl, 2,1,3-benzothiadiazolyl, thienopyridinyl, purinyl, imidazo[1,2-a]pyridinyl, 6-oxo-pyridazin-1(6H)-yl, 2-oxopyridin-1(2H)-yl, 6-oxo-pyridazin-1(6H)-yl, 2-oxopyridin-1(2H)-yl, 1,3-benzodioxolyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, quinoxalinyl.

[0105] The term "heteroarylene" as used herein means divalent carbocyclic aromatic ring systems including pyridinylene and the like.

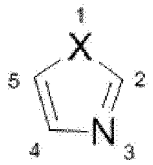
[0106] The ring atoms of heteroaryl or heteroarylene moieties are numbered on scheme below:



X is selected from:
N, O or S

Examples:

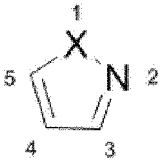
pyrrolyl
furanyl
thiophenyl



X is selected from:
N, O or S

Examples:

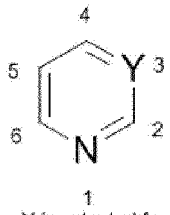
imidazolyl
oxazolyl
thiazolyl



X is selected from:
N, O or S

Examples:

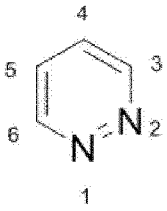
pyrazolyl
isooxazolyl
isothiazolyl



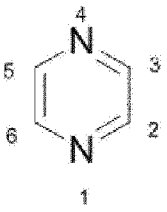
Y is selected from:
C, N

Examples:

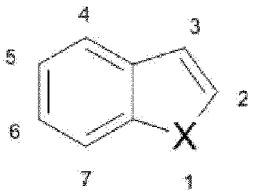
pyridyl
pyrimidinyl



pyridazinyl

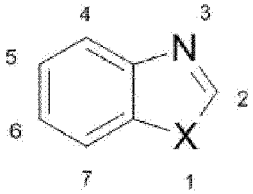


pyrazinyl



X is selected from:
N, O or S

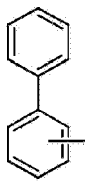
Examples:
indolyl
benzofuranyl
benzothiophenyl



X is selected from:
N, O or S

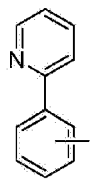
Examples:
benzimidazolyl
benzoxazolyl
benzothiazolyl

[0107] The term "biaryl" as used herein designates two aryl moieties as defined herein linked via a single bond. Non-limiting examples of such biaryl moieties include biphenyl.

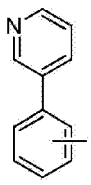


biphenyl

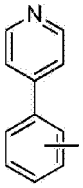
[0108] The term "heterobiaryl" as used herein designates two heteroaryl moieties as defined herein or a heteroaryl moiety and an aryl moity as defined herein linked via a single bond. Non-limiting examples of such heterobiaryl moieties include pyridinylphenyl which is meant to include (2-pyridinyl)phenyl, (3-pyridinyl)phenyl and (4-pyridinyl)phenyl, bipyridinyl.



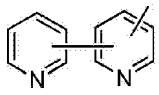
(2-pyridinyl)phenyl



(3-pyridinyl)phenyl



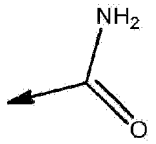
(4-pyridinyl)phenyl



bipyridinyl

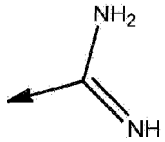
[0109] The term "alkylamino" as used herein means an amino group substituted with one or two alkyl groups. This includes monoalkylamino and dialkylamino groups.

[0110] The term "carbamoyl" as used herein means a group of formula



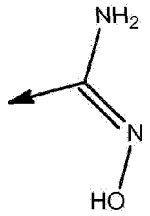
wherein the arrow defines the attachment point.

[0111] The term "carbamimidoyl" as used herein means a group of formula



wherein the arrow defines the attachment point.

[0112] The term "hydroxycarbamimidoyl" as used herein means a group of formula



wherein the arrow defines the attachment point.

[0113] The compounds of Formula Ia-1b' and subformulae thereof contain at least one asymmetric center and thus may exist as different stereoisomeric forms. Accordingly, the present invention includes all possible stereoisomers and includes not only racemic compounds but the individual enantiomers and their non racemic mixtures as well. When a compound is desired as a single enantiomer, such may be obtained by stereospecific synthesis, by resolution of the final product or any convenient intermediate, or by chiral chromatographic methods as each are known in the art. Resolution of the final product, an intermediate, or a starting material may be effected by any suitable method known in the art. See, for example, Stereochemistry of Organic Compounds by E. L. Eliel, S. H. Wilen, and L. N. Mander (Wiley- Interscience, 1994), incorporated by reference with regard to stereochemistry.

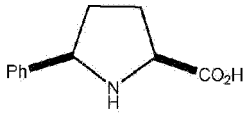
[0114] The bonds from an asymmetric carbon in compounds of the present invention may be depicted herein using a solid line (

—

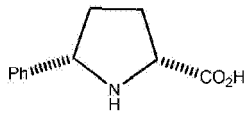
), a zigzag line (

), a solid wedge (
), or a dotted wedge (
), a solid bar (
) or a dotted bar (
). The use of a solid line to depict bonds from an asymmetric carbon atom is meant to indicate that all possible stereoisomers are meant to be included, unless it is clear from the context that a specific stereoisomer is intended. The use of either a solid or dotted wedge to depict bonds from an asymmetric carbon atom is meant to indicate that only the stereoisomer shown is meant to be included.

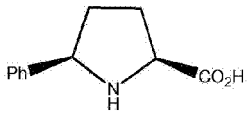
[0115] The compounds of the invention may also contain more than one asymmetric carbon atom. In those compounds, the use of a solid line to depict bonds from asymmetric carbon atoms is meant to indicate that all possible stereoisomers are meant to be included, unless it is clear from the context that a specific stereoisomer is intended. In those compounds, the use of solid or dotted bars is meant to indicate relative stereochemistry. As an example,



or

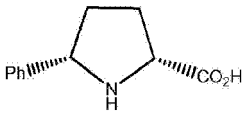


mean a racemic mixture of



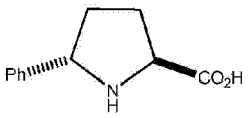
cis

and

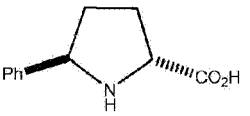


cis

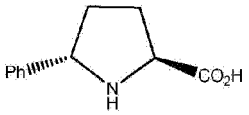
similarly,



or

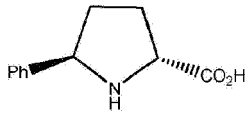


mean a racemic mixture of



trans

and



trans

[0116] The compounds of the invention may be in the form of pharmaceutically acceptable salts. Pharmaceutically acceptable salts of the compounds of formula Ia-1b' include the acid addition and base salts thereof. Suitable acid addition salts are formed from acids which form non-toxic salts. Examples include the acetate, adipate, aspartate, benzoate, besylate, bicarbonate/carbonate, bisulphate/sulphate, borate, camsylate, citrate, cyclamate, edisylate, esylate, formate, fumarate, gluceptate, gluconate, glucuronate, hexafluorophosphate, hibenzate, hydrochloride/chloride, hydrobromide/bromide, hydroiodide/iodide, isethionate, lactate, malate, maleate, malonate, mesylate, methylsulphate, naphthylate, 2-napsylate, nicotinate, nitrate, orotate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, pyroglutamate, saccharate, stearate, succinate, tannate,

tartrate, tosylate, trifluoroacetate and xinofoate salts. Suitable base salts are formed from bases which form non-toxic salts. Examples include the aluminium, arginine, benzathine, calcium, choline, diethylamine, diolamine, glycine, lysine, magnesium, meglumine, olamine, potassium, sodium, tromethamine, 2-(diethylamino)ethanol, ethanolamine, morpholine, 4-(2-hydroxyethyl)morpholine and zinc salts. Hemisalts of acids and bases may also be formed, for example, hemisulphate and hemicalcium salts. Preferred, pharmaceutically acceptable salts include hydrochloride/chloride, hydrobromide/bromide, bisulphate/sulphate, nitrate, citrate, and acetate.

[0117] When the compounds of the invention contain an acidic group as well as a basic group the compounds of the invention may also form internal salts, and such compounds are within the scope of the invention. When the compounds of the invention contain a hydrogen-donating heteroatom (e.g. NH), the invention also covers salts and/or isomers formed by transfer of said hydrogen atom to a basic group or atom within the molecule.

[0118] Pharmaceutically acceptable salts of compounds of Formula Ia-1b' may be prepared by one or more of these methods:

1. (i) by reacting the compound of Formula Ia-1b' with the desired acid;
2. (ii) by reacting the compound of Formula Ia-1b' with the desired base;
3. (iii) by removing an acid- or base-labile protecting group from a suitable precursor of the compound of Formula Ia-1b' or by ring-opening a suitable cyclic precursor, for example, a lactone or lactam, using the desired acid; or
4. (iv) by converting one salt of the compound of Formula Ia-1b' to another by reaction with an appropriate acid or by means of a suitable ion exchange column.

[0119] All these reactions are typically carried out in solution. The salt, may precipitate from solution and be collected by filtration or may be recovered by evaporation of the solvent. The degree of ionization in the salt may vary from completely ionized to almost non-ionized.

[0120] The term "solvate" is used herein to describe a molecular complex comprising the compound of the invention and one or more pharmaceutically acceptable solvent molecules, for example, ethanol. The term 'hydrate' is employed when said solvent is water.

[0121] All references to compounds of formula Ia-1b' include references to salts, solvates, multi- component complexes and liquid crystals thereof.

[0122] The compounds of the invention include compounds of formula Ia-1b' as hereinbefore defined, including all polymorphs and crystal habits thereof, isomers thereof (including optical, geometric and tautomeric isomers) and isotopically- labeled compounds of formula Ia-1b'.

[0123] In addition, although generally, with respect to the salts of the compounds of the invention, pharmaceutically acceptable salts are preferred, it should be noted that the invention

in its broadest sense also included non-pharmaceutically acceptable salts, which may for example be used in the isolation and/or purification of the compounds of the invention. For example, salts formed with optically active acids or bases may be used to form diastereoisomeric salts that can facilitate the separation of optically active isomers of the compounds of Formula Ia-1b' above.

[0124] The term "patient" refers to a warm-blooded animal, more preferably a human, who/which is awaiting or receiving medical care or is or will be the object of a medical procedure.

[0125] The term "human" refers to suject of both genders and at any stage of development (i.e. neonate, infant, juvenile, adolescent, adult).

[0126] The terms "treat", "treating" and "treatment, as used herein, are meant to include alleviating or abrogating a condition or disease and/or its attendant symptoms.

[0127] The terms "prevent", "preventing" and "prevention", as used herein, refer to a method of delaying or precluding the onset of a condition or disease and/or its attendant symptoms, barring a patient from acquiring a condition or disease, or reducing a patient's risk of acquiring a condition or disease.

[0128] The term "therapeutically effective amount" (or more simply an "effective amount") as used herein means the amount of active agent or active ingredient (e. g. GPR43 agonist or partial agonist) which is sufficient to achieve the desired therapeutic or prophylactic effect in the individual to which it is administered.

[0129] The term "administration", or a variant thereof (e.g.,"administering"), means providing the active agent or active ingredient (e. g. a GPR43 agonist or partial agonist), alone or as part of a pharmaceutically acceptable composition, to the patient in whom/which the condition, symptom, or disease is to be treated or prevented.

[0130] By "pharmaceutically acceptable" is meant that the ingredients of a pharmaceutical composition are compatible with each other and not deleterious to the patient thereof.

[0131] The term "agonist" as used herein means a ligand that activates an intracellular response when it binds to a receptor. An agonist according to the invention may promote internalization of a cell surface receptor such that the cell surface concentration of a receptor is decreased or remove.

[0132] The term "partial agonist" as used herein means an agonist which is unable to induce maximal activation of a receptor, regardless of the amount of compound applied on the receptor.

[0133] The term "pharmaceutical vehicle" as used herein means a carrier or inert medium

used as solvent or diluent in which the pharmaceutically active agent is formulated and/or administered. Non-limiting examples of pharmaceutical vehicles include creams, gels, lotions, solutions, and liposomes.

[0134] As used herein the term "inflammatory diseases" are those pertaining to, characterized by, causing, resulting from or becoming affected by inflammation. Such inflammatory diseases include but are not limited to rheumatoid arthritis; inflammatory bowel disease (IBD) including but not limited to Crohn's disease, ulcerative colitis and colitis; Pagets disease; osteoporosis; multiple myeloma; uveitis; acute and chronic myelogenous leukemia; pancreatic β cell destruction; rheumatoid spondylitis; osteoarthritis; gouty arthritis and other arthritis conditions; gout; adult respiratory distress syndrome (ARDS); chronic pulmonary inflammatory diseases; silicosis; pulmonary sarcoidosis; psoriasis; rhinitis; anaphylaxis; contact dermatitis; pancreatitis; asthma; muscle degeneration; cachexia such as cachexia secondary to infection or malignancy, cachexia secondary to acquired immune deficiency syndrome; Reiter's syndrome; type I diabetes; bone resorption disease; graft vs. host reaction; ischemia reperfusion injury; brain trauma; multiple sclerosis; cerebral malaria; sepsis; septic shock; toxic shock syndrome; endotoxic shock; gram negative sepsis; fever and myalgias due to infection such as influenza; pyrosis.

[0135] As used herein the term "cytokine" refers to any secreted polypeptide that affects the functions of cells and is a molecule which modulates interactions between cells in the immune, inflammatory or hematopoietic response. Examples of cytokines include, but are not limited to Interleukine 1 (IL-1), preferably IL-1β, Interleukine 6 (IL-6), Interleukine 8 (IL-8) and Tumor Necrosis Factor, preferably TNF-α.

[0136] As used herein the term "TNF, IL-1, IL-6, and/or IL-8 mediated diseases or disease states" means all disease states wherein TNF, IL-1, IL-6, and/or IL-8 plays a role, either directly as TNF, IL-1, IL-6, and/or IL-8 itself, or by TNF, IL-1, IL-6, and/or IL-8 inducing another cytokine to be released. For example, a disease state in which IL-1 plays a major role, but in which the production of, or the action of IL-1 is a result of TNF, would be considered mediated by TNF.

[0137] The present invention will be better understood with reference to the following examples. These examples are intended to representative of specific embodiments of the invention, and are not intended as limiting the scope of the invention.

CHEMISTRY EXAMPLES

[0138] All temperatures are expressed in °C and all reactions were carried out at room temperature (RT) unless otherwise stated.

[0139] Analytical thin layer chromatography (TLC) was used to monitor reactions, establish flash chromatography conditions and verify purity of intermediates or final products. TLC plates

used were Merck TLC aluminium sheet silica gel 60 F_{254}. TLC plates were revealed using ultraviolet irradiation (wavelength=254 nm) at RT or bromocresol green spray reagent at 0.1% in propan-2-ol or $KMnO_4$ revelator ($KMnO_4$, Na_2CO_3, NaOH, H_2O) upon heating at 160°C.

[0140] HPLC-MS spectra were obtained on Agilent LCMS using Electropsray ionization (ESI). The Agilent instrument includes an Autosampler 1200, a binary pump 1100, a 5 wave length detector 1100 and a 6100 Single Quad. The column used was an XBridge C18.

[0141] Eluent was a mixture of solution A (0.1% TFA in H_2O) and solution B (0.1% TFA in ACN). Gradients used are as follows: gradient A (intermediates characterization): held the initial conditions of 5% solution B for 1 min, increased linearly to 95% solution B in 4 min, held at 95% during 1 min, returned to initial conditions in 0.5 min and maintained for 1 min; gradient B (examples characterization): held the initial conditions of 5% solution B for 1 min, increased linearly to 60% in 10 min, increased linearly to 95% in 0.5 min, held at 95% during 3 min, returned to initial conditions in 0.5 min and maintained for 1 min.

[0142] Determination of enantiomeric excess was performed on an Agilent 1100 (binary pump and 5 wavelengths detector) with manual or automatic (Autosampler 1100) injection. Columns used were CHIRALPAK IA CHIRALPAK IB or CHIRALPAK IC in isocratic mode. Mixtures of eluents were selected depending on the separation obtained of enantiomers or diastereosiomers. Usual mixtures were:

- Hexane and Ethanol (0.1% TFA)
- Hexane and Propanol (0.1% TFA)
- Hexane and Ethyl acetate (0.1% TFA)
- Hexane and Dichloromethane (0.1% TFA)
- Hexane and *tert*-butyl methyl ether (0.1% TFA)

[0143] Preparative HPLC purifications were carried out on Fractionlynx instrument, from Waters. This instrument consists of a Fraction Collector, a 2767 Sample Manager, a pump control a module II, a 515 HPLC Pump, a 2525 Binary Gradient Module, a Switching Valve, a 2996 Photodiode Array Detector and a Micromass ZQ. The column used was a Waters Sunfire C18 Eluent was a mixture of solution A (0.1% TFA in H_2O) and solution B (0.1% TFA in ACN). The gradient was adapted depending on impurities present in samples, to allow sufficient separation between impurities and target compound.

[0144] Chiral preparative HPLC purification were performed on an Agilent 1100 instrument (binary pump and 5 wavelengths detector) with manual injection using a CHIRALPAK IA or a CHIRALPAK IB column in isocratic mode. Mixtures of eluents were selected depending on the separation of enantiomers or diastereosiomers obtained with the analytical method. Usual mixtures were the same as those used for the determination of ee.

[0145] ^{1}H and ^{13}C NMR spectra were recorded on a Bruker ARX 300MHz. Chemical shifts are expressed in parts per million, (ppm, δ units). Coupling constants are expressed in Hertz units (Hz). Splitting patterns describe apparent multiplicities and are described as s (singlet), d (doublet), t (triplet), q (quintet), m (multiplet), or br (broad).

[0146] Solvents, reagents and starting materials were purchased from well known chemical suppliers such as for example Sigma Aldrich, Acros Organics, VWR Int., Sopachem or Polymer labs and the following abbreviations are used:

ACN or MeCN: Acetonitrile,

DCM: Dichloromethane,

DCE: 1,2-Dichloroethane,

EtOAc or AcOEt: Ethyl acetate,

EtOH: Ethanol,

MeOH: Methanol,

IPA: isopropanol,

PE: Petroleum ether,

NMP: N-methylpyrrolidinone,

RT: Room temperature,

DIEA: N,N-diisopropylethylamine,

HATU: O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tretramethyluronium hexafluorophosphate ,

HOBt: 1-hydroxybenzotriazole or 1-hydroxybenzotriazole hydrate,

DMAP: N, N-Dimethylaminopyridine,

Y: Yield,

g: Grams,

mg: Milligrams,

L: Liters,

mL: Milliliters,

µL: Microliters,

mol: Moles,

mmol: Millimoles,

h: Hours,

min or mn: Minutes,

TLC: Thin layer chromatography,

MW: Molecular weight,

eq: Equivalent,

THF: Tetrahydrofuran,

TFA: Trifluoroacetic acid,

Ac: Acetyl,

ee: Enantiomeric excess,

*t*Bu: *tert*-Butyl,

P: UV purity at 254nm determined by HPLC-MS,

rt: Retention time,

BuLi: butyllithium,

CDI: carbonyldiimidazole,

TBDPS: *tert*-butyl-diphenylsilyl,

Boc_2O: di-*tert*-butyldicarbonate,

TBAF: tetrabutylammonium fluoride,

S-Phos: 2-Dicyclohexylphosphino-2',6'-dimethoxybiphenyl,

RM: reaction mixture,

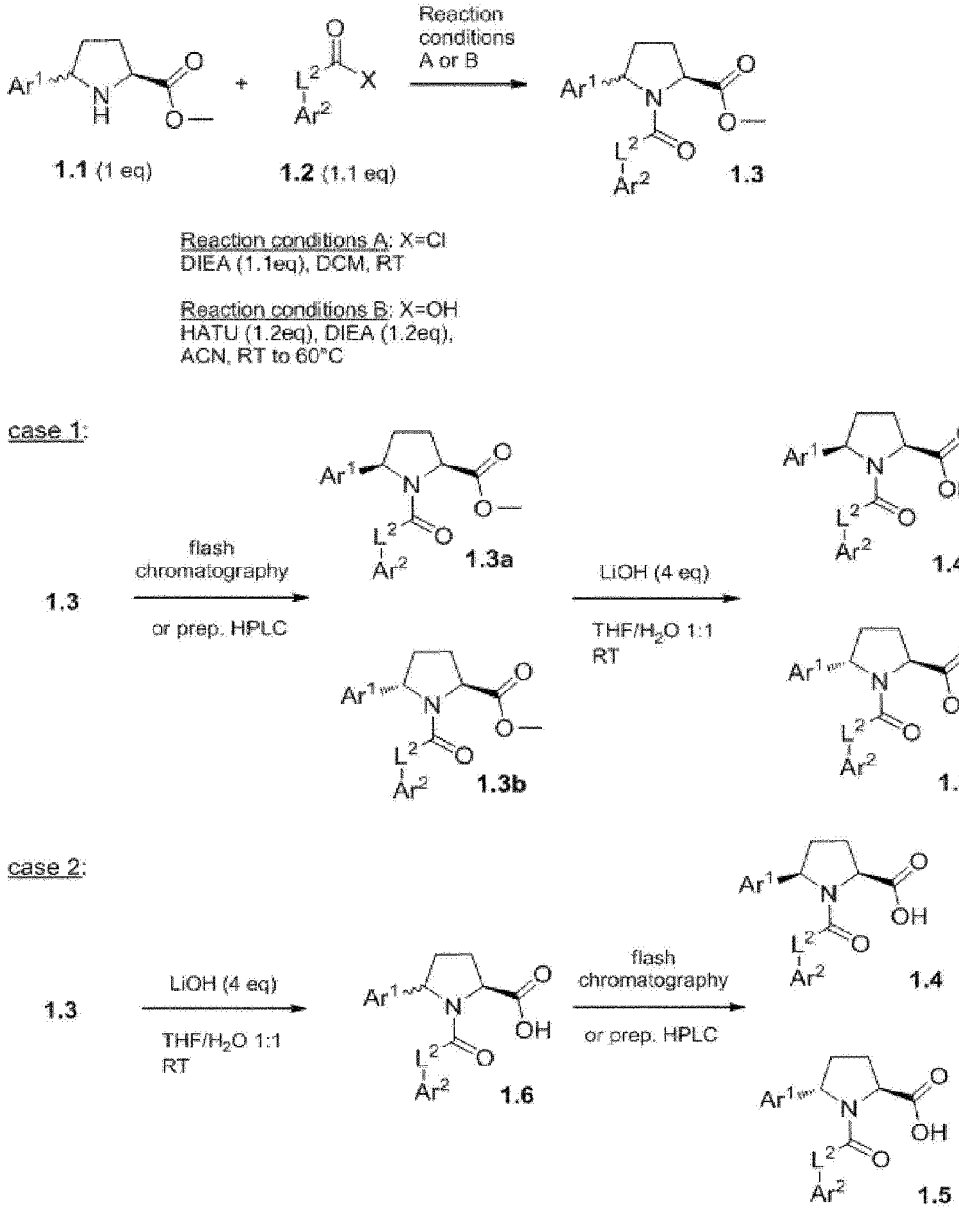
Nu: Nucleophile,

DMF: N,N-dimethylformamide,

TMS: trimethylsilyl.

General synthetic schemes

[0147] A general method for the synthesis of most compounds of the invention is outlined in **scheme 1.**



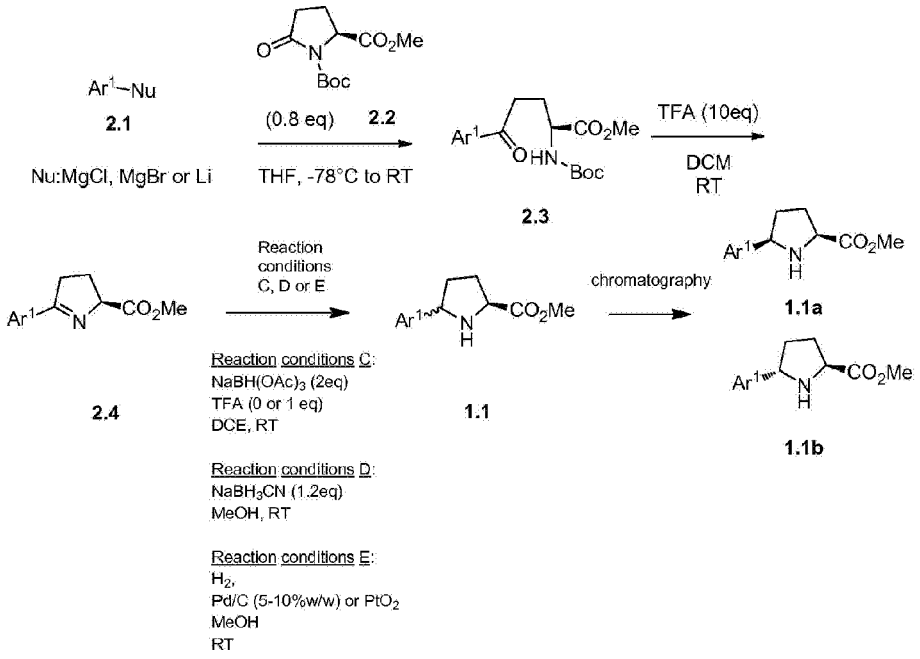
Scheme 1: A general method for the synthesis of most compounds of the invention

[0148] Pyrrolidine methyl acetate intermediate **1.1** was acylated with acyl chlorides or carboxylic acids intermediates **1.2** using standard amide coupling procedures to give epimeric mixture compound **1.3.**

[0149] In some cases epimers **1.3a** and **1.3b** were separated by chromatography (flash chromatography or preparative HPLC); subsequent saponification of intermediates **1.3a** and **1.3b** with lithium hydroxide afforded the desired carboxylic acid products **1.4** and **1.5** respectively.

[0150] Otherwise intermediate **1.3** was saponified with lithium hydroxide to give epimeric mixture **1.6** which was purified by chromatography (flash chromatography or preparative HPLC) to give desired carboxylic acid products **1.4** and **1.5.**

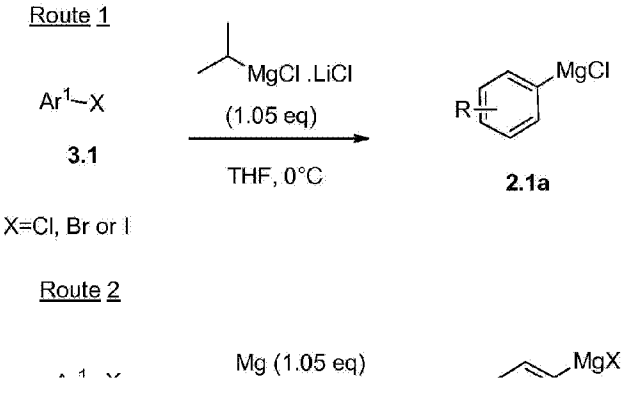
[0151] Pyrrolidine ester intermediates **1.1** were synthesized from aryl or alkyl Grignard or aryl-lithium reagents as shown in **scheme 2.**

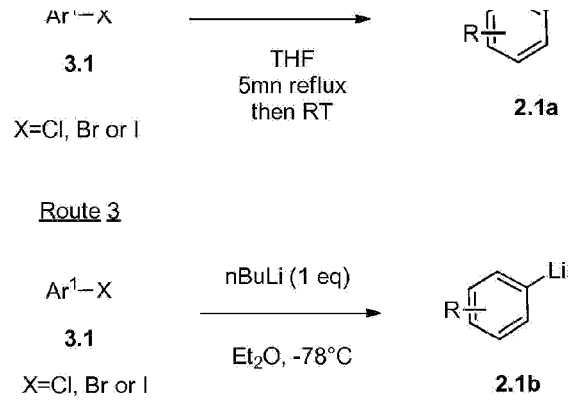


Scheme 2: Synthetic scheme for the preparation of pyrrolidine ester intermediates **1.1**

[0152] Addition of aryl or alkyl Grignard or aryl-lithium **2.1** to N-Boc-L-pyroglutamic acid methyl ester **2.2** provided intermediate **2.3,** as described by Colandrea et al. in Bioorg. & Med. Chem. Lett. 2006, 16, 2905-2908 and Ying-zi Xu et al. in J. Org. Chem. 1999, 64, 4069-4078. One pot Boc deprotection and cyclic imine formation under acidic conditions afforded cyclic imine intermediate **2.4** which could be reduced either by hydrogenation or by borohydride reagent to give the pyrrolidine ester intermediate **1.1.** In some cases epimers **1.1a** and **1.1b** were separated by flash chromatography.

[0153] Aryl or alkyl Grignard and aryl-lithium reagents **2.1** were prepared using the methodologies shown in **scheme 3.**

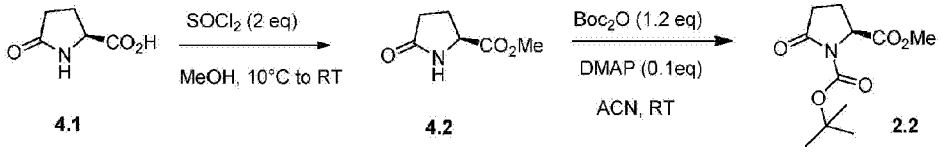




Scheme 3: Synthetic scheme for the preparation of aryl or alkyl magnesium and aryl-lithium reagents

[0154] Aryl or alkyl Grignard reagents **2.1a** were prepared from aryl halides either by method 1 (isopropyl megnasium chloride/lithium chloride) or by method 2 (magnesium) and aryl-lithium reagents **2.1b** were synthesized by method 3 (n-butyllithium).

[0155] N-Boc-L-pyroglutamic acid methyl ester **2.2** was synthesized using the methodology shown in **scheme 4.**

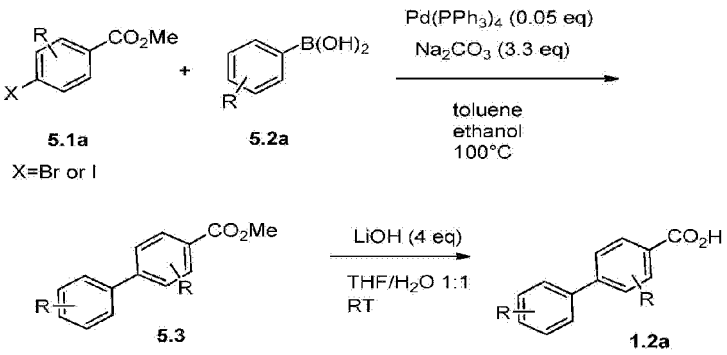


Scheme 4: Synthetic scheme for the preparation of N-Boc-L-pyroglutamic acid methyl ester **2.2**

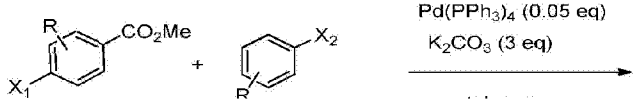
L-pyroglutamic acid **4.1** was converted to the methyl ester **4.2** which upon Boc protection with di-*tert*-butyl dicarbonate afforded intermediate **2.2.**

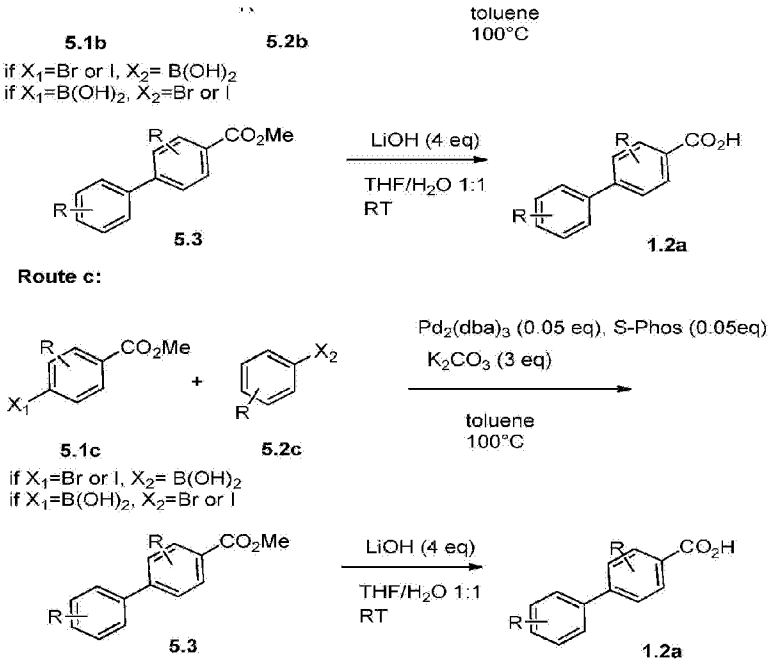
[0156] Biaryl and heterobiaryl carboxylic acid intermediates **1.2a** were synthesized using one of the three routes (a, b or c) shown in **scheme 5.**

Route a:



Route b:

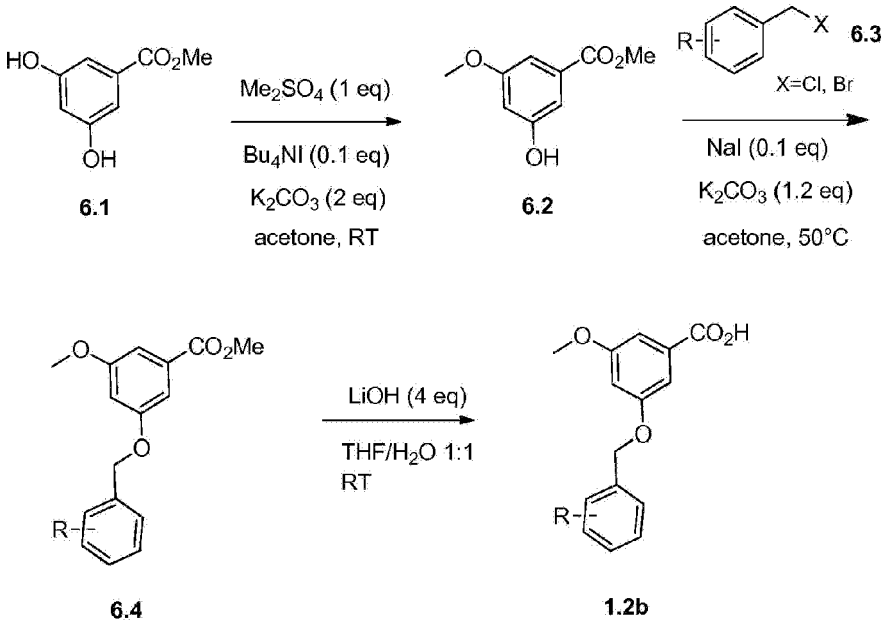




Scheme 5: Synthetic scheme for the preparation of biaryl carboxylic acid intermediates **1.2a**

[0157] Suzuki coupling between **5.1** and **5.2** provided biaryl ester intermediate **5.3,** subsequent saponification with lithium hydroxide afforded biaryl carboxylic acid intermediate **1.2a.**

[0158] Aralkyloxyaryl carboxylic acid intermediates **1.2** were synthesized using the methodology shown in **scheme 6** for benzyloxybenzoic acid intermediates **1.2b.**

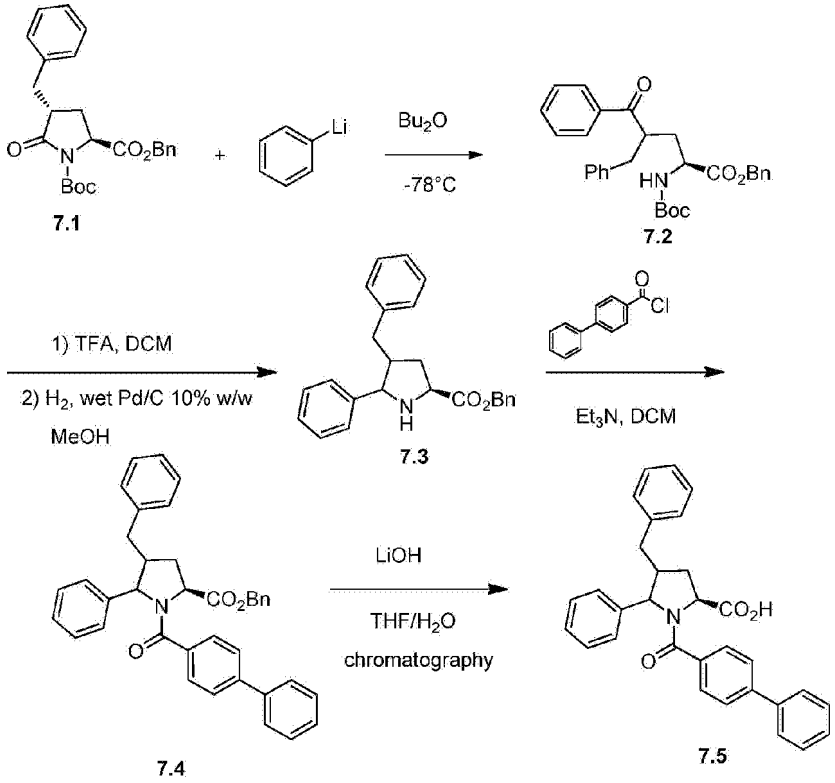


Scheme 6: Synthetic scheme for the preparation of benzyloxybenzoic acid intermediates **1.2b**

[0159] Methyl 3,5-dihydroxybenzoate **6.1** was methylated with dimehylsulfate to give intermediate **6.2.** Benzylation with benzyl halide reagent **6.3** provided ester intermediate **6.4** which upon subsequent saponification with lithium hydroxide afforded benzyloxybenzoic acid intermediates **1.2b**

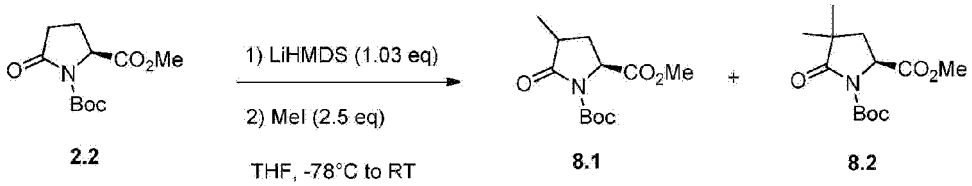
Additional synthetic schemes

[0160] Synthesis of compound n°24 is depicted in **scheme 7.**



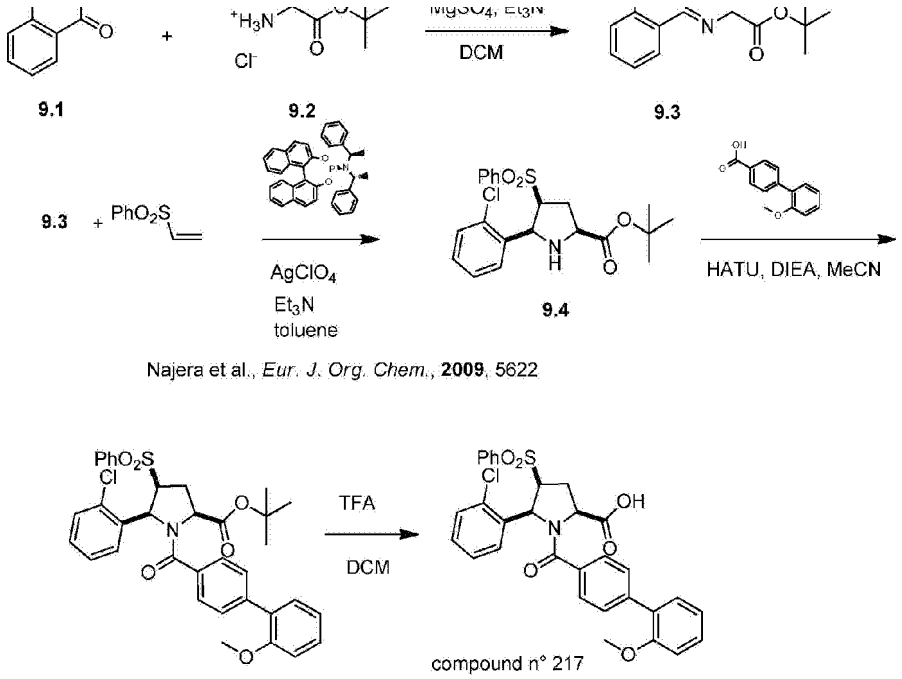
Scheme 7: Synthesis of compound n°24

[0161] Synthesis of methyl substituted pyrrolidinone intermediates **2.2** is depicted in **scheme 8.**



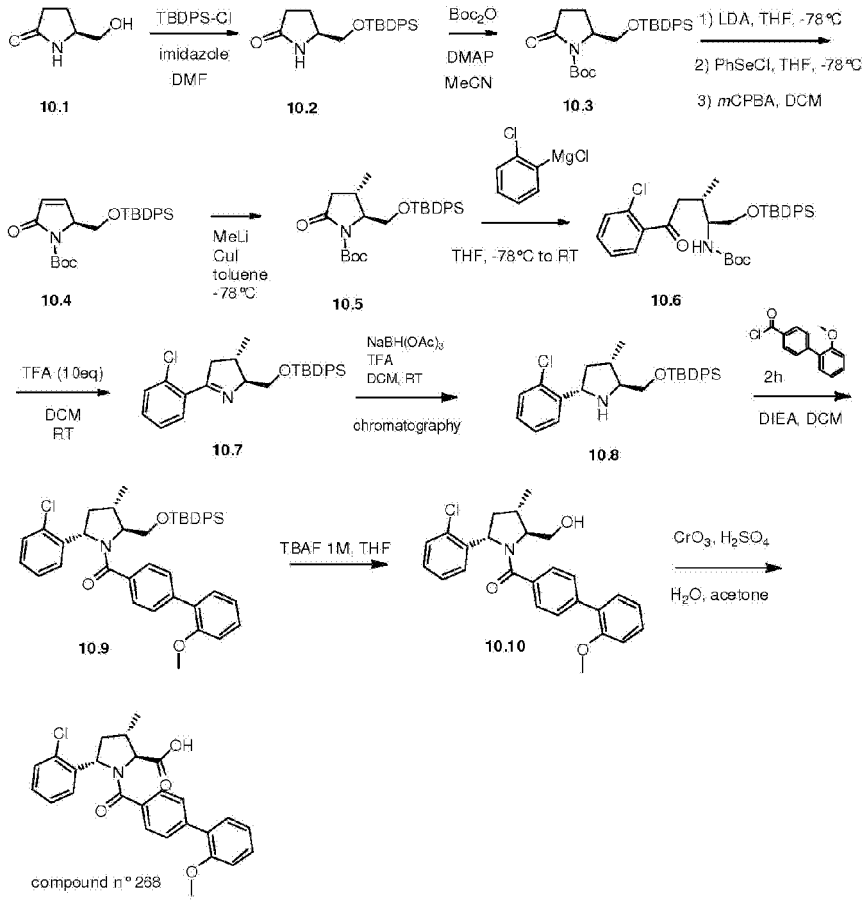
Scheme 8: Synthesis of methyl substituted pyrrolidinone intermediates

[0162] Dipolar cycloaddition methodology is exemplified with the synthesis of compound n° 217 and is depicted in **scheme 9.**



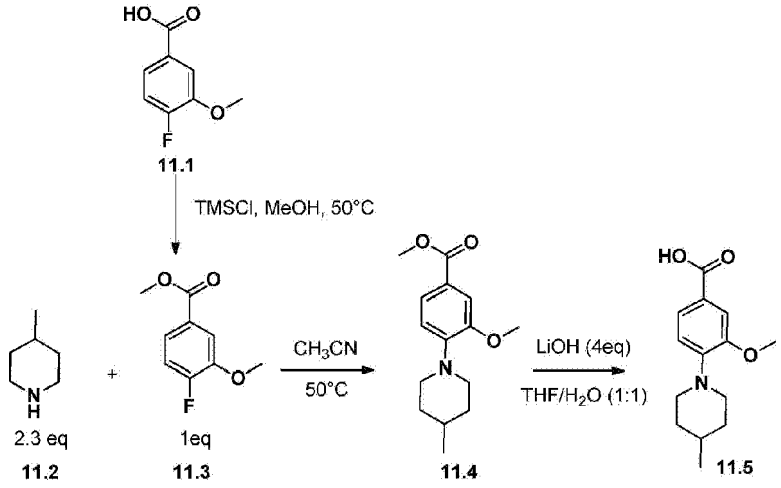
Scheme 9: Dipolar cycloaddition methodology

[0163] Synthesis of compound n° 268 is depicted in **scheme 10.**



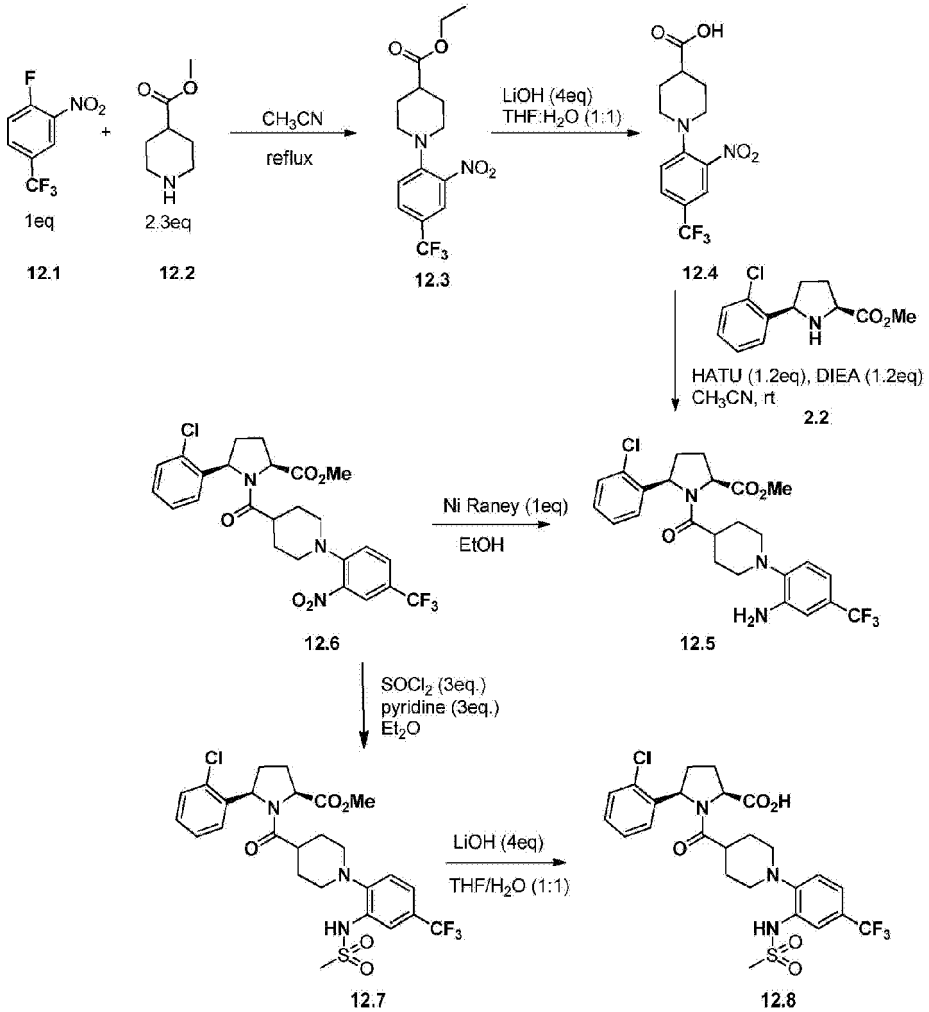
Scheme 10: Synthesis of compound n° 268

[0164] Synthesis of intermediate 3-methoxy-4-(4-methylpiperidin-1-yl)benzoic acid used in the preparation of compound n°261 is depicted in **scheme 11.**



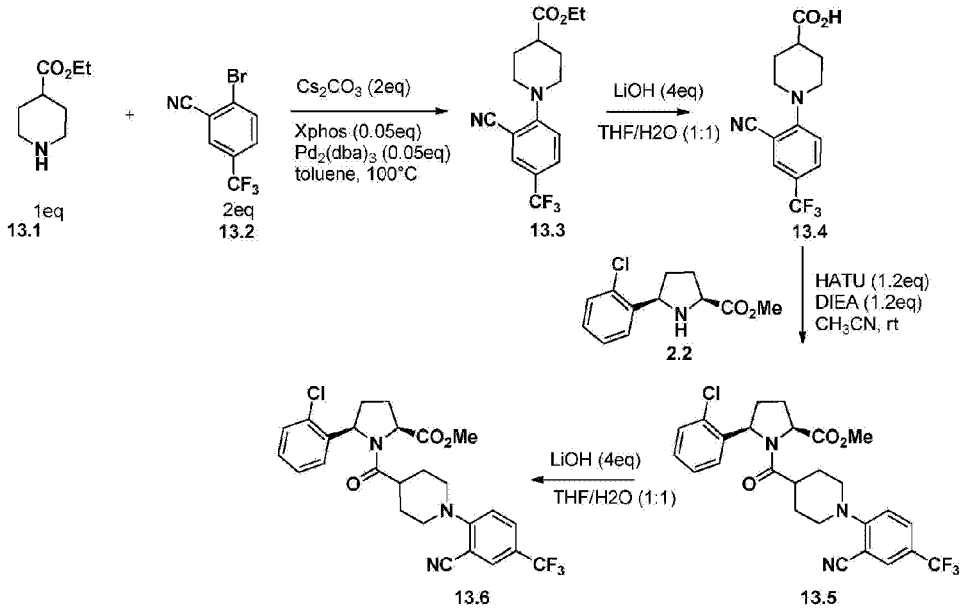
Scheme 11: Synthesis of intermediate 3-methoxy-4-(4-methylpiperidin-1-yl)benzoic acid

[0165] The synthesis of compound n° 393 is depicted in **scheme 12.**



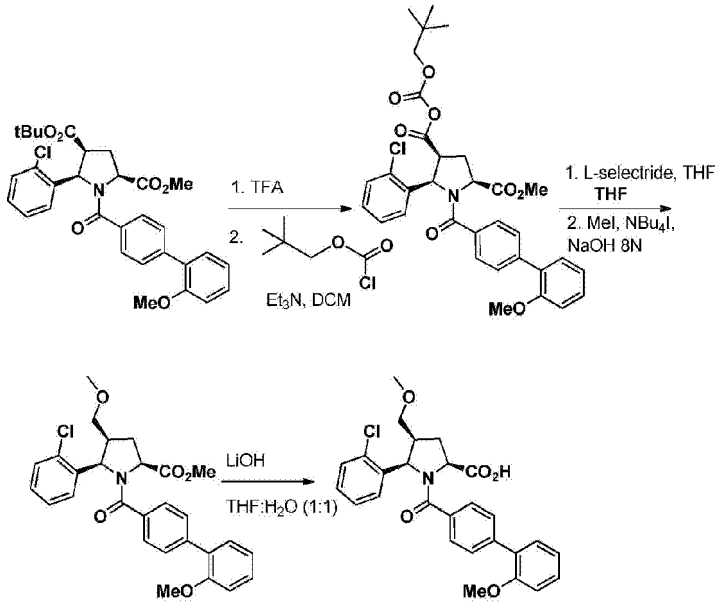
Scheme 12: synthesis of compound n°393

[0166] The synthesis of compound n°369 is depicted in **scheme 13.**



Scheme 13: synthesis of compound n°369

[0167] Synthesis of compound n° 279 is depicted in **scheme 14.**



Scheme 14: synthesis of compound n°279

General methods

General method A: synthesis of pyrrolidine ester intermediates 1.1

[0168] General method A is examplified with the synthesis of intermediate **1a** (2S,5R)-methyl 5-(2-chlorophenyl)pyrrolidine-2-carboxylate, intermediate **1b** (2S,5S)-methyl 5-(2-chlorophenyl)pyrrolidine-2-carboxylate and intermediate **1f** (2S,5R)-methyl 5-(pyridin-2-yl)pyrrolidine-2-carboxylate from 2-bromopyridine (route 3, conditions E).

Step 1: synthesis of (2-chlorophenyl)magnesium chloride: route 1.

[0169] To a 2M solution of isopropylmagnesium chloride in anhydrous THF (5.76 mmol) was added lithium chloride (5.76 mmol) in distilled THF in a Schlenk tube under Ar atmosphere at RT. The reaction mixture was cooled to -15°C and 1-bromo-2-chlorobenzene (5.35 mmol) was added and the RM was stirred at -15°C for another 3h. This crude solution of (2-chlorophenyl)magnesium chloride was cooled to -40°C and used as such in step 2.

Step 2: synthesis of (S)-methyl 2-((tert-butoxycarbonyl)amino)-5-(2-chlorophenyl)-5-oxopentanoate.

[0170] To the crude solution of (2-chlorophenyl)magnesium chloride obtained in step 1 was added at -40°C under Ar a solution of (S)-1-*tert*-butyl 2-methyl 5-oxopyrrolidine-1,2-dicarboxylate (4.11 mmol) in distilled THF (4mL). The reaction mixture was stirred at-40°C for 2h and then quenched with 10mL of a saturated aqueous solution of ammonium chloride. The mixture was extracted three times with AcOEt, combined organics were dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Crude was purified by flash chromatography (eluent: cyclohexane/AcOEt) to yield title compound. Y: 425 mg (29%), P: >95%, rt=4.24 min, $(M+H)^+$= 256.

Step 3: synthesis of (S)-methyl 5-(2-chlorophenyl)-3,4-dihydro-2H-pyrrole-2-carboxylate.

[0171] TFA (2 mL) was added to a solution of (S)-methyl 2-((*tert*-butoxycarbonyl)amino)-5-(2-chlorophenyl)-5-oxopentanoate (1.08 mmol) in DCM (2mL) and the reaction mixture was stirred at RT for 2h. The RM was evaporated to dryness to yield title compound. Y: 574 mg (56%), P: >95%, rt=2.85 min, $(M+H)^+$= 238.

Step 4:

Reaction conditions C: **synthesis of intermediate 1a (2S,5R)-methyl 5-(2-chlorophenyl)pyrrolidine-2-carboxylate and intermediate 1b (2S,5S)-methyl 5-(2-chlorophenyl)pyrrolidine-2-carboxylate.**

[0172] Sodium triacetoxyborohydride (0.091 mol) was added portionwise to a stirred solution of (S)-methyl 5-(2-chlorophenyl)-3,4-dihydro-2H-pyrrole-2-carboxylate (0.076 mol) in 1,2-dichloroethane (200 mL) at RT under a nitrogen atmosphere. TFA (0.76 mol) was added and the reaction mixture was stirred at RT for 1.5 h. LCMS showed starting material still remaining so further TFA (~10mL) was added (to give pH 3-4) and stirring continued for a further 1.5 h. All starting material was consumed, water (30 mL) was added followed by saturated aqueous $NaHCO_3$ (~400 mL) until neutral pH. The separated aqueous layer was extracted with DCM (2 x 300ml) and the combined organics dried over anhydrous $MgSO_4$ and evaporated *in vacuo* to give a yellow oil (17.5 g). Crude was purified by column chromatography (eluent: PE/EtOAc) to give, as colourless oils, intermediate **1a:** Y: 12 g (66%), P: >95%, rt=2.73 min, $(M+H)^+$= 240 and intermediate **1b** Y: 3 g (16%), P: >95%, $(M+H)^+$= 240.

Reaction conditions D: **synthesis of intermediate (2S)-methyl 5-(2-chlorophenyl)pyrrolidine-2-carboxylate.**

[0173] Sodium cyanobrorohydride (2.9 mmol) was added to a solution of (S)-methyl 5-(2-chlorophenyl)-3,4-dihydro-2H-pyrrole-2-carboxylate (2.42 mmol) in anhydrous MeOH (20 mL) and the reaction mixture was stirred at RT for 1h. The RM was quenched with water and extracted with DCM. Combined organics were dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to yield title compound. Y: 338 mg (59%), P: >95%, rt=2.73 min, $(M+H)^+$= 240.

Reaction conditions E: synthesis of **intermediate 1f: (2S,5R)-methyl 5-(pyridin-2-yl)pyrrolidine-2-carboxylate from 2-bromopyridine (route 3).**

[0174] In a 10mL round bottomed flask was dissolved (S)-methyl 5-(pyridin-2-yl)-3,4-dihydro-2H-pyrrole-2-carboxylate (0.208 mmol) in IPA (550 µL) to give a brown solution. Palladium on carbon (3.95 µmol) (10%w/w) was added, and reaction was stirred under H_2 atmosphere.

[0175] Reaction mixture was stirred overnight at RT. The mixture was filtered through celite and concentrated under reduced pressure to give intermediate **1f** in a quantitative yield. Y: 12 g (66%), P: >95%, rt=2.34 min, $(M+H)^+$= 207.

[0176] The following intermediates were synthesized from ad-hoc reagents using general method A:

intermediate **1c:** (2S,5R)-methyl 5-(3-chloropyridin-2-yl)pyrrolidine-2-carboxylate from 2-bromo-3-chloropyridine (route 3, conditions C);

intermediate **1e:** (2S)-methyl 5-([1,1'-biphenyl]-3-yl)pyrrolidine-2-carboxylate from biphenyl-3-ylmagnesium bromide (conditions C);

intermediate **1g:** (2S)-methyl 5-(2-fluorophenyl)pyrrolidine-2-carboxylate from 1-bromo-2-fluorobenzene (route 1, conditions C), rt=2.5 min (gradient A);

intermediate **1i:** (2S)-methyl 5-(2-methoxyphenyl)pyrrolidine-2-carboxylate from 1-bromo-2-methoxybenzene (route 1, conditions D);

intermediate **1j:** (2R)-methyl 5-(2-chlorophenyl)pyrrolidine-2-carboxylate from 1-bromo-2-chlorobenzene (route 1, conditions D);

intermediate **1k:** (2S)-methyl 5-(4-chlorophenyl)pyrrolidine-2-carboxylate from 4-chlorophenylmagnesium bromide (conditions C);

intermediate **1l:** (2S)-methyl 5-([1,1'-biphenyl]-4-yl)pyrrolidine-2-carboxylate from [1,1'-biphenyl]-4-ylmagnesium bromide (conditions C);

intermediate **1m:** (2S)-methyl 5-(2-chlorobenzyl)pyrrolidine-2-carboxylate from 2-chlorobenzylmagnesium chloride (conditions C);

intermediate **1n:** (2S)-methyl 5-cyclohexylpyrrolidine-2-carboxylate from cyclohexylmagnesium chloride (conditions C);

intermediate **1o:** (2S)-methyl 5-([1,1'-biphenyl]-2-yl)pyrrolidine-2-carboxylate from [1,1'-biphenyl]-2-ylmagnesium bromide (conditions C);

intermediate **1p:** (2S,5R)-methyl 5-(2-chlorophenyl)-4,4-dimethylpyrrolidine-2-carboxylate (conditions C), starting from (S)-1-*tert*-butyl 2-methyl 4,4-dimethyl-5-oxopyrrolidine-1,2-dicarboxylate obtained using the synthetic route described in **scheme 8;**

intermediate **1q:** (2S,5R)-methyl 5-(2-chlorophenyl)-4-methylpyrrolidine-2-carboxylate (conditions C), starting from (S)-1-*tert*-butyl 2-methyl-4-dimethyl-5-oxopyrrolidine-1,2-dicarboxylate;

intermediate **1r:** (2S,5R)-methyl 5-(pyridin-3-yl)pyrrolidine-2-carboxylate;

intermediate **1s:** (2S,5R)-methyl 5-(o-tolyl)pyrrolidine-2-carboxylate;

intermediate **1t:** (2S,5R)-methyl 5-phenylpyrrolidine-2-carboxylate (condition E);

intermediate **1u:** (2S,5R)-methyl 5-(3-chlorophenyl)pyrrolidine-2-carboxylate (route 1, conditions C);

intermediate **1v:** (2S,5R)-methyl 5-(4-chlorophenyl)pyrrolidine-2-carboxylate (route 1, conditions C);

intermediate **1w:** (2S,5R)-5-(3-fluorophenyl)pyrrolidine-2-carboxylic acid (route 1, conditions E);

intermediate **1x:** (2S,5R)-methyl 5-(4-fluorophenyl)pyrrolidine-2-carboxylate (route 1, conditions E);

intermediate **1y:** (2S,5R)-methyl 5-cyclohexylpyrrolidine-2-carboxylate was synthesized by hydrogenation of intermediate **1t** using PtO_2 in MeOH,

intermediate **1z:** (2R,5R)-methyl 5-(2-fluorophenyl)pyrrolidine-2-carboxylate (route 1, conditions C);

intermediate **1a1:** (2S,5S)-methyl 5-(2-fluorophenyl)pyrrolidine-2-carboxylate(route 1, conditions C);

intermediate **1b1:** (2R,5S)-methyl 5-(2-fluorophenyl)pyrrolidine-2-carboxylate(route 1, conditions C);

intermediate **1c1:** (2S,5R)-methyl 5-(2,6-difluorophenyl)pyrrolidine-2-carboxylate(route 1, conditions E);

intermediate **1d1:** (2S,5R)-methyl 5-(2,4-difluorophenyl)pyrrolidine-2-carboxylate(route 1, conditions E);

intermediate **1e1:** (2S,5R)-methyl 5-(2,4-dichlorophenyl)pyrrolidine-2-carboxylate(route 1, conditions C);

intermediate **1f1:** (2S,5R)-methyl 5-isobutylpyrrolidine-2-carboxylate(route 2, conditions E);

intermediate **1g1:** (2S,5R)-methyl 5-isopropylpyrrolidine-2-carboxylate(route 1, conditions E);

intermediate **1h1:** (2S,5R)-methyl 5-cyclopentylpyrrolidine-2-carboxylate (conditions E);

intermediate **1i1:** (2S,5R)-methyl 5-(2-bromophenyl)pyrrolidine-2-carboxylate (route 1, conditions C);

intermediate **1j1:** (2S,5S)-methyl 5-isopentylpyrrolidine-2-carboxylate (route 2, conditions E);

intermediate **1k1:** (2S,5R)-methyl 5-(2,4-difluorophenyl)pyrrolidine-2-carboxylate (route 1, conditions E);

intermediate **1l1:** (2S,5R)-methyl 5-(3,5-difluorophenyl)pyrrolidine-2-icarboxylate (route 1, conditions C);

intermediate **1m1:** (2S,5R)-methyl 5-(3,4-difluorophenyl)pyrrolidine-2-carboxylate (route 1, conditions C);

intermediate **1n1:** (2S,5R)-methyl 5-(2,3-difluorophenyl)pyrrolidine-2-carboxylate (route 1, conditions C), rt=2.6min (gradient A);

intermediate **1o1:** (2S,5R)-methyl 5-(2,5-difluorophenyl)pyrrolidine-2-carboxylate (route 1, conditions C);

intermediate **1p1:** (2S,5R)-methyl 5-(4-cyanophenyl)pyrrolidine-2-carboxylate (route 1, conditions C).

General method B: synthesis of aryloxyaryl carboxylic acid intermediates 1.2b

[0177] General method B is examplified with the synthesis of intermediate **2a** 3-(benzyloxy)-5-methoxybenzoic acid.

Step 1: synthesis of methyl 3-hydroxy-5-methoxybenzoate.

[0178] To a solution of methyl 3,5-dihydroxybenzoate (29.76 mmol) in anhydrous acetone (40 mL) was added dimethylsulfate (29.69 mmol), tetrabutylammonium iodide (2.97 mmol) and potassium carbonate (59.42 mmol). The reaction mixture was stirred at RT overnight. The RM was diluted with water and extracted with AcOEt. Combined organics were dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Crude was purified by flash chromatography (eluent: PE/AcOEt) to yield title compound. Y: 1.7 g (31%), P: >95%, rt=3.75 min, $(M+H)^+$= 183.

Step 2: synthesis of methyl 3-(benzyloxy)-5-methoxybenzoate.

[0179] To a solution of methyl 3-hydroxy-5-methoxybenzoate (0.55 mmol) in anhydrous acetone (2 mL) was added benzyl bromide (0.55 mmol), potassium carbonate (0.66 mmol) and sodium iodide (0.055 mmol). The reaction mixture was stirred at 55°C for 5h. The RM was diluted with AcOEt and a 1M aqueous solution of sodium hydroxide. The organic layer was separated, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Crude was purified by flash chromatography (eluent: PE/AcOEt) to yield title compound. Y: 104 mg (69%), P: >95%, rt=4.53 min, $(M+H)^+$= 273.

Step 3: synthesis of intermediate 2a 3-(benzyloxy)-5-methoxybenzoic acid.

[0180] To a solution of methyl 3-(benzyloxy)-5-methoxybenzoate (0.38 mmol) in THF (1 mL) was added a solution of lithium hydroxide (1.53 mmol) in water (1 mL). The reaction mixture was stirred at RT overnight. The RM was quenched with a 1M HCl aqueous solution and extracted three times with DCM. Combined organics were dried over anhydrous $MgSO_4$ and

concentrated *in vacuo* to yield title compound. Y: 92 mg (94%), P: >95%, rt=3.95 mn, $(M+H)^+$= 259.

[0181] The following intermediates were synthesized from ad-hoc reagents using general method B:

intermediate **2b:** 3-((4-chlorobenzyl)oxy)-5-methoxybenzoic acid,

intermediate **2c:** 3-methoxy-5-phenethoxybenzoic acid,

intermediate **2d:** 3-(3,3-diphenylpropoxy)-5-methoxybenzoic acid,

intermediate **2e:** 3-methoxy-5-((4-(methylsulfonyl)benzyl)oxy)benzoic acid,

intermediate **2f:** 3-methoxy-5-(2-methoxyethoxy)benzoic acid,

intermediate **2g:** 3-((3,5-dimethylisoxazol-4-yl)methoxy)-5-methoxybenzoic acid.

General method C: synthesis of most compounds of the invention

[0182] General method C is examplified with the synthesis of Example 1: compound n°1: (2S,5R)-5-(2-chlorophenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid.

Step 1: synthesis of (2S,5R)-methyl 5-(2-chlorophenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylate.

Conditions A:

[0183] In a 100mL round bottom flask, under argon, was dissolved 2'-methoxybiphenyl-4-carboxylic acid (15.714 g, 68.8 mmol) in DCM (138 mL). A white suspension was obtained to which were successively added thionyl chloride (7.49 mL, 103 mmol) and DMF (0.107 mL, 1.377 mmol). Reaction mixture was heated at reflux (40°C) 3 hours. The solution was allowed to reach spontaneously RT (yellow-orange solution). RM was concentrated under reduced pressure. Removal of the excess of thionyl chloride was done by two co-evaporation cycles with DCM. The resulting brown residue was dried under vacuum to afford 17g of a brown solid. Crude product was used without further purification in the next step.

[0184] In a 500 mL round bottom flask were introduced under argon methyl (2S,5R)-5-(2-chlorophenyl)pyrrolidine-2-carboxylate (15 g, 62.6 mmol), DCM (62.4 mL) and Et_3N (9.59 mL,

68.8 mmol). To this solution cooled to 0°C, was added dropwise (via an addition funnel) a solution of 2'-methoxybiphenyl-4-carbonyl chloride (16.98 g, 68.8 mmol) in DCM (83 mL) (dark brown solution). The RM was stirred from 0°C to RT overnight. The RM was transferred to a separation funnel and washed with 25 mL of HCl 6M diluted with 75mL water. The organic layer was dried under stirring with $MgSO_4$ in the presence of 0.3g of Norit AS, filtered and concentrated to afford 34 g of a light brown foaming oily residue. Purification by column chromatography (eluent: EtOAc/PE: 1/2) yielded desired product as a beige solid. Y: 25.4 g (90 %), P > 95%.

[0185] Conditions B: To a solution of 2'-methoxybiphenyl-4-carboxylic acid **2b** (1.1 mmol) in anhydrous ACN (2 mL) was added HATU (1.1 mmol). After 5 min was added (2S,5R)-methyl 5-(2-chlorophenyl)pyrrolidine-2-carboxylate **1a** (1 mmol) and DIEA (1.2 mmol). Reaction mixture was stirred at RT for 4 days. Reaction mixture was diluted with AcOEt and washed with saturated aqueous solution of $NaHCO_3$ and with water. The organic phase was dried over $MgSO_4$ and evaporated. Crude was purified by flash chromatography (eluent: cyclohexane/AcOEt) to yield title compound. Y: 300 mg (67%), P>95%, rt= 4.85 min, $(M+H)^+$ =451.

Step 2: synthesis of Example 1: compound n°1: (2S,5R)-5-(2-chlorophenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid.

[0186] To a solution of (2S,5R)-methyl 5-(2-chlorophenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylate (0.67 mmol) in THF (5 mL) was added a solution of lithium hydroxide (2.67 mmol) in water (5 mL). The reaction mixture was stirred at RT overnight. The RM was quenched with a 1M HCl aqueous solution and extracted twice with AcOEt. Combined organics were dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to yield title compound as a colorless solid. Y: 250 mg (86%), P: >95%, rt=6.05 min, $(M+H)^+$= 436.

General method D: synthesis of biaryl carboxylic acid intermediates 1.2a

[0187] Three **routes** (**a, b** and **c**) were used in the preparation of biaryl or heterobiaryl intermediates.

[0188] Route a is examplified with the synthesis of intermediate **2h** 2'-methoxy-[1,1'-biphenyl]-4-carboxylic acid.

Step 1: synthesis of methyl 2'-methoxy-[1,1'-biphenyl]-4-carboxylate.

[0189] A mixture of methyl-4-iodobenzoate (86.2g, 0.33 mol) and 2-methoxyphenyl boronic

acid (50.0 g, 0.33 mol) in toluene (975 mL) and EtOH (525 mL) was degassed with nitrogen bubbling for 30 minutes. $Pd(PPh_3)_4$ (19.0 g, 16.5 mmol) and 4M aqueous Na_2CO_3 (271.5 mL, 1.09 mol) were added and the mixture stirred at 100°C under a nitrogen atmosphere overnight. After cooling to room temperature, EtOAc (1.5 L) and water (1.5 L) were added, and the separated organic layer was dried (Na_2SO_4) and evaporated *in vacuo* to leave a brown oily solid (107 g). The residue was purified by column chromatography using an increasing gradient from 5-50% EtOAc/petrol to give title product as a yellow solid. Y: 51 g (64%), P>80%.

Step 2: synthesis of intermediate 2h 2'-methoxy-[1,1'-biphenyl]-4-carboxylic acid.

[0190] $LiOH.H_2O$ (89 g, 2.1 mol) was added to a stirred suspension of methyl 2'-methoxy-[1,1'-biphenyl]-4-carboxylate (51 g, 0.21 mol) in a mixture of THF (500 mL) and H_2O (1 L). Further amounts of THF (~500 mL) and H_2O (~1 L) were added to dissolve the majority of the solids. After stirring overnight at room temperature, more solids had precipitated and starting material still remained. The mixture was heated to 50°C for 4 hours, after which time all solids had dissolved and no starting material remained. After cooling to room temperature, saturated aqueous citric acid was added until pH = 6-7, which produced a white precipitate. THF was removed by evaporation *in vacuo* and the resulting suspension filtered. The solid was washed with water several times and dried at 50°C overnight to give intermediate **2h** as an off-white solid. Y: 43 g (90%), P>90%.

[0191] Route b is exemplified with the synthesis of intermediate **2s2** 4-(2-methoxypyrimidin-4-yl)benzoic acid.

Step 1: synthesis of methyl 4-(2-methoxypyrimidin-4-yl)benzoate.

[0192] In an oven dried glass tube, were introduced under argon 4-methoxycarbonylphenylboronic acid (381 mg, 2.116 mmol) and 4-bromo-2-methoxypyrimidine (200mg, 1.058 mmol).Three vacuum/Argon cycles were performed and toluene (5 mL) was added, followed by a 2M aqueous solution of K_2CO_3 (0.106 mmol). The resulting mixture was degassed (argon bubbling into the solution for 5-10 minutes).

[0193] Tetrakis(triphenylphosphine)palladium(0) (0.1 mmol) was then added and the mixture was heated to 95°C overnight. The mixture was cooled down to room temperature and then diluted with EtOAc and washed with brine. The aqueous layer was further extracted with EtOAc and the combined organic layers were dried and concentrated. The residue was purified on silica gel (cyclohexane / EtOAc), furnishing 243 mg of desired product as a pale yellow solid (94% yield).

Step 2: synthesis of intermediate 2s2 4-(2-methoxypyrimidin-4-yl)benzoic acid.

[0194] The same conditions as in step 2 of **route a** were used.

[0195] The following intermediates were synthesized from ad-hoc reagents using general method D **route b:**

intermediate **2i:** 2',5'-dichloro-[1,1'-biphenyl]-4-carboxylic acid;

intermediate **2j:** 4-(pyrimidin-5-yl)benzoic acid;

intermediate **2k:** 4-(furan-3-yl)benzoic acid;

intermediate **21:** 4-(6-methoxypyridin-3-yl)benzoic acid,

intermediate **2m:** 4-(3-fluoropyridin-4-yl)benzoic acid;

intermediate **2n:** 4-(pyridin-3-yl)benzoic acid;

intermediate **2o:** 4-(6-(dimethylamino)pyridin-3-yl)benzoic acid;

intermediate **2p:** 4-(pyridin-4-yl)benzoic acid;

intermediate **2q:** 4-(6-methylpyridin-3-yl)benzoic acid;

intermediate **2r:** 4-(2-methoxypyridin-3-yl)benzoic acid, rt=3.4 min (gradient A);

intermediate **2s:** 4'-methoxy-[1,1'-biphenyl]-4-carboxylic acid;

intermediate **2t:** 4'-cyano-[1,1'-biphenyl]-4-carboxylic acid;

intermediate **2u:** 4-(4-methoxypyridin-3-yl)benzoic acid;

intermediate **2v:** 4'-chloro-[1,1'-biphenyl]-4-carboxylic acid;

intermediate **2w:** 3'-chloro-[1,1'-biphenyl]-4-carboxylic acid;

intermediate **2x:** 2'-chloro-[1,1'-biphenyl]-4-carboxylic acid;

intermediate **2y:** 4'-(methylsulfonamido)-[1,1'-biphenyl]-4-carboxylic acid;

intermediate **2z:** 3'-(methylsulfonamido)-[1,1'-biphenyl]-4-carboxylic acid;

intermediate **2a1**: 2'-(methylsulfonamido)-[1,1'-biphenyl]-4-carboxylic acid;

intermediate **2b1**: 4-(naphthalen-2-yl)benzoic acid;

intermediate **2c1**: 3',5'-difluoro-[1,1'-biphenyl]-4-carboxylic acid;

intermediate **2d1**: 2'-hydroxy-[1,1'-biphenyl]-4-carboxylic acid;

intermediate **2e1**: 2'-(trifluoromethoxy)-[1,1'-biphenyl]-4-carboxylic acid;

intermediate **2f1**: 4-(3-fluoropyridin-4-yl)benzoic acid;

intermediate **2g1**: 4-(6-chloropyridin-3-yl)benzoic acid;

intermediate **2h1**: 4-(6-fluoropyridin-3-yl)benzoic acid;

intermediate **2i1**: 5-methoxy-6-phenylnicotinic acid;

intermediate **2j1**: 4-(3-methoxypyridin-4-yl)benzoic acid;

intermediate **2k1**: 2-methoxy-[1,1'-biphenyl]-4-carboxylic acid;

intermediate **2l1:** 4-(6-chloropyridin-3-yl)benzoic acid;

intermediate **2m1**: 4-(6-fluoropyridin-3-yl)benzoic acid;

intermediate **2n1**: 4-(thiophen-3-yl)benzoic acid;

intermediate **2o1**: 4-cyclohexylbenzoic acid;

intermediate **2p1**: 2'-(methylsulfonyl)-[1,1'-biphenyl]-4-carboxylic acid;

intermediate **2q1**: 4-(pyrimidin-2-yl)benzoic acid;

intermediate **2r1**: 4-(4,6-dimethoxypyrimidin-2-yl)benzoic acid;

intermediate **2s1**: 4-(2,4-dimethoxypyrimidin-5-yl)benzoic acid, rt=3.4 min (gradient A);

intermediate **2t1**: 4-(2-methoxypyrimidin-5-yl)benzoic acid;

intermediate **2u1**: 4-(pyridin-2-yl)benzoic acid;

intermediate **2v1**: 2'-cyano-[1,1'-biphenyl]-4-carboxylic acid;

intermediate **2w1**: 2',6'-dimethoxy-[1,1'-biphenyl]-4-carboxylic acid,

intermediate **2x1**: 2',4'-dichloro-[1,1'-biphenyl]-4-carboxylic acid;

intermediate **2y1:** 2'-(trifluoromethyl)-[1,1'-biphenyl]-4-carboxylic acid;

intermediate **2z1**: 2,2'-dimethoxy-[1,1'-biphenyl]-4-carboxylic acid;

intermediate **2a2:** 4'-chloro-2'-methoxy-[1,1'-biphenyl]-4-carboxylic acid;

intermediate **2b2:** 4-(4-methoxypyrimidin-5-yl)benzoic acid;

intermediate **2c2:** 4-(3-fluoropyridin-4-yl)benzoic acid;

intermediate **2d2:** 2-chlorobiphenyl-4-carboxylic acid;

intermediate **2e2:** 2'-chloro-2-methoxybiphenyl-4-carboxylic acid,

intermediate **2f2:** 3-methoxy-4-(pyrimidin-5-yl)benzoic acid;

intermediate **2g2:** 2'-(methoxymethyl)biphenyl-4-carboxylic acid;

intermediate **2h2:** 4-(2,6-dimethoxypyridin-3-yl)benzoic acid;

intermediate **2i2:** 3-methoxy-4-(2-methoxypyrimidin-5-yl)benzoic acid, rt=3.2 min (gradient A);

intermediate **2j2:** 4-(5-methoxypyrazin-2-yl)benzoic acid;

intermediate **2k2:** 4-(3-methoxypyrazin-2-yl)benzoic acid;

intermediate **2l2:** 4-(2-chloro-4-(dimethylamino)pyrimidin-5-yl)benzoic acid;

intermediate **2m2:** 4-(2,6-dimethoxypyrimidin-4-yl)benzoic acid;

intermediate **2n2:** 4-(2-methylthiophen-3-yl)benzoic acid;

intermediate **2o2:** methyl 2',6'-dichlorobiphenyl-4-carboxylate;

intermediate **2p2:** 2'-chloro-4'-methoxy-[1,1'-biphenyl]-4-carboxylic acid;

intermediate **2q2:** 2'-(dimethylamino)-[1,1'-biphenyl]-4-carboxylic acid;

intermediate **2r2:** 3-methoxy-[1,1'-biphenyl]-4-carboxylic acid;

intermediate **2t2:** 4-(2-chloro-4-methoxypyrimidin-5-yl)benzoic acid;

intermediate **2u2:** 4-(3-methoxypyridin-2-yl)benzoic acid;

intermediate **2v2:** 2-(trifluoromethyl)-[1,1'-biphenyl]-4-carboxylic acid;

intermediate **2w2:** 2',4'-difluoro-[1,1'-biphenyl]-4-carboxylic acid;

intermediate **2x2:** 2-methyl-[1,1'-biphenyl]-4-carboxylic acid;

intermediate **2y2:** 3-chloro-4-(pyrimidin-4-yl)benzoic acid;

intermediate **2z2:** 2-fluoro-[1,1'-biphenyl]-4-carboxylic acid;

intermediate **2a3:** 2'-fluoro-4'-methoxy-[1,1'-biphenyl]-4-carboxylic acid;

intermediate **2b3:** 4'-fluoro-2'-methoxy-[1,1'-biphenyl]-4-carboxylic acid;

intermediate **2c3:** 4-(6-ethoxypyridin-3-yl)benzoic acid;

intermediate **2d3:** 4-(6-isopropoxypyridin-3-yl)benzoic acid;

intermediate **2e3:** 4-(6-methoxy-2-methylpyridin-3-yl)benzoic acid;

intermediate **2f3:** 3-chloro-4-(2-methoxypyrimidin-4-yl)benzoic acid;

intermediate **2g3:** 3-chloro-4-(pyrimidin-5-yl)benzoic acid;

intermediate **2h3:** 2',3'-dimethoxy-[1,1'-biphenyl]-4-carboxylic acid;

intermediate **2i3:** 3',4'-dimethoxy-[1,1'-biphenyl]-4-carboxylic acid;

intermediate **2j3:** 2',3',4'-trimethoxy-[1,1'-biphenyl]-4-carboxylic acid;

intermediate **2k3:** 2',3',6'-trimethoxy-[1,1'-biphenyl]-4-carboxylic acid;

intermediate **2l3:** 3',5'-dimethoxy-[1,1'-biphenyl]-4-carboxylic acid;

intermediate **2m3:** 2',5'-dimethoxy-[1,1'-biphenyl]-4-carboxylic acid;

intermediate **2n3:** 2'-isopropyl-[1,1'-biphenyl]-4-carboxylic acid;

intermediate **2o3** ;2'-ethyl-[1,1'-biphenyl]-4-carboxylic acid;

intermediate **2p3** :4-(2,6-dimethylpyridin-3-yl)benzoic acid;

intermediate **2q3** :4-(2,4-bis(benzyloxy)pyrimidin-5-yl)benzoic acid;

intermediate **2r3** :3-chloro-4-(6-methoxypyridin-3-yl)benzoic acid;

intermediate **2s3** :5-methoxy-6-(2-methoxyphenyl)nicotinic acid;

intermediate **2t3** :5-methoxy-6-(2-methoxyphenyl)nicotinic acid;

intermediate **2u3** :3'-cyano-2'-methoxy-[1,1'-biphenyl]-4-carboxylic acid;

intermediate **2v3** :3'-cyano-2',4'-bis(2,2,2-trifluoroethoxy)-[1,1'-biphenyl]-4-carboxylic acid;

intermediate **2w3** :3'-amino-2'-methyl-[1,1'-biphenyl]-4-carboxylic acid;

intermediate **2x3:** 2'-methyl-3'-(methylsulfonamido)-[1,1'-biphenyl]-4-carboxylic acid was obtained by sulfonylation of methyl 3'-amino-2'-methyl-[1,1'-biphenyl]-4-carboxylate (which was synthesized using general method D, route b) and subsequent saponification. Sulfonylation procedure (as in J. Org. Chem. 2003, 68, 5300-5309): methyl 3'-amino-2'-methylbiphenyl-4-carboxylate (0.83 mmol) was dissolved in dry Et_2O (5 mL) and cooled to 0 °C. Then pyridine (5.00 mmol) was added, followed by dropwise addition of methanesulfonyl chloride (5.00 mmol). The reaction was stirred at RT for 2h. The precipitate was filtered and washed with Et_2O. The organic layer was washed with HCl 1M aqueous solution, brine, dried and concentrated, furnishing 265 mg of desired prioduct as a brown oil in a quantitative yield;

intermediate **2y3:** 3'-acetamido-2'-methyl-[1,1'-biphenyl]-4-carboxylic acid was obtained by acetylation of methyl 3'-amino-2'-methyl-[1,1'-biphenyl]-4-carboxylate (which was synthesized using general method D, route b) and subsequent saponification. Acetylation procedure: to a solution of methyl 3'-amino-2'-methylbiphenyl-4-carboxylate (0.83 mmol) in dry DCM (5 mL) under N_2 was added acetyl chloride (0.95 mmol), followed by Et_3N (0.91 mmol). The RM was stirred at RT overnight.The RM was then concentrated and the crude purified on silica gel (cyclohexane / EtOAc), furnishing 205 mg of desired product as a yellow oil (87% yield);

intermediate **2z3:** 5'-cyano-2'-methoxy-[1,1'-biphenyl]-4-carboxylic acid, rt=3.7 min (gradient A);

intermediate **2a4:** 5'-cyano-2'-methyl-[1,1'-biphenyl]-4-carboxylic acid, rt=3.9 min (gradient A);

intermediate **2b4:** 4-(4,6-dimethoxypyridin-3-yl)benzoic acid;

intermediate **2c4:** 4'-acetamido-2'-methoxy-[1,1'-biphenyl]-4-carboxylic acid was obtained by the nitro group reduction of methyl 2'-methoxy-4'-nitro-[1,1'-biphenyl]-4-carboxylate (which was synthesized using general method D, route b) followed by acetylation with acetyl chloride (procedure described in the synthesis of intermediate **2y3**) and saponification;

intermediate **2d4:** 3-methoxy-4-(5-methoxypyridin-3-yl)benzoic acid;

intermediate **2e4:** 2',3,6'-trimethoxy-[2,3'-bipyridine]-5-carboxylic acid;

intermediate **2f4:** 5'-cyano-2',3'-dimethoxy-[1,1'-biphenyl]-4-carboxylic acid;

intermediate **2g4:** 2'-cyano-4',5'-dimethoxy-[1,1'-biphenyl]-4-carboxylic acid;

intermediate **2h4:** 3',4',5'-trimethoxy-[1,1'-biphenyl]-4-carboxylic acid;

intermediate **2i4:** 2'-(cyanomethyl)-4',5'-dimethoxy-[1,1'-biphenyl]-4-carboxylic acid;

intermediate **2j4:** 3',4'-dicyano-[1,1'-biphenyl]-4-carboxylic acid;

intermediate **2k4:** 5'-cyano-2'-fluoro-[1,1'-biphenyl]-4-carboxylic acid;

intermediate **214:** 2-fluoro-3',4'-dimethoxy-[1,1'-biphenyl]-4-carboxylic acid;

intermediate **2m4:** 4-(2,6-dimethoxypyridin-3-yl)-3-fluorobenzoic acid;

intermediate **2n4:** 3-fluoro-4-(6-methoxypyridin-3-yl)benzoic acid;

intermediate **2r4:** 4-(3,6-dimethoxypyridazin-4-yl)benzoic acid, rt=3.2 min (gradient A);

intermediate **2s4:** 2'-cyano-4'-methoxy-[1,1'-biphenyl]-4-carboxylic acid;

intermediate **2u4:** 3'-cyano-4'-fluoro-[1,1'-biphenyl]-4-carboxylic acid;

intermediate **2v4:** 2'-chloro-5'-cyano-[1,1'-biphenyl]-4-carboxylic acid;

intermediate **2w4:** 2'-cyano-4'-(trifluoromethyl)-[1,1'-biphenyl]-4-carboxylic acid;

intermediate **2x4:** 2'-methyl-3'-(N-methylmethylsulfonamido)-[1,1'-biphenyl]-4-carboxylic acid was obtained by sulfonylation of methyl 3'-amino-2'-methyl-[1,1'-biphenyl]-4-carboxylate, followed by sulfonamide N-methylation with iodomethane, and subsequent saponification. Methyl 3'-amino-2'-methyl-[1,1'-biphenyl]-4-carboxylate was synthesized using general method D (route b); sulfonamide N-methylation procedure: in a glass tube was introduced methyl 2'-methyl-3'-(methylsulfonamido)biphenyl-4-carboxylate (0.438 mmol) and sodium hydride (0.570

mmol) in dry DMF (2 mL) at room temperature under argon atmosphere. After 30 minutes at room temperature, iodomethane (1.315 mmol) was added and the mixture was stirred at room temperature for 1.5 h. Brine was then added and the aqueous layer was extracted with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure, furnishing crude desired product as a pale yellow oil in a quantitative yield; rt=3.4 min (gradient A)

intermediate **2y4:** 6-(5-cyano-2-methoxyphenyl)-5-methoxynicotinic acid;

intermediate **2z4:** 6-(2,4-dimethoxyphenyl)-5-methoxynicotinic acid;

intermediate **2a5:** 6-(2,4-dimethoxyphenyl)nicotinic acid;

intermediate **2f5:** 4-(4,6-dimethoxypyrimidin-5-yl)benzoic acid.

[0196] Route c is exemplified for the synthesis of intermediate **2g5** 3-chloro-4-(2,4-dimethoxypyrimidin-5-yl)benzoic acid.

***Step 1*: synthesis of methyl 3-chloro-4-(2,4-dimethoxypyrimidin-5-yl)benzoate.**

[0197] In a oven dried glass tube were introduced under argon 2-chloro-4-(methoxycarbonyl)phenylboronic acid (2.0 mmol) and 5-iodo-2,4-dimethoxypyrimidine (1.0 mmol). The tube was subjected to three vacuum/argon cycles and toluene (5 mL) was added, followed by a 2M aqueous solution of K_2CO_3 (3.0 mmol). The resulting mixture was degassed (argon bubbling into the solution for 5-10 minutes). Tris(dibenzylideneacetone)dipalladium(0) (5%) and S-Phos (10%) were then added and mixture was heated to 95°C overnight. The mixture was cooled down to room temperature and then diluted with EtOAc and washed with brine. The aqueous layer was further extracted with EtOAc and the combined organic layers were dried and concentrated. The residue was purified on silica gel (cyclohex / EtOAc), furnishing 143 mg of desired product as a pale yellow solid (93% yield).

***Step 2*: saponification using same procedure of 2h synthesis.**

[0198] The following intermediates were synthesized from ad-hoc reagents using general method D **route c:**

intermediate **2h5:** 2-fluoro-2'-methoxy-[1,1'-biphenyl]-4-carboxylic acid;

intermediate **2j5:** 5-(2-methoxyphenyl)pyrazine-2-carboxylic acid;

intermediate **2k5:** 3-methoxy-4-(4-methoxypyridin-3-yl)benzoic acid;

intermediate **2l5:** 3-methoxy-4-(6-methoxypyridin-3-yl)benzoic acid;

intermediate **2m5:** 3-chloro-4-(2-methoxypyrimidin-5-yl)benzoic acid (exemplified above);

intermediate **2n5:** 4-(2,4-dimethoxypyrimidin-5-yl)-3-methoxybenzoic acid;

intermediate **2r4:** 4-(3,6-dimethoxypyridazin-4-yl)benzoic acid;

intermediate **2p5:** 2'-methoxy-4'-(methylsulfonamido)-[1,1'-biphenyl]-4-carboxylic acid was obtained by the nitro group reduction of methyl 2'-methoxy-4'-nitro-[1,1'-biphenyl]-4-carboxylate (which was synthesized using general method D, route c) followed by sulfonylation with methanesulfonyl chloride (procedure described in the synthesis of intermediate **2x3**) and saponification. Nitro reduction procedure: to a solution of methyl 2'-methoxy-4'-nitrobiphenyl-4-carboxylate (1.184 mmol) in anhydrous EtOH (35 ml) was added a slurry of Raney Ni in water (0.4 mL). The mixture was stirred at 50°C overnight. The RM was filtered on celite, and the solid was washed with MeOH. The filtrate was evaporated to yield desired product which was used without further purification;

intermediate **2q5:** 4-(2,6-dimethoxypyridin-3-yl)benzoic acid;

intermediate **2s5:** 2-fluoro-4'-(methylsulfonamido)-[1,1'-biphenyl]-4-carboxylic acid was obtained by sulfonylation of methyl 4'-amino-2-fluoro-[1,1'-biphenyl]-4-carboxylate and subsequent saponification, methyl 4'-amino-2-fluoro-[1,1'-biphenyl]-4-carboxylate was synthetized using general method D, route c;

intermediate **2t5:** 2-fluoro-3'-(methylsulfonamido)-[1,1'-biphenyl]-4-carboxylic acid was obtained by sulfonylation of methyl 3'-amino-2-fluoro-[1,1'-biphenyl]-4-carboxylate and subsequent saponification, methyl 3'-amino-2-fluoro-[1,1'-biphenyl]-4-carboxylate was synthetized using general method D, route c;

intermediate **2u5:** 2'-cyano-2-fluoro-[1,1'-biphenyl]-4-carboxylic acid;

intermediate **2v5:** 2'-methoxy-4'-(N-methylmethylsulfonamido)-[1,1'-biphenyl]-4-carboxylic acid was obtained by the nitro group reduction of 2'-methoxy-4'-nitro-[1,1'-biphenyl]-4-carboxylate, followed by sulfonylation with methanesulfonyl chloride, followed by sulfonamide N-methylation with iodomethane, and subsequent saponification; rt=3.7 min (gradient A). Methyl 2'-methoxy-4'-nitro-[1,1'-biphenyl]-4-carboxylate was synthesized using general method D (route c).

Intermediate **2w5** 4-(3,6-dimethoxypyridazin-4-yl)-3-fluorobenzoic acid which was obtained from methyl 4-bromo-3-fluorobenzoate and (3,6-dimethoxypyridazin-4-yl)boronic acid using a suzuki coupling procedure described in the literature (J. Org. Chem., 2008, 73, 2176-2181); rt=3.5 min (gradient A).

[0199] Unless otherwise stated compounds in examples **2** to **44** were synthesized from intermediate **1a** and commercially available carboxylic acids or acyl chlorides using general method C.

Example **2:** compound n°2: (2S,5R)-5-(2-chlorophenyl)-1-(2'-methyl-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid.

Example **3:** compound n°3: (2S,SR)-1-(3-((4-chlorobenzyl)oxy)-5-methoxybenzoyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid.

Example **4:** compound n°4: (2S,5R)-5-(2-chlorophenyl)-1-(2'-fluoro-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2b** using general method C.

Example **5:** compound n°5: (2S,5R)-5-(2-chlorophenyl)-1-(4'-methyl-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid.

Example **6:** compound n°6: (2S,5R)-5-(2-chlorophenyl)-1-(3-methoxy-5-phenethoxybenzoyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2c** using general method C.

Example **8:** compound n°8: (2S,5R)-1-([1,1'-biphenyl]-4-carbonyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid.

Example **9:** compound n°9: (2S,5R)-5-(2-chlorophenyl)-1-(3-(3,3-diphenylpropoxy)-5-methoxybenzoyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2d** using general method C.

Example **10:** compound n°10: (2S,5R)-5-(2-chlorophenyl)-1-(3'-fluoro-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid.

Example **11:** compound n°11: (2S,5R)-5-(2-chlorophenyl)-1-(3'-methyl-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid.

Example **12:** compound n°12: (2S,5R)-5-(2-chlorophenyl)-1-(3-methoxy-5-((4-(methylsulfonyl)benzyl)oxy)benzoyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2e** using general method C.

Example **13:** compound n°13: (2S,SR)-5-(2-chlorophenyl)-1-(3'-methoxy-[1,1'-biphenyl] -4-carbonyl)pyrrolidine-2-carboxylic acid.

Example **14:** compound n°14: (2S,5R)-5-(2-chlorophenyl)-1-(3,5-dimethoxybenzoyl)pyrrolidine-2-carboxylic acid.

Example **15:** compound n°15: (2S,5R)-5-(2-chlorophenyl)-1-(4-(phenoxymethyl)benzoyl)pyrrolidine-2-carboxylic acid.

Example **16:** compound n°16: (2S,5R)-5-(2-chlorophenyl)-1-(4-((2-fluorobenzyl)oxy)benzoyl)pyrrolidine-2-carboxylic acid.

Example **17:** compound n°17: (2S,5R)-1-(3-chloro-5-methoxybenzoyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid.

Example **18:** compound n°18: (2S,5R)-5-(2-chlorophenyl)-1-(4'-fluoro-[1,1'-biphenyl] -4-carbonyl)pyrrolidine-2-carboxylic acid.

Example **19:** compound n°19: (2S,5R)-5-(2-chlorophenyl)-1-(4-phenethoxybenzoyl)pyrrolidine-2-carboxylic acid.

Reference Example **20:** compound n°20: (2S,5R)-5-(2-chlorophenyl)-1-(chroman-3-carbonyl)pyrrolidine-2-carboxylic acid.

Example **21:** compound n°21: (2S,5R)-5-(2-chlorophenyl)-1-(3,5-diethoxybenzoyl)pyrrolidine-2-carboxylic acid.

Example **23:** compound n°23: (2S,5R)-5-(2-chlorophenyl)-1-(3-phenethoxybenzoyl)pyrrolidine-2-carboxylic acid.

Example **24:** compound n°24: (2S)-1-([1,1'-biphenyl]-4-carbonyl)-4-benzyl-5-phenylpyrrolidine-2-carboxylic acid was synthesized as described in scheme 24.

Example **25:** compound n°25: (2S,5R)-5-(2-chlorophenyl)-1-(1,2,3,4-tetrahydronaphthalene-2-carbonyl)pyrrolidine-2-carboxylic acid.

Example **26:** compound n°26: (2S,5R)-5-(2-chlorophenyl)-1-(4-isobutylbenzoyl)pyrrolidine-2-carboxylic acid.

Example **27:** compound n°27: (2S,5R)-5-(2-chlorophenyl)-1-(2,2-difluorobenzo[d][1,3]dioxole-6-carbonyl)pyrrolidine-2-carboxylic acid.

Example **28:** compound n°28: (2S,5R)-1-([1,1'-biphenyl]-4-carbonyl)-5-phenylpyrrolidine-2-carboxylic acid.

Example **29:** compound n°29: (2S,5R)-5-(2-chlorophenyl)-1-(3-fluoro-5-methoxybenzoyl)pyrrolidine-2-carboxylic acid.

Example **30:** compound n°30: (2S,5R)-5-(2-chlorophenyl)-1-(6-phenylnicotinoyl)pyrrolidine-2-carboxylic acid.

Example **31:** compound n°31: (2S,5R)-5-(2-chlorophenyl)-1-(3-methoxy-5-(2-methoxyethoxy)benzoyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2f** using general method C.

Example **32:** compound n°32: (2S,SR)-5-(2-chlorophenyl)-1-(3'-methoxy-[1,1'-biphenyl]-3-carbonyl)pyrrolidine-2-carboxylic acid.

Example **33:** compound n°33: (2S,5R)-5-(2-chlorophenyl)-1-(3-methoxy-5-(trifluoromethyl)benzoyl)pyrrolidine-2-carboxylic acid.

Example **34:** compound n°34: (2S,5R)-5-(2-chlorophenyl)-1-(1-(4-methoxyphenyl)-5-phenyl-1H-pyrazole-3-carbonyl)pyrrolidine-2-carboxylic acid.

Example **35:** compound n°35: (2S,5R)-5-(2-chlorophenyl)-1-(4-isopropoxybenzoyl)pyrrolidine-2-carboxylic acid.

Example **36:** compound n°36: (2S,SR)-5-(2-chlorophenyl)-1-(3-((3,5-dimethylisoxazol-4-yl)methoxy)-5-methoxybenzoyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2g** using general method C.

Example **37:** compound n°37: (2S,5R)-5-(2-chlorophenyl)-1-(2,3-dihydro-1H-indene-2-carbonyl)pyrrolidine-2-carboxylic acid.

Example **38:** compound n°38: (2S,5R)-5-(2-chlorophenyl)-1-(3-methyl-5-(trifluoromethoxy)benzoyl)pyrrolidine-2-carboxylic acid.

Example **39:** compound n°39: (2S,5R)-1-(3-(benzyloxy)benzoyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid.

Example **40:** compound n°40: (2S,5R)-5-(2-chlorophenyl)-1-(3-methoxybenzoyl)pyrrolidine-2-carboxylic acid.

Example **41:** compound n°41: (2S,5R)-5-(2-chlorophenyl)-1-(2-phenylpyrimidine-5-carbonyl)pyrrolidine-2-carboxylic acid.

Example **42:** compound n°42: (2S,5R)-5-(2-chlorophenyl)-1-(4-(trifluoromethoxy)benzoyl)pyrrolidine-2-carboxylic acid.

Example **43:** compound n°43: (2S,5R)-5-(2-chlorophenyl)-1-(4-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)benzoyl)pyrrolidine-2-carboxylic acid.

Example **44:** compound n°44: 4-((2S,5R)-2-carboxy-5-(2-chlorophenyl)pyrrolidine-1-carbonyl)-2,6-dimethoxypyrimidin-1-ium formate.

Example **45:** compound n°45: (2S,5R)-5-(2-chlorophenyl)-1-(4-phenylbutanoyl)pyrrolidine-2-carboxylic acid.

Example **46:** compound n°46: (2S,5R)-5-(2-chlorophenyl)-1-(3-methyl-5-(trifluoromethyl)benzoyl)pyrrolidine-2-carboxylic acid.

Example **47:** compound n°47: (2S,5R)-1-([1,1'-biphenyl]-4-carbonyl)-5-(3-chloropyridin-2-yl)pyrrolidine-2-carboxylic acid was synthesized from intermediate **1c** using general method C.

Example **48:** compound n°48: (2S,5R)-5-(2-chlorophenyl)-1-(3-hydroxy-5-(trifluoromethyl)benzoyl)pyrrolidine-2-carboxylic acid.

Example **49:** compound n°49: (2S,5S)-5-(2-chlorophenyl)-1-(3-methoxybenzoyl)pyrrolidine-2-carboxylic acid was synthesized from intermediate **1b** using general method C.

Example **50:** compound n°50: (2S,5R)-1-(3,5-dimethoxybenzoyl)-5-phenylpyrrolidine-2-carboxylic acid was synthesized from intermediate **Id** ((2S,5R)-methyl 5-phenylpyrrolidine-2-carboxylate). **Id** was synthesized from commercially available (2S,5R)-1-(*tert*-

butoxycarbonyl)-5-phenylpyrrolidine-2-carboxylic acid using the synthetic steps described in scheme 4.

Example **51:** compound n°51: (S)-5-([1,1'-biphenyl]-3-yl)-1-(3-methoxybenzoyl)pyrrolidine-2-carboxylic acid was synthesized from intermediate **1e** using general method C.

Example **52:** compound n°52: (2S,5R)-5-(2-chlorophenyl)-1-(3-phenylpropanoyl)pyrrolidine-2-carboxylic acid.

Example **53:** compound n°53: (2S,5S)-5-(2-chlorophenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid was synthesized from intermediate **1b** using general method C.

Example **54:** compound n°54: (2S,SR)-1-([1,1'-biphenyl]-4-carbonyl)-5-(pyridin-2-yl)pyrrolidine-2-carboxylic acid was synthesized from intermediate **If** using general method C.

Example **55:** compound n°55: (2S,5R)-5-(2-chlorophenyl)-1-(5-phenylpicolinoyl)pyrrolidine-2-carboxylic acid.

Example **57:** compound n°57: (2S,5R)-5-(2-fluorophenyl)-1-(3-methoxybenzoyl)pyrrolidine-2-carboxylic acid was synthesized from intermediate **1g** using general method C.

Reference Example **58:** compound n°58: (2S,5R)-1-(2-([1,1'-biphenyl]-4-yl)acetyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid.

Example **59:** compound n°59: (2R,5S)-1-([1,1'-biphenyl]-4-carbonyl)-5-phenylpyrrolidine-2-carboxylic acid was synthesized from intermediate **1h** using general method C. **1h** was synthesized from commercially available *(*2R,5S*)*-1-(*tert*-butoxycarbonyl)-5-phenylpyrrolidine-2-carboxylic acid using the synthetic steps described in scheme 4.

Reference Example **60:** compound n°60: (2S,5R)-5-phenyl-1-(2-phenylacetyl)pyrrolidine-2-carboxylic acid was synthesized from intermediate **Id** using general method C.

Reference Example **61:** compound n°61: (2R,5S)-5-phenyl-1-(2-phenylacetyl)pyrrolidine-2-carboxylic acid was synthesized from intermediate **1h** using general method C.

Example **62:** compound n°62: (2S,5R)-1-(3-methoxybenzoyl)-5-(2-methoxyphenyl)pyrrolidine-2-carboxylic acid was synthesized from intermediate **1i** using general method C.

Example **63:** compound n°63: (2R,5S)-5-(2-chlorophenyl)-1-(3-methoxybenzoyl)pyrrolidine-2-carboxylic acid was synthesized from intermediate **1j** using general method C.

Example **64:** compound n°64: (2R,5R)-5-(2-chlorophenyl)-1-(3-methoxybenzoyl)pyrrolidine-2-carboxylic acid was synthesized from intermediate **1j** using general method C.

Example **65:** compound n°65: (2S)-5-(4-chlorophenyl)-1-(3-methoxybenzoyl)pyrrolidine-2-carboxylic acid was synthesized from intermediate **1k** using general method C.

Example **66:** compound n°66: (2S)-5-([1,1'-biphenyl]-4-yl)-1-(3-methoxybenzoyl)pyrrolidine-2-

carboxylic acid was synthesized from intermediate **1l** using general method C.

Example **67:** compound n°67: (2S,5R)-methyl 5-(2-chlorophenyl)-1-(3-methoxybenzoyl)pyrrolidine-2-carboxylate was synthesized using general method C without the last saponification step.

Reference Example **68:** compound n°68: (2S)-5-(2-chlorobenzyl)-1-(3-methoxybenzoyl)pyrrolidine-2-carboxylic acid was synthesized from intermediate **1m** using general method C.

Example **69:** compound n°69: (2S)-5-cyclohexyl-1-(3-methoxybenzoyl)pyrrolidine-2-carboxylic acid was synthesized from intermediate **1n** using general method C.

Reference Example **70:** compound n°70: (2S,5R)-5-(2-chlorophenyl)-1-(2-(3-methoxyphenyl)acetyl)pyrrolidine-2-carboxylic acid.

Example **71:** compound n°71: (2S,5S)-5-(2-chlorophenyl)-1-(3,5-dimethoxybenzoyl)pyrrolidine-2-carboxylic acid was synthesized from intermediate **1b** using general method C.

Example **72:** compound n°72: (2S,5R)-5-([1,1'-biphenyl]-2-yl)-1-(3-methoxybenzoyl)pyrrolidine-2-carboxylic acid was synthesized from intermediate **1o** using general method C.

Reference **74:** compound n°74: 2-((2S,5R)-5-(2-chlorophenyl)-1-(3-methoxybenzoyl)pyrrolidin-2-yl)acetic acid. Compound n°40 was reacted with ethyl chloroformate (1.03 eq) in THF in the presence of triethylamine (1.03 eq) and then was added a solution of diazomethane in diethyl ether (2 eq), the mixture was stirred at RT for 2.5 days. Reaction mixture was quenched with a 10% aqueous solution of citric acid and diluted with diethyl ether. The organic layer was washed with a saturated aqueous solution of sodium bicarbonate and brine, then concentrated in vacuo. The residue was dissolved in MeOH and silver benzoate (1 eq) and triethylamine (2 eq) were added. The RM was stirred at RT for 45 min and diluted with AcOEt, washed with a saturated aqueous solution of sodium bicarbonate and brine 1M aqueous HCl, dried over anhydrous $MgSO_4$ and evaporated to dryness to yield title compound.

Example **75:** compound n°75: (2S,5R)-5-(2-chlorophenyl)-1-(6-phenylpyrimidine-4-carbonyl)pyrrolidine-2-carboxylic acid.

Example **76:** compound n°77: (2S,5R)-5-(2-chlorophenyl)-1-(6-(2-chlorophenyl)nicotinoyl)pyrrolidine-2-carboxylic acid.

Example **77:** compound n°78: (2S,5R)-5-(2-chlorophenyl)-1-(6-(2-methoxyphenyl)nicotinoyl)pyrrolidine-2-carboxylic acid.

Example **78:** compound n°79: (2S,5R)-5-(2-chlorophenyl)-1-(6-(3-fluorophenyl)nicotinoyl)pyrrolidine-2-carboxylic acid.

Example **79:** compound n°80: (2S,5R)-5-(2-chlorophenyl)-1-(6-(3-methoxyphenyl)nicotinoyl)pyrrolidine-2-carboxylic acid.

Example **80:** compound n°81: (2S,5R)-5-(2-chlorophenyl)-1-(6-(4-methoxyphenyl)nicotinoyl)pyrrolidine-2-carboxylic acid.

Example **81:** compound n°82: (2S,5R)-5-(2-chlorophenyl)-1-(6-(4-fluorophenyl)nicotinoyl)pyrrolidine-2-carboxylic acid.

Example **82:** compound n°83: (2S,5R)-5-(2-chlorophenyl)-1-(2-(2-chlorophenyl)pyrimidine-5-carbonyl)pyrrolidine-2-carboxylic acid.

Example **83:** compound n°84: (2S,5R)-5-(2-chlorophenyl)-1-(2-methyl-6-phenylnicotinoyl)pyrrolidine-2-carboxylic acid.

Example **84:** compound n°88: (2S,5R)-5-(2-chlorophenyl)-1-(4-(pyridin-2-yl)benzoyl)pyrrolidine-2-carboxylic acid was was synthesized from intermediates **1a** and **2u1** using general method C.

Example **85:** compound n°89: (2S,5R)-1-(4-((4-chlorophenoxy)methyl)benzoyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid.

Example **86:** compound n°91: (2S,5R)-5-(2-chlorophenyl)-1-(4-((4-methoxyphenoxy)methyl)benzoyl)pyrrolidine-2-carboxylic acid.

Example **87:** compound n°92: (2S,5R)-1-(4-((2-chlorophenoxy)methyl)benzoyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid was synthesized from intermediate **1b** using general method C.

Example **88:** compound n°95: (2S,5R)-1-(4-((3-chlorophenoxy)methyl)benzoyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid.

Example **89:** compound n°96: (2S,5R)-5-(2-chlorophenyl)-1-(4-((p-tolyloxy)methyl)benzoyl)pyrrolidine-2-carboxylic acid.

Example **90:** compound n°99: (2S,5R)-5-(2-chlorophenyl)-1-(4-((3,5-dimethylisoxazol-4-yl)methoxy)benzoyl)pyrrolidine-2-carboxylic acid.

Example **91:** compound n°102: (2S,5R)-5-(2-chlorophenyl)-1-(4-(pyridin-4-ylmethoxy)benzoyl)pyrrolidine-2-carboxylic acid.

Example **92:** compound n°104: (2S,5R)-5-(2-chlorophenyl)-1-(4-(5-methyl-1H-pyrazol-1-yl)benzoyl)pyrrolidine-2-carboxylic acid.

Example **93:** compound n°105: (2S,5R)-5-(2-chlorophenyl)-1-(4-(isoxazol-5-yl)benzoyl)pyrrolidine-2-carboxylic acid.

Example **94:** compound n°106: (2S,5R)-1-(4-(4H-1,2,4-triazol-4-yl)benzoyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid.

Example **95:** compound n°107: (2S,5R)-5-(2-chlorophenyl)-1-(4-(5-(p-tolyl)-1H-1,2,3-triazol- 1-yl)benzoyl)pyrrolidine-2-carboxylic acid.

Example **96:** compound n°108: (2S,5R)-5-(2-chlorophenyl)-1-(4-(5-oxo-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl)benzoyl)pyrrolidine-2-carboxylic acid.

Example **97:** compound n°109: (2S,5R)-5-(2-chlorophenyl)-1-(4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzoyl)pyrrolidine-2-carboxylic acid.

Example **98:** compound n°110: (2S,5R)-1-(4-(1H-pyrazol-1-yl)benzoyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid.

Example **99:** compound n°111: (2S,5R)-5-(2-chlorophenyl)-1-(4-(oxazol-5-yl)benzoyl)pyrrolidine-2-carboxylic acid.

Example **100:** compound n°112: (2S,5R)-5-(2-chlorophenyl)-1-(4-(3,5-dimethyl-1H-pyrazol- 1-yl)benzoyl)pyrrolidine-2-carboxylic acid.

Example **101:** compound n°113: (2S,5R)-5-(2-chlorophenyl)-1-(2',5'-dichloro-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2i** using general method C.

Example **102:** compound n°114: (2S,5R)-5-(2-chlorophenyl)-1-(4-(pyrimidin-5-yl)benzoyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2j** using general method C.

Example **103:** compound n°115: (2S,5R)-5-(2-chlorophenyl)-1-(4-(furan-3-yl)benzoyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2k** using general method C.

Example **104:** compound n°116: (2S,5R)-5-(2-chlorophenyl)-1-(4-(6-methoxypyridin-3-yl)benzoyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2l** using general method C.

Example **105:** compound n°117: (2S,5R)-5-(2-chlorophenyl)-1-(4-(3-fluoropyridin-4-yl)benzoyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2m** using general method C.

Example **106:** compound n°118: (2S,5R)-5-(2-chlorophenyl)-1-(4-(pyridin-3-yl)benzoyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2n** using general method C.

Example **107:** compound n°119: (2S,5R)-5-(2-chlorophenyl)-1-(4-(6-(dimethylamino)pyridin-3-yl)benzoyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2o** using general method C.

Example **108:** compound n°120: (2S,SR)-5-(2-chlorophenyl)-1-(4-(pyridin-4-yl)benzoyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2p** using general method C.

Example **109:** compound n°121: (2S,5R)-5-(2-chlorophenyl)-1-(4-(6-methylpyridin-3-yl)benzoyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2q** using general method C.

Example **110:** compound n°122: (2S,5R)-5-(2-chlorophenyl)-1-(4-(2-methoxypyridin-3-yl)benzoyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2r** using general method C.

Example **111**: compound n°123: (2S,SR)-5-(2-chlorophenyl)-1-(4'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2s** using general method C.

Example **112:** compound n°124: (2S,5R)-5-(2-chlorophenyl)-1-(4'-cyano-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2t** using general method C.

Example **113:** compound n°125: (2S,5R)-5-(2-chlorophenyl)-1-(4-(4-methoxypyridin-3-yl)benzoyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2u** using general method C.

Example **114:** compound n°126: (2S,5R)-1-(4'-chloro-[1,1'-biphenyl]-4-carbonyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2v** using general method C.

Example **115:** compound n°127: (2S,5R)-1-(3'-chloro-[1,1'-biphenyl]-4-carbonyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2w** using general method C.

Example **116:** compound n°128: (2S,5R)-1-(2'-chloro-[1,1'-biphenyl]-4-carbonyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2x** using general method C.

Example **117:** compound n°129: (2S,5R)-5-(2-chlorophenyl)-1-(4'-(methylsulfonamido)- [1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2y** using general method C.

Example **118:** compound n°130: (2S,5R)-5-(2-chlorophenyl)-1-(3'-(methylsulfonamido)- [1,1'-biphenyl] -4-carbonyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2z** using general method C.

Example **119:** compound n°131: (2S,SR)-5-(2-chlorophenyl)-1-(2'-(methylsulfonamido)- [1,1 '-biphenyl] -4-carbonyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2a1** using general method C.

Example **120:** compound n°132: (2S,5R)-5-(2-chlorophenyl)-1-(4-(naphthalen-2-yl)benzoyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2b1** using general method C.

Example **121:** compound n°133: (2S,5R)-5-(2-chlorophenyl)-1-(3',5'-difluoro-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2c1** using general method C.

Example **122:** compound n°134: (2S,5R)-5-(2-chlorophenyl)-1-(2'-hydroxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2d1** using general method C.

Example **123:** compound n°135: (2S,5R)-5-(2-chlorophenyl)-1-(2'-(trifluoromethoxy)-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2e1** using general method C.

Example **124:** compound n°136: (2S,5R)-1-(2'-(benzyloxy)-[1,1'-biphenyl]-4-carbonyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid.

Example **125:** compound n°137: (2S,SR)-5-(2-chlorophenyl)-1-(2'-phenoxy-[1,1'-biphenyl] -4-carbonyl)pyrrolidine-2-carboxylic acid.

Example **126:** compound n°138: (2S,SR)-5-(2-chlorophenyl)-1-(2'-isopropoxy-[1,1'-biphenyl] -4-carbonyl)pyrrolidine-2-carboxylic acid.

Example **127:** compound n°139: (2S,SR)-5-(2-chlorophenyl)-1-(2'-isobutoxy-[1,1'-biphenyl] -4-carbonyl)pyrrolidine-2-carboxylic acid.

Example **128:** compound n°140: (2S,SR)-5-(2-chlorophenyl)-1-(2'-(cyclopropylmethoxy)-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid.

Example **129:** compound n°141: (2S,SR)-5-(2-chlorophenyl)-1-(2'-((4-fluorobenzyl)oxy)-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid.

Example **130:** compound n°142: (2S,5R)-5-(2-chlorophenyl)-1-(4-(6-chloropyridin-3-yl)benzoyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2l1** using general method C.

Example **131:** compound n°143: (2S,5R)-5-(2-chlorophenyl)-1-(4-(6-fluoropyridin-3-yl)benzoyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2m1** using general method C.

Example **132:** compound n°149: (2S,5R)-5-(2-chlorophenyl)-1-(4-(thiophen-3-yl)benzoyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2n1** using general method C.

Example **133:** compound n°150: (2S,5R)-5-(2-chlorophenyl)-1-(4-cyclohexylbenzoyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2o1** using general method C.

Example **134:** compound n°152: (2S,5R)-5-(2-chlorophenyl)-1-(9-oxo-9H-fluorene-2-carbonyl)pyrrolidine-2-carboxylic acid.

Example **135:** compound n°153: (2S,5R)-5-(2-chlorophenyl)-1-(2'-(methylsulfonyl)-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2p1** using general method C.

Reference Example **136:** compound n°155: (2S,5R)-5-(2-chlorophenyl)-1-(9-methyl-9H-carbazole-2-carbonyl)pyrrolidine-2-carboxylic acid.

Example **137:** compound n°156: (2S,5R)-5-(2-chlorophenyl)-1-(4-phenoxybenzoyl)pyrrolidine-2-carboxylic acid.

Example **138:** compound n°157: (2S,5R)-1-(4-benzylbenzoyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid.

Example **139:** compound n°158: (2S,5R)-1-(4-benzoylbenzoyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid.

Example **140:** compound n°159: (2S,5R)-5-(2-chlorophenyl)-1-(4-(pyrimidin-2-yl)benzoyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2q1** using general method C.

Example **141:** compound n°160: (2S,5R)-5-(2-chlorophenyl)-1-(4-(4,6-dimethoxypyrimidin-2-yl)benzoyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2r1** using general method C.

Example **142:** compound n°161: (2S,5R)-5-(2-chlorophenyl)-1-(4-(2,4-dimethoxypyrimidin-5-yl)benzoyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2s1** using general method C.

Example **143:** compound n°162: (2S,5R)-5-(2-chlorophenyl)-1-(4-(2-methoxypyrimidin-5-yl)benzoyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2t1** using general method C.

Example **144:** compound n°168: (2S,5R)-5-(2-chlorophenyl)-1-(cyclohexanecarbonyl)pyrrolidine-2-carboxylic acid.

Example **145:** compound n°169: (2S,5R)-5-(2-chlorophenyl)-1-(4-methylpentanoyl)pyrrolidine-2-carboxylic acid.

Example **146:** compound n°172: (2S,5R)-5-(2-chlorophenyl)-1-(4-(4-methylpiperidin-1-yl)-3-nitrobenzoyl)pyrrolidine-2-carboxylic acid.

Example **147:** compound n°173: (2S,5R)-5-(2-chlorophenyl)-1-(4-(2-oxopiperidin-1-yl)benzoyl)pyrrolidine-2-carboxylic acid.

Example **148:** compound n°174: (2S,5R)-5-(2-chlorophenyl)-1-(3-methyl-4-morpholinobenzoyl)pyrrolidine-2-carboxylic acid.

Example **149:** compound n°175: (2S,5R)-5-(2-chlorophenyl)-1-(4-(piperidin-1-yl)benzoyl)pyrrolidine-2-carboxylic acid.

Example **150:** compound n°176: (2S,5R)-5-(2-chlorophenyl)-1-(4-morpholinobenzoyl)pyrrolidine-2-carboxylic acid.

Example **151:** compound n°177: (2S,5R)-5-(2-chlorophenyl)-1-(1-(2-cyanophenyl)piperidine-4-carbonyl)pyrrolidine-2-carboxylic acid.

Example **152:** compound n°178: (2S,5R)-5-(2-chlorophenyl)-1-(4-(4-chlorophenyl)cyclohexanecarbonyl)pyrrolidine-2-carboxylic acid.

Example **153:** compound n°179: (2S,5R)-5-(2-chlorophenyl)-1-(4-phenylcyclohexanecarbonyl)pyrrolidine-2-carboxylic acid.

Reference Example **154:** compound n°183: ((2R,5S)-2-(2-chlorophenyl)-5-(1H-tetrazol-5-yl)pyrrolidin-1-yl)(2'-methoxy-[1,1'-biphenyl]-4-yl)methanone:

Step 1: synthesis of (2S,5R)-5-(2-chlorophenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine- 2 -carboxamide.

In a glass tube containing compound n°1 (0.2 g, 0.459 mmol) in THF (5 mL) were added CDI (0.167 g, 0.11 mmol). The RM was stirred at RT for 30mn, then NH_3 bubbling in the RM for 1 mn. The RM was diluted with HCl 1M and extracted with EtOAc. The organic layer was dried overnight over MgSO4. The RM was concentrated in vacuo and the residue (164 mg) diluted in MeCN and passed through a new PE-AX (2 g) cartridge. The filtrate was concentrated to yield title intermediate. Y: 0.14 g (70%), P> 80%, rt=4.08 mn (gradient A).

Step 2: synthesis of (2S,5R)-5-(2-chlorophenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carbonitrile.

In a 50 mL round bottom flask containing (2S,5R)-5-(2-chlorophenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxamide (0.14 g, 0.322 mmol) were added DMF (3.22 mL). The RM was degassed and placed under Ar. Cyanuric chloride (0.059 g, 0.322 mmol) was added and the RM stirred at RT for 90 mn.The RM was diluted with $NaHCO_3$ (aqueous saturated solution) and extracted with AcOEt. The organic phase was washed with brine (2x), dried over $MgSO_4$ filtered and concentrated to afford 126mg of title product. Y: 0.126 g (94%), P > 80%, rt = 4.53 mn (gradient A), $(M+H)^+$ =417 /419.

Step 3: synthesis of compound n° 183.

In a oven-dried glass tube were added under Ar sodium azide (0.086 g, 1.330 mmol) and THF (5 mL). Were added successively aluminium chloride (0.101 g, 0.756 mmol) and (2S,5R)-5-(2-chlorophenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carbonitrile (0.126 g, 0.302 mmol) diluted in 1mL THF. The RM was heated at 60°C overnight. Sodium azide (0.086 g, 1.33 mmol) and aluminium chloride (0.101 g, 0.756 mmol) were added and the RM stirred at 60°C for another 7h. The RM was allowed to reach RT and quenched with HCl 6N and extracted with AcOEt (2x). The organic layer was dried over $MgSO_4$, filtered and concentrated to afford 160mg of crude product as a yellow oil. Crude was purified by flash chromatography (DCM/MeOH : 95/5) and SPE using a PEAX cartridge and elution with ACN, then ACN + HCl. Crude in MeCN solution from the PEAX fractions were concentrated in vacuo. Residue

lyophilized in ACN/Water (2 mL / 1 mL). Y: 13mg (9%), P=100 %, rt =5.19 mn (gradient B), $(M+H)^+$=460.

Example **155:** compound n°184: (2R,5S)-5-(2-chlorophenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1j** and **2h** using general method C.

Example **160:** compound n°189: (2S,5R)-5-(2-chlorophenyl)-1-(6-(2-fluorophenyl)nicotinoyl)pyrrolidine-2-carboxylic acid.

Example **162:** compound n°191: (2S,5R)-5-(2-chlorophenyl)-1-(5-methoxy-6-phenylnicotinoyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2i1** using general method C.

Example **163:** compound n°192: (2S,5R)-5-(2-chlorophenyl)-1-(4-(2-methoxyphenoxy)benzoyl)pyrrolidine-2-carboxylic acid.

Example **164:** compound n°193: (2S,5R)-5-(2-chlorophenyl)-1-(4-(3-methoxypyridin-4-yl)benzoyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2j1** using general method C.

Example **165:** compound n°194: (2S)-5-(2-chlorophenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)-4,4-dimethylpyrrolidine-2-carboxylic acid was synthesized from intermediates **1p** and **2h** using general method C.

Example **166:** compound n°195: (2S)-5-(2-chlorophenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)-4-methylpyrrolidine-2-carboxylic acid was synthesized from intermediates **1q** and **2h** using general method C.

Example **167:** compound n°196: (2S,5R)-5-(2-chlorophenyl)-1-(2-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2k1** using general method C.

Example **168:** compound n°197: (2S,5R)-5-(2-chlorophenyl)-1-(2'-cyano-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2v1** using general method C.

Example **169:** compound n°198: (2S,5R)-5-(2-chlorophenyl)-1-(2',6'-dimethoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2w1** using general method C.

Example **170:** compound n°199: (2S,5R)-5-(2-chlorophenyl)-1-(2',4'-dichloro-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2x1** using general method C.

Example **171:** compound n°200: (2S,SR)-5-(2-chlorophenyl)-1-(2'-(trifluoromethyl)-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2y1** using general method C.

Example **172:** compound n°201: (2S,5R)-5-(2-chlorophenyl)-1-(2,2'-dimethoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2z1** using general method C.

Example **173:** compound n°202: (2S,5R)-1-(4'-chloro-2'-methoxy-[1,1'-biphenyl]-4-carbonyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2a2** using general method C.

Example **174:** compound n°203: (2S,5R)-5-(2-chlorophenyl)-1-(4-(4-methoxypyrimidin-5-yl)benzoyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2b2** using general method C.

Example **175:** compound n°204: (2S,5R)-5-(2-chlorophenyl)-1-(2',4'-dimethoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2c2** using general method C.

Example **176:** compound n°205: (2S,5R)-1-([1,1'-biphenyl]-4-carbonyl)-5-(pyridin-3-yl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1r** using general method C.

Example **177:** compound n°206: (2R,5R)-5-(2-chlorophenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid was synthesized from intermediate **1j** using general method C.

Example **178:** compound n°207: (2S,5R)-5-(2-chlorophenyl)-1-(1-phenyl-1H-benzo[d]imidazole-5-carbonyl)pyrrolidine-2-carboxylic acid.

Example **179:** compound n°208: (2S,5R)-methyl 5-(2-chlorophenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylate was obtained in step 1 of general method C.

Example **180:** compound n°217: (2S,4S,5S)-5-(2-chlorophenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)-4-(phenylsulfonyl)pyrrolidine-2-carboxylic acid was synthesized using the methodology described in **scheme 9.**

Example **181:** compound n°220: (2S,5R)-5-(2-chlorophenyl)-4-cyano-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid was synthesized using the methodology described in **scheme 9.**

Example **182:** compound n°224: (2S,5R)-1-(2-chloro-[1,1'-biphenyl]-4-carbonyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2d2** using general method C.

Example **183:** compound n°225: (2S,SR)-1-(2'-chloro-2-methoxy-[1,1'-biphenyl]-4-carbonyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2e2** using general method C.

Example **184:** compound n°226: (2S,5R)-5-(2-chlorophenyl)-1-(2'-(2-methoxyethoxy)-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid was synthesized from intermediate **1a** and

2'-(2-methoxyethoxy)biphenyl-4-carboxylic acid which was obtained by saponification of methyl 2'-(2-methoxyethoxy)biphenyl-4-carboxylate. The latter intermediate was prepared using Mitsunobu chemistry:
To a solution of methyl 2'-hydroxybiphenyl-4-carboxylate (300 mg, 1.31 mmol), triphenylphosphine (517 mg, 1.97 mmol) and 2-methoxyethanol (130 µL, 1.64 mmol) in THF (12.5 mL) was added slowly diisopropylazodicarboxylate (388 µL, 1.97 mmol) at 0°C. The mixture was stirred at RT overnight and the reaction was quenched with methanol. The reaction mixture was diluted with water and extracted with DCM (25 mL). The organic layer was washed with water, dried and concentrated in vacuo. Crude was purified by column chromatography (cyclohexane/ EtOAc = 1/1) to yield 2'-(2-methoxyethoxy)biphenyl-4-carboxylate as a yellow oil. Y: 450 mg (78 %), P: 65%, rt= 2.5 mn (gradient A), Rf (cyclohexane/EtOAc = 95/5)=0.75.

Example **185:** compound n°230: (2S,5R)-5-(2-chlorophenyl)-1-(3-methoxy-4-(pyrimidin-5-yl)benzoyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2f2** using general method C.

Example **186:** compound n°231: (2S,SR)-1-(2'-carbamimidoyl-[1,1'-biphenyl]-4-carbonyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid.

Step 1: To a solution of compound n° 197 precursor (2S,5R)-methyl-5-(2-chlorophenyl)-1- (2'-cyano- [1,1 '-biphenyl] -4-carbonyl)pyrrolidine-2-carboxylate (100 mg, 0.225 mmol) and hydoxylamine hydrochloride (32 mg, 0.45 mmol) in EtOH (1 mL) was triethylamine(64 µL, 0.45 mmol) dropwise at room temperature. The mixture was stirred at reflux for 2 days. The mixture was cooled to RT and concentrated. Crude was purified by column chromatography (DCM/ MeOH = 98/2) to yield (2S,5R)-methyl-5-(2-chlorophenyl)-1-(2'-((E)-N'-hydroxycarbamimidoyl)biphenylcarbonyl)pyrrolidine-2-carboxylate as a colorless solid. Y: 113 mg (63 %), P: >80%, rt= 3.6 mn (gradient A), Rf (DCM/ MeOH = 9/1)=0.3.

Step 2:
A solution of (2S,5R)-methyl-5-(2-chlorophenyl)-1-(2'-((E)-N'-hydroxycarbamimidoyl)biphenylcarbonyl)pyrrolidine-2-carboxylate in (EtOH/THF/AcOH=1/1/0.025) (2 mL) was hydrogenated at RT for 45 min. under atmospheric pressure of H_2 using a slurry solution of Raney nickel catalyst in water (2 vacuum/N2 cycles and then 2 vacuum/H_2 cycles). The catalyst was filtered off over Celite and the filtrate was concentrated in vacuo to yield (2S,5R)-methyl 1-(2'-carbamimidoylbiphenylcarbonyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylate as a greenish solid. Y: 64 mg (99 %), P: 70%, rt= 3.5 mn (gradient A).

Step 3:
(2S,5R)-methyl 1-(2'-carbamimidoylbiphenylcarbonyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylate was saponified as exemplified in general method C to provide compound n° 231.

Example **187:** compound n°232: (2S,5R)-5-(2-fluorophenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1g** using general method C.

Example **188:** compound n°233: (2S,5R)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)-5-(o-tolyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1s** using general method C.

Example **189:** compound n°234: (2S,5R)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)-5-(2-methoxyphenyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1i** using general method C.

Example **190:** compound n°235: (2S,5R)-5-(2-chlorophenyl)-1-(2'-(methoxymethyl)-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2g2** using general method C.

Example **191:** compound n°236: (2S,5R)-5-(2-chlorophenyl)-1-(4-(2,6-dimethoxypyridin-3-yl)benzoyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2h2** using general method C.

Example **192:** compound n°237: (2S,5R)-5-(2-chlorophenyl)-1-(3-methoxy-4-(2-methoxypyrimidin-5-yl)benzoyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2i2** using general method C.

Example **193:** compound n°238: (2S,5R)-5-(2-chlorophenyl)-1-(4-(5-methoxypyrazin-2-yl)benzoyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2j2** using general method C.

Example **194:** compound n°239: (2S,5R)-5-(2-chlorophenyl)-1-(4-(2-(2-methoxyethoxy)pyridin-3-yl)benzoyl)pyrrolidine-2-carboxylic acid was synthesized from intermediate **1a** and 4-(2-(2-methoxyethoxy)pyridin-3-yl)benzoic acid which was obtained by saponification of methyl 4-(2-(2-methoxyethoxy)pyridin-3-yl)benzoate. The latter intermediate was prepared using Mitsunobu chemistry as described for the synthesis of compound n° 226.

Example **195:** compound n°240: (2S,5R)-5-(2-chlorophenyl)-1-(4-(3-methoxypyrazin-2-yl)benzoyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2k2** using general method C.

Example **196:** compound n°241: (2S,5R)-1-(4-(2-chloro-4-(dimethylamino)pyrimidin-5-yl)benzoyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2l2** using general method C.

Example **197:** compound n°242: (2S,5R)-5-(2-chlorophenyl)-1-(4-(2,6-dimethoxypyrimidin-4-yl)benzoyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2m2** using general method C.

Example **198:** compound n°227: (2S,5R)-5-(2-chlorophenyl)-1-(4-(2-methylthiophen-3-yl)benzoyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2n2** using general method C and further purified by preparative HPLC.

Example **199:** compound n°228: (2S,5R)-5-(2-chlorophenyl)-1-(2',6'-dichloro-[1,1'-biphenyl]-4-

carbonyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2o2** using general method C.

Example **200:** compound n°229: (2S,5R)-1-(2'-chloro-4'-methoxy-[1,1'-biphenyl]-4-carbonyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2p2** using general method C.

Example **201:** compound n°243: (2S,5R)-5-(2-chlorophenyl)-1-(2'-(dimethylamino)-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2q2** using general method C.

Example **202:** compound n°246: (2S,5R)-5-(2-fluorophenyl)-1-(4-(2-methoxypyridin-3-yl)benzoyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1g** and **2r** using general method C.

Example **203:** compound n°247: (2S,5R)-1-(4-(2,4-dimethoxypyrimidin-5-yl)benzoyl)-5-(2-fluorophenyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1g** and **2s1** using general method C.

Example **204:** compound n°249: (2S,5R)-5-(2-chlorophenyl)-1-(3-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2r2** using general method C.

Example **205:** compound n°269: (2S,5R)-1-(4-(2,6-dimethoxypyridin-3-yl)benzoyl)-5-(2-fluorophenyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1g** and **2h2** using general method C.

Example **206:** compound n°261: (2S,5R)-5-(2-chlorophenyl)-1-(3-methoxy-4-(4-methylpiperidin-1-yl)benzoyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and 3-methoxy-4-(4-methylpiperidin-1-yl)benzoic acid using general method C (condition B). The synthesis of 3-methoxy-4-(4-methylpiperidin-1-yl)benzoic acid is depicted in **scheme 11.**

Example **207:** compound n°272: (2S,5R)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)-5-phenylpyrrolidine-2-carboxylic acid was synthesized from intermediates **1t** and **2h** using general method C (condition A).

Example **208:** compound n°273: (2S,5R)-5-(3-chlorophenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1u** and **2h** using general method C (condition A).

Example **209:** compound n°274: (2S,5R)-5-(4-chlorophenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1v** and **2h** using general method C (condition A).

Example **210:** compound n°275: (2S,5R)-5-(3-fluorophenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1w** and **2h** using general method C (condition A).

Example **211:** compound n°276: (2S,5R)-5-(4-fluorophenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1x** and **2h** using general method C (condition A).

Example **212:** compound n°278: (2S,5R)-4-acetyl-5-(2-chlorophenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid was synthesized from (2S,4S,5R)-methyl 4-acetyl-5-(2-chlorophenyl)pyrrolidine-2-carboxylate using the same dipolar cycloaddition methodology as shown in **scheme 9,** except for the last step (Me_3SnOH (10eq), DCE, 90°C) instead of (TFA, DCM).

Example **213:** compound n°279: (2S,4S,5R)-5-(2-chlorophenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)-4-(methoxymethyl)pyrrolidine-2-carboxylic acid was synthesized from (2S,4S,5R)-4-*tert*-butyl 2-methyl 5-(2-chlorophenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2,4-dicarboxylate which was obtained using the dipolar cycloaddition methodology shown in **scheme 9.** Last steps to perform the synthesis of compound n°279 are depicted in **scheme 14.**

Example **214:** compound n°280: (2S,5R)-5-(2-chlorophenyl)-1-(4-(2-methoxypyrimidin-4-yl)benzoyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2s2** using general method C (condition B).

Example **215:** compound n°281: (2S,5R)-5-cyclohexyl-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1y** and **2h** using general method C (condition B).

Example **216:** compound n°283: (2S,5R)-1-(4-(2-chloro-4-methoxypyrimidin-5-yl)benzoyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2t2** using general method C (condition B).

Example **217:** compound n°284: (2S,5R)-5-(2-chlorophenyl)-1-(4-(3-methoxypyridin-2-yl)benzoyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2u2** using general method C (condition B).

Example **218:** compound n°285: (2R,5R)-5-(2-fluorophenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1z** and **2h** using general method C (condition A).

Example **219:** compound n°286: (2S,5S)-5-(2-fluorophenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a1** and **2h** using general method C (condition A).

Example **220:** compound n°287: (2R,5S)-5-(2-fluorophenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1b1** and **2h** using general method C (condition A).

Example **221:** compound n°288: (2S,5R)-5-(2-chlorophenyl)-1-(2-(trifluoromethyl)-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and

2v2 using general method C (condition B).

Example **222:** compound n°289: (2S,5R)-5-(2-chlorophenyl)-1-(2',4'-difluoro-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2w2** using general method C (condition B).

Example **223:** compound n°290: (2S,5R)-5-(2-chlorophenyl)-1-(2-methyl-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2x2** using general method C (condition B).

Example **224:** compound n°291: (2S,5R)-5-(2,6-difluorophenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1c1** and **2h** using general method C (condition A).

Example **225:** compound n°292: (2S,5R)-5-(2,4-difluorophenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1d1** and **2h** using general method C (condition A).

Example **226:** compound n°293: (2S,5R)-5-(2,4-dichlorophenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acidwas synthesized from intermediates **1e1** and **2h** using general method C (condition A).

Example **227:** compound n°294: (2S,5R)-5-isobutyl-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1f1** and **2h** using general method C (condition A).

Example **228:** compound n°295: (2S,5R)-5-isopropyl-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1g1** and **2h** using general method C (condition A).

Example **229:** compound n°296: (2S,5R)-1-(3-chloro-4-(pyrimidin-4-yl)benzoyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2y2** using general method C (condition B).

Example **230:** compound n°297: (2S,5R)-5-(2-chlorophenyl)-1-(2-fluoro-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2z2** using general method C (conditions B).

Example **231:** compound n°298: (2S,5R)-5-(2-chlorophenyl)-1-(2'-fluoro-4'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2a3** using general method C (conditions B).

Example **232:** compound n°299: (2S,5R)-5-(2-chlorophenyl)-1-(4'-fluoro-2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2b3** using general method C (conditions B).

Example **233:** compound n°300: (2S,5R)-5-(2-chlorophenyl)-1-(4-(6-ethoxypyridin-3-yl)benzoyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2c3** using

general method C (conditions B).

Example **234a:** compound n°301: (2S,5R)-5-(2-chlorophenyl)-1-(4-(6-isopropoxypyridin-3-yl)benzoyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2d3** using general method C (condition B).

Example **234b:** compound n°302: (2S,5R)-5-(2-chlorophenyl)-1-(4-(6-methoxy-2-methylpyridin-3-yl)benzoyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2e3** using general method C (condition B).

Example **235:** compound n°303: (2S,5R)-1-(3-chloro-4-(2-methoxypyrimidin-4-yl)benzoyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2f3** using general method C (condition B).

Example **236:** compound n°304: (2S,5R)-1-(3-chloro-4-(pyrimidin-5-yl)benzoyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2g3** using general method C (condition B).

Example **237:** compound n°305: (2S,5R)-5-(2-chlorophenyl)-4-cyano-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)-3-methylpyrrolidine-2-carboxylic acid was synthesized using the 1,3-dipolar cycloaddition shown in **scheme 9.**

Example **238:** compound n°306: (2S,4S,5R)-5-(2-chlorophenyl)-4-cyano-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)-4-methylpyrrolidine-2-carboxylic acid was synthesized using the 1,3-dipolar cycloaddition shown in **scheme 9.**

Example **239:** compound n°307: (2S,5R)-5-(2-chlorophenyl)-1-(2',3'-dimethoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2h3** using general method C (condition B).

Example **240:** compound n°308: (2S,5R)-5-(2-chlorophenyl)-1-(3',4'-dimethoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2i3** using general method C (condition B).

Example **241:** compound n°309: (2S,5R)-5-(2-chlorophenyl)-1-(2',3',4'-trimethoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2j3** using general method C (condition B).

Example **242:** compound n°310: (2S,5R)-5-(2-chlorophenyl)-1-(2',3',6'-trimethoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2k3** using general method C (condition B).

Example **243:** compound n°311: (2S,5R)-5-(2-chlorophenyl)-1-(3',5'-dimethoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2l3** using general method C (condition B).

Example **244:** compound n°312: (2S,5R)-5-(2-chlorophenyl)-1-(2',5'-dimethoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and

2m3 using general method C (condition B).

Example **245:** compound n°313: (2S,5R)-5-(2-chlorophenyl)-1-(2'-isopropyl-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2n3** using general method C (condition B).

Example **246:** compound n°314: (2S,5R)-1-(2,2'-dimethoxy-[1,1'-biphenyl]-4-carbonyl)-5-(2-fluorophenyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1g** and **2z1** using general method C (condition B).

Example **247:** compound n°315: (2S,5R)-1-(2-fluoro-2'-methoxy-[1,1'-biphenyl]-4-carbonyl)-5-(2-fluorophenyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1g** and **2h5** using general method C (condition B).

Example **248:** compound n°316: (2S,5R)-5-(2-chlorophenyl)-1-(2-fluoro-2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2h5** using general method C (condition B).

Example **249:** compound n°318: (2S,5R)-5-cyclopentyl-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1h1** and **2h** using general method C (condition A).

Example **250:** compound n°319: (2S,5R)-5-(2-chlorophenyl)-1-(2'-ethyl-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2o3** using general method C (condition B).

Example **251:** compound n°320: (2S,5R)-5-(2-chlorophenyl)-1-(4-(2,6-dimethylpyridin-3-yl)benzoyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2p3** using general method C (condition B).

Example **252:** compound n°321: (2S,5R)-1-(4-(2,4-bis(benzyloxy)pyrimidin-5-yl)benzoyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2q3** using general method C (conditions B).

Example **253:** compound n°322: (2S,5R)-1-([1,1':4',1"-terphenyl]-4-carbonyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid was synthesized from intermediate **1a** and commercial 1,1':4',1"-terphenyl]-4-carboxylic acid using general method C (conditions B).

Example **254:** compound n°323: (2S,5R)-5-(2-chlorophenyl)-1-(4'-propyl-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid was synthesized from intermediate **1a** and commercial 4'-propyl-[1,1'-biphenyl]-4-carboxylic acid using general method C (conditions B).

Example **255:** compound n°324: (2S,SR)-1-(4'-(tert-butyl)-[1,1'-biphenyl]-4-carbonyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid was synthesized from intermediate **1a** and commercial 4'-(tert-butyl)-[1,1'-biphenyl]-4-carboxylic acid using general method C (conditions B).

Example **256:** compound n°325: (2S,5R)-1-(3-chloro-4-(2,4-dimethoxypyrimidin-5-

yl)benzoyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2g5** using general method C (conditions B).

Example **257:** compound n°326: (2S,5R)-5-(2-chlorophenyl)-1-(5-(2-methoxyphenyl)pyrazine-2-carbonyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2j5** using general method C (conditions B).

Example **258:** compound n°327: (2S,5R)-5-(2-chlorophenyl)-1-(3-methoxy-4-(4-methoxypyridin-3-yl)benzoyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2k5** using general method C (conditions B).

Example **259:** compound n°328: (2S,5R)-5-(2-chlorophenyl)-1-(3-methoxy-4-(6-methoxypyridin-3-yl)benzoyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2l5** using general method C (conditions B).

Example **260:** compound n°329: (2S,5R)-1-(3-chloro-4-(2-methoxypyrimidin-5-yl)benzoyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2m5** using general method C (conditions B).

Example **261:** compound n°330: (2S,5R)-1-(3-chloro-4-(6-methoxypyridin-3-yl)benzoyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2r3** using general method C (conditions B).

Example **262:** compound n°331: (2S,5R)-5-(2-chlorophenyl)-1-(1-(4-(4-chlorophenyl)thiazol-2-yl)piperidine-4-carbonyl)pyrrolidine-2-carboxylic acid was synthesized from intermediate **1a** and commercial 1-(4-(4-chlorophenyl)thiazol-2-yl)piperidine-4-carboxylic acid using general method C (conditions B).

Example **263:** compound n°332: (2S,5R)-5-(2-fluorophenyl)-1-(5-methoxy-6-(2-methoxyphenyl)nicotinoyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1g** and **2s3** using general method C (conditions B).

Example **264:** compound n°333: (2S,5R)-1-(1-(benzo[d]oxazol-2-yl)piperidine-4-carbonyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid was synthesized from intermediate **1a** and commercial 1-(benzo[d]oxazol-2-yl)piperidine-4-carboxylic acid using general method C (conditions B).

Example **265:** compound n°334: (2S,5R)-5-(2-chlorophenyl)-1-(3-methoxy-4-(pyrrolidin-1-yl)benzoyl)pyrrolidine-2-carboxylic acid was synthesized using the same methodology as shown in **scheme 11,** replacing 4-methylpiperidine with pyrrolidine.

Example **266:** compound n°335: (2S,5R)-5-(2-chlorophenyl)-1-(5-methoxy-6-(2-methoxyphenyl)nicotinoyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2t3** using general method C (conditions B).

Example **267:** compound n°336: (2S,5R)-5-(2-chlorophenyl)-1-(1-(2-methoxyphenyl)piperidine-4-carbonyl)pyrrolidine-2-carboxylic acid was synthesized using the same methodology as shown in scheme 13 replacing 2-cyano-4-trifluoromethyl-bromobenzene

with 2-methoxy-bromobenzene.

Example **268:** compound n°337: (2S,5R)-5-(2-chlorophenyl)-1-(4-(2,4-dimethoxypyrimidin-5-yl)-3-methoxybenzoyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2n5** using general method C (conditions B).

Example **269:** compound n°338: (2S,5R)-5-(2-bromophenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1i1** and **2h** using general method C (conditions A).

Example **270:** compound n°339: (2S,5R)-5-(2-chlorophenyl)-1-(3'-cyano-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid was synthesized from intermediate **1a** and commercial 3'-cyano-[1,1'-biphenyl]-4-carboxylic acid using general method C (conditions B).

Example **271:** compound n°340: (2S,5R)-5-(2-chlorophenyl)-1-(3'-cyano-2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2u3** using general method C (conditions A).

Example **272:** compound n°341: (2S,5R)-5-(2-chlorophenyl)-1-(3'-cyano-2',4'-bis(2,2,2-trifluoroethoxy)- [1,1 '-biphenyl] -4-carbonyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2v3** using general method C (conditions B).

Example **273:** compound n°342: (2S,5R)-1-(3'-amino-2'-methyl-[1,1'-biphenyl]-4-carbonyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2w3** using general method C (conditions B).

Example **274:** compound n°343: (2S,5R)-5-(2-chlorophenyl)-1-(2'-methyl-3'-(methylsulfonamido)-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2x3** using general method C (conditions B).

Example **275:** compound n°344: (2S,5R)-1-(3'-acetamido-2'-methyl-[1,1'-biphenyl]-4-carbonyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2y3** using general method C (conditions B).

Example **276:** compound n°345: (2S,5R)-5-(2-chlorophenyl)-1-(5'-cyano-2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2z3** using general method C (conditions B).

Example **277:** compound n°346: (2S,5R)-5-(2-chlorophenyl)-1-(5'-cyano-2'-methyl-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2a4** using general method C (conditions B).

Example **278:** compound n°347: (2S,5R)-5-(2-chlorophenyl)-1-(4-(4,6-dimethoxypyridin-3-yl)benzoyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2b4** using general method C (conditions B).

Example **279:** compound n°348: (2S,5R)-5-(2-chlorophenyl)-1-(4-(3,6-dimethoxypyridazin-4-yl)benzoyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2r4** using

general method C (conditions B).

Example **280:** compound n°349: (2S,5S)-5-isopentyl-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1j1** and **2h** using general method C (conditions A).

Example **281:** compound n°350: (2S,5R)-5-(2-chlorophenyl)-1-(2'-methoxy-4'-(methylsulfonamido)-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2p5** using general method C (conditions B).

Example **282:** compound n°351: (2S,5R)-1-(4'-acetamido-2'-methoxy-[1,1'-biphenyl]-4-carbonyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2c4** using general method C (conditions B).

Example **283:** compound n°352: (2S,5R)-1-(3'-carbamimidoyl-[1,1'-biphenyl]-4-carbonyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid was synthesized from (2S,5R)-methyl 5-(2-chlorophenyl)-1 -(3'-cyanobiphenylcarbonyl)pyrrolidine-2-carboxylate which was obtained from intermediate **1a** and commercial 3'-cyanobiphenyl-4-carboxylic acid using general method C (conditions B).

Step 1: To a solution of (2S,5R)-methyl 5-(2-chlorophenyl)-1-(3'-cyanobiphenylcarbonyl)pyrrolidine-2-carboxylate (1.0 mmol) and hydoxylamine hydrochloride (2.0 mmol) in dry EtOH (5 mL) under N_2 was added NEt_3 (2.0 mmol) dropwise at RT. The mixture was stirred under reflux overnight. The mixture was cooled down to RT, concentrated and purified on silica gel (cyclohex / EtOAc), furnishing 300 mg of (2S,5R)-methyl 5-(2-chlorophenyl)-1-(3'-((E)-N'-hydroxycarbamimidoyl)biphenylcarbonyl)pyrrolidine-2-carboxylate as a white solid (60% yield).

Step 2: A solution of (2S,5R)-methyl 5-(2-chlorophenyl)-1-(3'-((E)-N'-hydroxycarbamimidoyl)biphenylcarbonyl)pyrrolidine-2-carboxylate (0.42 mmol) in EtOH/THF/AcOH (3mL/3mL/0.1mL) was hydrogenated at RT under atmospheric pressure using a slurry solution of Raney nickel catalyst in water (0.5 mL) for 5h. The catalyst was filtered off over Celite and the filtrate was concentrated, furnishing 160 mg of white solid (83% yield).

Step 3: Saponification using standard methodology described in general method C.

Example **284:** compound n°353: (2S,5R)-5-(2-chlorophenyl)-1-(3'-((E)-N'-hydroxycarbamimidoyl)-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid was obtained from (2S,5R)-methyl 5-(2-chlorophenyl)-1-(3'-((E)-N'-hydroxycarbamimidoyl)biphenylcarbonyl)pyrrolidine-2-carboxylate (step 1 of synthesis of compound n°352) using the saponification standard methodology described in general method C: (2S,5R)-1-(3'-carbamoyl-[1,1'-biphenyl]-4-carbonyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid was obtained by hydrolysis and saponification using LiOH of (2S,5R)-methyl 5-(2-chlorophenyl)-1-(3'-cyanobiphenylcarbonyl)pyrrolidine-2-carboxylate which was obtained from intermediate **1a** and commercial 3'-cyanobiphenyl-4-carboxylic acid using general method C (conditions B).

Example **285:** compound n°360: (2S,5R)-5-(2-chlorophenyl)-1-(5'-cyano-2',3'-dimethoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2f4** using general method C (conditions B).

Example **286:** compound n°361: (2S,5R)-5-(2-chlorophenyl)-1-(2'-cyano-4',5'-dimethoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2g4** using general method C (conditions B).

Example **287:** compound n°362: (2S,5R)-5-(2-chlorophenyl)-1-(3',4',5'-trimethoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2h4** using general method C (conditions B).

Example **288:** compound n°363: (2S,5R)-5-(2-chlorophenyl)-1-(2'-(cyanomethyl)-4',5'-dimethoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2i4** using general method C (conditions B).

Example **289:** compound n°364: (2S,5R)-5-(2-chlorophenyl)-1-(3',4'-dicyano-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2j4** using general method C (conditions B).

Example **290:** compound n°365: (2S,5R)-5-(2-chlorophenyl)-1-(5'-cyano-2'-fluoro-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2k4** using general method C (conditions B).

Example **291:** compound n°366: (2S,5R)-5-(2-chlorophenyl)-1-(2-fluoro-3',4'-dimethoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2l4** using general method C (conditions B).

Example **292:** compound n°367: (2S,5R)-5-(2-chlorophenyl)-1-(4-(2,6-dimethoxypyridin-3-yl)-3-fluorobenzoyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2m4** using general method C (conditions B).

Example **293:** compound n°368: (2S,5R)-5-(2-chlorophenyl)-1-(3-fluoro-4-(6-methoxypyridin-3-yl)benzoyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1a** and **2n4** using general method C (conditions B).

Example **294:** compound n°369: (2S,5R)-5-(2-chlorophenyl)-1-(1-(2-cyano-4-(trifluoromethyl)phenyl)piperidine-4-carbonyl)pyrrolidine-2-carboxylic acid was synthesized using the methodology shown in **scheme 13.**

Example **295:** compound n°370: (2S,5R)-1-(1-(2-chloro-4-(trifluoromethyl)phenyl)piperidine-4-carbonyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid was synthesized using the methodology shown in **scheme 13** replacing 2-cyano-4-trifluoromethyl-bromobenzene with 2-chloro-4-trifluoromethyl-bromobenzene.

Example **296:** compound n°371: (2S,5R)-1-(5'-cyano-2'-methoxy-[1,1'-biphenyl]-4-carbonyl)-5-(2-fluorophenyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1g** and **2z3**

using general method C (conditions B).

Example **297:** compound n°372: (2S,5R)-1-(4-(2,6-dimethoxypyridin-3-yl)-3-fluorobenzoyl)-5-(2-fluorophenyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1g** and **2m4** using general method C (conditions B).

Example **298:** compound n°373: (2S,5R)-1-(3-fluoro-4-(6-methoxypyridin-3-yl)benzoyl)-5-(2-fluorophenyl)pyrrolidine-2-carboxylic acid was synthesized from intermediates **1g** and **2n4** using general method C (conditions B).

Example **299:** compound n°374: (2S,5R)-1-(4-(3,6-dimethoxypyridazin-4-yl)benzoyl)-5-(2-fluorophenyl)pyrrolidine-2-carboxylic acid was obtained from intermediates **1a** and intermediate **2r4** using general method C (conditions B).

Example **300:** compound n°375: (2S,5R)-1-(3'-carbamoyl-4'-cyano-[1,1'-biphenyl]-4-carbonyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid was obtained by the hydrolysis of the nitrile moiety of (2S,5R)-methyl 5-(2-chlorophenyl)-1-(3',4'-dicyano-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylate and subsequent saponification using LiOH. (2S,5R)-methyl 5-(2-chlorophenyl)-1-(3',4'-dicyano-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylate was obtained from intermediates **1a** and intermediate **2j4** using general method C (conditions B).

Example **302:** compound n°376: (2S,5R)-5-(2-chlorophenyl)-1-(1-(2-nitro-4-(trifluoromethyl)phenyl)piperidine-4-carbonyl)pyrrolidine-2-carboxylic acid was synthesized from intermediate **1a** and commercial 1-(2-nitro-4-(trifluoromethyl)phenyl)piperidine-4-carboxylic acid using general method C (conditions B).

Example **303:** compound n°377: (2S,5R)-5-(2-chlorophenyl)-1-(1-(4-(morpholinosulfonyl)-2-nitrophenyl)piperidine-4-carbonyl)pyrrolidine-2-carboxylic acid was synthesized from intermediate **1a** and commercial 1-(2-nitro-4-(piperidin-1-ylsulfonyl)phenyl)piperidine-4-carboxylic acid using general method C (conditions B).

Example **304:** compound n°378: (2S,SR)-5-(2-chlorophenyl)-1-(1-(2-nitro-4-(piperidin-1-ylsulfonyl)phenyl)piperidine-4-carbonyl)pyrrolidine-2-carboxylic acid was synthesized from intermediate **1a** and commercial 1-(4-(N,N-diethylsulfamoyl)-2-nitrophenyl)piperidine-4-carboxylic acid using general method C (conditions B).

Example **305:** compound n°379: (2S,5R)-5-(2-chlorophenyl)-1-(1-(4-(N,N-diethylsulfamoyl)-2-nitrophenyl)piperidine-4-carbonyl)pyrrolidine-2-carboxylic acid was synthesized from intermediate **1a** and commercial 1-(4-methyl-2-nitrophenyl)piperidine-4-carboxylic acid using general method C (conditions B).

Example **306:** compound n°380: (2S,5R)-5-(2-chlorophenyl)-1-(1-(4-methyl-2-nitrophenyl)piperidine-4-carbonyl)pyrrolidine-2-carboxylic acid was synthesized using the same methodology as depicted in **scheme 12,** replacing 2-nitro-4-trifluoromethyl-fluorobenzene by 2-nitro-4-methyl-fluorobenzene.

Example **307:** compound n°381: (2S,5R)-5-(2-chlorophenyl)-1-(1-(2-cyano-4-

nitrophenyl)piperidine-4-carbonyl)pyrrolidine-2-carboxylic acid was synthesized using the same methodology as depicted in **scheme 12,** replacing 2-nitro-4-trifluoromethyl-fluorobenzene by 2-cyano-4-methyl-fluorobenzene.

Example **308:** compound n°382: (2S,5R)-5-(2-chlorophenyl)-1-(1-(4-nitrophenyl)piperidine-4-carbonyl)pyrrolidine-2-carboxylic acid was synthesized from intermediate **1a** and commercial 1-(4-nitrophenyl)piperidine-4-carboxylic acid using general method C (conditions B).

Example **309:** compound n°383: (2S,5R)-5-(2-chlorophenyl)-1-(1-(2-fluoro-4-nitrophenyl)piperidine-4-carbonyl)pyrrolidine-2-carboxylic acid was synthesized using the same methodology as depicted in **scheme 13,** replacing 2-cyano-4-trifluoromethyl-bromobenzene by 2-fluoro-4-nitro-bromobenzene.

Example **310:** compound n°384: (2S,5R)-5-(2-chlorophenyl)-1-(1-(3-methoxy-4-nitrophenyl)piperidine-4-carbonyl)pyrrolidine-2-carboxylic acid was synthesized from intermediate **1a** and commercial 1-(3-methoxy-4-nitrophenyl)piperidine-4-carboxylic acid using general method C (conditions B).

Example **311:** compound n°385: (2S,5R)-1-(1-(5-chloro-2-nitrophenyl)piperidine-4-carbonyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid was synthesized from intermediate **1a** and commercial 1-(5-chloro-2-nitrophenyl)piperidine-4-carboxylic acid using general method C (conditions B).

Example **312:** compound n°386: (2S,5R)-5-(2-cyanophenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid was obtained by cyanation of (2S,5R)-methyl 5-(2-bromophenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylate and subsequent saponification. (2S,5R)-methyl 5-(2-bromophenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylate was obtained from intermediates **1i1** and **2h** using general method C, (conditions A). Cyanation method of cyanation: In a carrousel tube were introduced NMP (0.2 mL), *i*-PrOH (9.7 µL), sodium carbonate (0.021 g, 0.202 mmol), palladium(II) acetate (0.908 mg, 4.05 µmol) and (2S,5R)-methyl 5-(2-bromophenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylate (0.1 g, 0.202 mmol). The RM was heated at 140°C and potassium ferrocyanide.$3H_2O$ (0.026 g, 0.061 mmol) was added. Heating was stopped and the RM was stirred overnight. The RM was diluted with water and extracted with three times with EtOAc. The aqueous layer was acidified (a color change from brown to blue was observed) and extracted twice with diethyl ether. The combined organic layers were dried over $MgSO_4$, filtered and concentrated to afford a brown residue. Crude was purified by flash chromatography (EtOAc/PE : 1/2) to yield compound n°386. Y=10%, P>90%.

Example **313:** compound n°387: (2S,SR)-5-(2-chlorophenyl)-1-(2'-cyano-4'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid was obtained from intermediates **1a** and intermediate **2s4** using general method C (conditions B).

Example **314:** compound n°388: (2S,5R)-5-(2-chlorophenyl)-1-(2-fluoro-4'-(methylsulfonamido)-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid was obtained from intermediates **1a** and intermediate **2s5** using general method C (conditions B).

Example **315:** compound n°389: (2S,5R)-5-(2-chlorophenyl)-1-(2-fluoro-3'-(methylsulfonamido)-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid was obtained from intermediates **1a** and intermediate **2t5** using general method C (conditions B).

Example **316:** compound n°390: (2S,5R)-5-(2-chlorophenyl)-1-(2'-cyano-2-fluoro-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid was obtained from intermediates **1a** and intermediate **2u5** using general method C (conditions B).

Example **317:** compound n°391: (2S,5R)-5-(2-chlorophenyl)-1-(1-(2-cyano-4-(methylsulfonamido)phenyl)piperidine-4-carbonyl)pyrrolidine-2-carboxylic acid was obtained by reduction of nitro, sulfonylation and saponification of (2S,5R)-methyl 5-(2-chlorophenyl)-1-(1-(2-cyano-4-nitrophenyl)piperidine-4-carbonyl)pyrrolidine-2-carboxylate which was obtained from intermediate **1a** and commercial 1-(2-cyano-4-nitrophenyl)piperidine-4-carboxylic acid using general method C, condition B.

Example **318:** compound n°392: (2S,5R)-5-(2-chlorophenyl)-1-(1-(2-cyano-4-methoxyphenyl)piperidine-4-carbonyl)pyrrolidine-2-carboxylic acid was obtained using the same methodology as shown in **scheme 13** replacing 2-cyano-4-trifluoromethyl-bromobenzene with 2-cyano-4-methoxy-bromobenzene.

Example **319:** compound n°393: (2S,5R)-5-(2-chlorophenyl)-1-(1-(2-(methylsulfonamido)-4-(trifluoromethyl)phenyl)piperidine-4-carbonyl)pyrrolidine-2-carboxylic acid was obtained by reduction of the nitro group of (2S,5R)-methyl 5-(2-chlorophenyl)-1-(1-(2-nitro-4-(trifluoromethyl)phenyl)piperidine-4-carbonyl)pyrrolidine-2-carboxylate, followed by sulfonylation with methane sulfonyl chloride, and subsequent saponification. (2S,5R)-methyl-5-(2-chlorophenyl)-1-(1-(2-nitro-4-(trifluoromethyl)phenyl)piperidine-4-carbonyl)pyrrolidine-2-carboxylate was obtained from intermediates **1a** and commercial 1-(2-nitro-4-(trifluoromethyl)phenyl)piperidine-4-carboxylic acid using general method C (conditions B).

Example **320:** compound n°394: (2S,5R)-5-(2-chlorophenyl)-1-(1-(2-nitrophenyl)piperidine-4-carbonyl)pyrrolidine-2-carboxylic acid was synthesized from intermediate **1a** and commercial 1-(2-nitrophenyl)piperidine-4-carboxylic acid using general method C (conditions B).

Example **321:** compound n°395: (2S,5R)-5-(2-chlorophenyl)-1-(1-(4-cyanophenyl)piperidine-4-carbonyl)pyrrolidine-2-carboxylic acid was synthesized from intermediate **1a** and commercial 1-(4-cyanophenyl)piperidine-4-carboxylic acid using general method C (conditions B).

Example **322:** compound n°396: (2S,5R)-5-(3,5-difluorophenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid was obtained from intermediates **1l1** and intermediate **2h** using general method C (conditions A).

Example **323:** compound n°397: (2S,5R)-5-(3,4-difluorophenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid was obtained from intermediates **1m1** and intermediate **2h** using general method C (conditions A).

Example **324:** compound n°398: (2S,5R)-5-(2,3-difluorophenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid was obtained from intermediates **1n1** and

intermediate **2h** using general method C (conditions A).

Example **325:** compound n°399: (2S,5R)-5-(2,5-difluorophenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid was obtained from intermediates **1o1** and intermediate **2h** using general method C (conditions A).

Example **326:** compound n°400: (2S,5R)-5-([1,1'-biphenyl]-2-yl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid was obtained by Suzuki coupling (2S,5R)-methyl 5- (2-bromophenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylate with phenylboronic acid and subsequent saponification. (2S,5R)-methyl 5-(2-bromophenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylate was obtained from intermediates **1i1** and **2h** using general method C (conditions A).

Example **327:** compound n°401: (2S,5R)-1-(2'-cyano-4'-methoxy-[1,1'-biphenyl]-4-carbonyl)-5-(2-fluorophenyl)pyrrolidine-2-carboxylic acid was obtained from intermediates **1g** and **2s4** using general method C (conditions B).

Example **328:** compound n°402: (2S,SR)-5-(4-cyanophenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid was obtained from intermediates **1p1** and **2h** using general method C (conditions A).

Example **329:** compound n°403: (2S,5R)-5-(2-chlorophenyl)-1-(4-(5-methyl-4-(phenylsulfonyl)-1H-1,2,3-triazol-1-yl)benzoyl)pyrrolidine-2-carboxylic acid was synthesized from intermediate **1a** and commercial 4-(5-methyl-4-(phenylsulfonyl)-1H-1,2,3-triazol-1-yl)benzoic acid using general method C (conditions B).

Example **330:** compound n°404: (2S,5R)-5-(2-chlorophenyl)-1-(3'-cyano-4'-fluoro-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid was obtained from intermediates **1a** and intermediate **2u4** using general method C (conditions B).

Example **331:** compound n°405: (2S,5R)-1-(2'-chloro-5'-cyano-[1,1'-biphenyl]-4-carbonyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid was obtained from intermediates **1a** and intermediate **2v4** using general method C (conditions B).

Example **332:** compound n°406: (2S,5R)-5-(2-chlorophenyl)-1-(2'-cyano-4'-(trifluoromethyl)-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid was obtained from intermediates **1a** and intermediate **2w4** using general method C (conditions B).

Example **333:** compound n°407: (2S,5R)-5-(2-chlorophenyl)-1-(1-(2-methoxy-4-(trifluoromethyl)phenyl)piperidine-4-carbonyl)pyrrolidine-2-carboxylic acid was obtained using the same methodology as depicted in **scheme 12,** replacing 2-nitro-4-trifluoromethyl-fluorobenzene by 2-methoxy-4-trifluoromethyl-fluorobenzene.

Example **334:** compound n°408: (2S,5R)-5-(2-chlorophenyl)-1-(2'-methyl-3'-(N-methylmethylsulfonamido)-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid was obtained from intermediates **1a** and intermediate **2x4** using general method C (conditions B).

Example **335:** compound n°409: (2S,5R)-5-(2-chlorophenyl)-1-(2'-methoxy-4'-(N-

methylmethylsulfonamido)-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid was obtained from intermediates **1a** and intermediate **2v5** using general method C (conditions B).

Example **336:** compound n°410: (2S,5R)-5-(2-chlorophenyl)-1-(6-(5-cyano-2-methoxyphenyl)-5-methoxynicotinoyl)pyrrolidine-2-carboxylic acid was obtained from intermediates **1a** and intermediate **2y4** using general method C (conditions B).

Example **337:** compound n°411: (2S,5R)-5-(2-chlorophenyl)-1-(6-(2,4-dimethoxyphenyl)-5-methoxynicotinoyl)pyrrolidine-2-carboxylic acid was obtained from intermediates **1a** and intermediate **2z4** using general method C (conditions B).

Example **338:** compound n°412: (2S,5R)-5-(2-chlorophenyl)-1-(6-(2,4-dimethoxyphenyl)nicotinoyl)pyrrolidine-2-carboxylic acid was obtained from intermediates **1a** and intermediate **2a5** using general method C (conditions B).

Example **339:** compound n°413: (2S,5R)-1-(2'-cyano-4'-(trifluoromethyl)-[1,1'-biphenyl]-4-carbonyl)-5-(2-fluorophenyl)pyrrolidine-2-carboxylic acid was obtained from intermediates **1g** and intermediate **2w4** using general method C (conditions B).

Example **340:** compound n°414: (2S,5R)-1-(3'-cyano-4'-fluoro-[1,1'-biphenyl]-4-carbonyl)-5-(2-fluorophenyl)pyrrolidine-2-carboxylic acid was obtained from intermediates **1g** and intermediate **2u4** using general method C (conditions B).

Example **341:** compound n°415: (2S,5R)-1-(2'-chloro-5'-cyano-[1,1'-biphenyl]-4-carbonyl)-5-(2-fluorophenyl)pyrrolidine-2-carboxylic acid was obtained from intermediates **1g** and intermediate **2v4** using general method C (conditions B).

Example **342:** compound n°416: (2S,5R)-5-(2-chlorophenyl)-1-(4-(3,6-dimethoxypyridazin-4-yl)-3-fluorobenzoyl)pyrrolidine-2-carboxylic acid was synthetized from **1a** and **2w5** using general method C (conditions B).

Example **343:** compound n°417: (2S,5R)-5-(2-fluorophenyl)-1-(2'-methyl-3'-(N-methylmethylsulfonamido)- [1,1'-biphenyl] -4-carbonyl)pyrrolidine-2-carboxylic acid was synthetized from intermediates **1g** and **2x4** using general method C (conditions B).

Example **344:** compound n°418: (2S,5R)-5-(2-fluorophenyl)-1-(2'-methoxy-4'-(N-methylmethylsulfonamido)- [1,1'-biphenyl] -4-carbonyl)pyrrolidine-2-carboxylic acid was synthetized from **1g** and **2v5** using general method C (conditions B).

Example **345:** compound n°419: (2S,5R)-5-(2-chlorophenyl)-1-(4-(4,6-dimethoxypyrimidin-5-yl)benzoyl)pyrrolidine-2-carboxylic acid was synthetized from **1a** and **2f5** using general method C (conditions B).

Example **346:** compound n°420: (2S,5R)-5-(2,3-difluorophenyl)-1-(4-(2,4-dimethoxypyrimidin-5-yl)benzoyl)pyrrolidine-2-carboxylic acid was synthetized from intermediates **1n1** and **2s1** using general method C (conditions B).

Example **347:** compound n°421: (2S,5R)-1-(5'-cyano-2'-methyl-[1,1'-biphenyl]-4-carbonyl)-5-

(2,3-difluorophenyl)pyrrolidine-2-carboxylic acid was synthetized from intermediates **1n1** and **2a4** using general method C (conditions B).

Example **348:** compound n°354: (2S,5R)-5-(2-fluorophenyl)-1-(2'-methoxy-4'-(methylsulfonamido)-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid was synthetized from intermediates **1g** and **2p5** using general method C (conditions B).

Example **349:** compound n°355: (2S,5R)-5-(2,4-difluorophenyl)-1-(4-(2,6-dimethoxypyridin-3-yl)benzoyl)pyrrolidine-2-carboxylic acid was synthetized from intermediates **1k1** and **2q5** using general method C (conditions B).

Example **350:** compound n°356: (2S,5R)-5-(2-chlorophenyl)-1-(3-methoxy-4-(5-methoxypyridin-3-yl)benzoyl)pyrrolidine-2-carboxylic acid was synthetized from intermediates **1a** and **2d4** using general method C (conditions B).

Example **351:** compound n°357: (2S,5R)-1-(4'-amino-2'-methoxy-[1,1'-biphenyl]-4-carbonyl)-5-(2-chlorophenyl)pyrrolidine-2-carboxylic acid was synthetized from intermediate **1a** and methyl 2'-methoxy-4'-amino-[1,1'-biphenyl]-4-carboxylate obtained in the synthesis of intermediate **2p5.**

Example **352:** compound n°358: (2S,5R)-5-(2-chlorophenyl)-1-(2',3,6'-trimethoxy-[2,3'-bipyridine]-5-carbonyl)pyrrolidine-2-carboxylic acid was synthetized from intermediates **1a** and **2e4** using general method C (conditions B).

BIOLOGY EXAMPLES

BRIEF DESCRIPTION OF THE DRAWINGS

[0200]

Figure 1 shows the response to two different compounds of the invention, relative to vehicle control (0.1% DMSO), on TNFα, release from human PBMC. Data are presented as percentage of LPS response.

Figure 2 shows the response to one compound of the invention, relative to vehicle control (0.1% DMSO), on IL-6 release from human PBMC. Data are presented as percentage of LPS response.

Figures 3A and 3B show the response to two compounds of the invention, relative to vehicle control (water), on TNFα, level in mouse plasma. Data are presented as mean ± SEM, n =8 mice per treatment group.

Figure 4 shows the response to one compound of the invention, relative to vehicle control

(water), on disease activity index (DAI) mouse colitis model. Data are presented as mean ± SEM, n =6 mice per treatment group.

Figure 5 shows the response to one compound of the invention, relative to vehicle control (water), on mouse colon length. Data are presented as mean ± SEM, n =6 mice per treatment group.

Figure 6 shows the response to one compound of the invention, relative to vehicle control (water), on mouse colonic tissues conductance. Data are presented as mean ± SEM, n =6 mice per treatment group.

Figure 7 shows the response to one compound of the invention, relative to vehicle control (NaCl 0.9%), on rheumatoid arthritis clinical score. Data are presented as mean ± SEM, n =6 mice per treatment group.

Figure 8 shows the comparative inhibition of *in-vitro* TNFα, release from LPS-stimulated PBMC following the activation by the compounds of the invention or by the compounds disclosed in WO2011/151436A2. Data are presented as mean ± SEM and the final concentration of each tested compound in the assay is 10μM. Statistical analysis was performed by 2-way ANOVA followed by Dunnet's comparison to vehicle group, ****$p<0.0001$.

Membrane binding assay: GTPγS binding assay.

[0201] The following assay can be used for determination of GPR43 activation. When a GPCR is in its active state, either as a result of ligand binding or constitutive activation, the receptor couples to a G protein and stimulates the release of GDP and subsequent binding of GTP to the G protein. The alpha subunit of the G protein-receptor complex acts as a GTPase and slowly hydrolyses the GTP to GDP, at which point the receptor normally is deactivated. Activated receptors continue to exchange GDP for GTP. The non-hydrolysable GTP analog, [^{35}S]GTPγS, was used to demonstrate enhance binding of [^{35}S]GTPγS to membranes expressing receptors. The assay uses the ability of GPCR to stimulate [^{35}S]GTPγS binding to membranes expressing the relevant receptors. The assay can, therefore, be used in the direct identification method to screen candidate compounds to endogenous or not endogenous GPCR.

Preparation of membrane extracts:

[0202] Membrane extracts were prepared from cells expressing the human GPR43 receptor (hGPR43) as follows: the medium was aspirated and the cells were scraped from the plates in Ca^{++} and Mg^{++}-free Phosphate-buffered saline (PBS). The cells were then centrifuged for 3

min at 1500 *g* and the pellets were resuspended in buffer A (15 mM Tris-HCl pH 7.5, 2 mM $MgCl_2$, 0.3 mM EDTA, 1 mM EGTA) and homogenized in a glass homogenizer. The crude membrane fraction was collected by two consecutive centrifugation steps at 40.000 x *g* for 25 min separated by a washing step in buffer A. The final pellet was resuspended in 500 µl of buffer B (75 mM Tris-HCl pH 7.5, 12.5 mM $MgCl_2$, 0.3 mM EDTA, 1mM EGTA, 250 mM sucrose) and flash frozen in liquid nitrogen. Protein content was assayed by the Folin method.

GTPγS assay (SPA method):

[0203] The assay was used to determine the activity of the compounds of the invention.

[0204] The [^{35}S]GTPγS assay was incubated in 20 mM HEPES pH7.4, 100 mM NaCl, 10 µg/ml saponin, 30 mM of $MgCl_2$, 10 µM of GDP, 5 µg membrane-expressing hGPR43, 250µg of wheatgerm agglutinin beads (Amersham, ref: RPNQ001), a range concentration of compounds of the invention (from 30 µM to 1 nM) in a final volume of 100 µl for 30 min at room temperature. The SCFA propionate was used at 1 mM final concentration as positive control. The plates were then centrifuged for 10 minutes at 2000 rpm, incubated for 2 hours at room temperature and counted for 1 min in a scintillation counter (TopCount, PerkinElmer). The results of the tested compounds are reported as the concentration of the compound required to reach 50% (EC_{50}) of the maximum level of the activation induced by these compounds.

[0205] When tested in the assay described above and by way of illustration the compounds in Table 3 activate GPR43 receptor. The EC_{50} value obtained is represented as follows: "+++" means EC_{50} < 200 nM; "++" means 200nM ≤ EC_{50} ≤1 µM; "+" means EC_{50} >1 µM.

Table 3: Compounds EC_{50} values in GTPγ^{35}S assay.

Compound No.	**EC_{50} (nM)**
1	+++
2	+++
3	+++
4	+++
5	+++
6	+++
8	++
9	++
10	++
11	++
12	++
13	++

Compound No.	EC_{50} (nM)
14	++
15	++
16	++
17	++
18	++
19	++
20	++
21	++
23	+
24	+
26	+
27	+
30	+
31	+
32	+
33	+
34	+
35	+
36	+
38	+
39	+
40	+
41	+
42	+
43	+
44	+
45	+
47	+
48	+
49	+
52	+
53	+
58	+
59	+

Compound No.	EC_{50} (nM)
77	+++
78	++
83	+
88	+
89	++
91	++
96	++
99	++
102	+
105	+
107	+
108	+
109	+
113	+++
114	+
116	++
117	++
120	+
121	++
122	+++
123	+++
125	++
126	+++
127	+++
128	+++
129	+++
130	+++
131	+
132	+++
133	++
134	++
135	+++
136	++
137	++

Compound No.	EC_{50} (nM)
138	+++
140	+++
141	++
143	+
149	++
150	++
151	++
153	+
155	+
156	++
157	+++
160	++
161	+++
162	+
169	+
174	+
176	+
177	+
178	++
179	+
183	+
184	++
189	++
191	++
192	++
193	+++
194	++
195	++
196	+++
197	+++
198	+++
199	+++
200	+++
201	+++

Compound No.	EC_{50} (nM)
202	+++
203	++
204	+++
206	+
207	+
224	+++
225	+++
226	++
227	+++
228	+++
229	+++
230	+
231	+
232	+++
233	++
234	+
235	+++
236	+++
237	++
239	++
240	++
242	++
246	+++
247	+++
261	++
268	+++
269	+++
272	++
273	++
274	++
275	+++
276	++
278	++
279	+

Compound No.	EC_{50} (nM)
280	+
281	++
283	+++
284	++
285	+
286	+
287	++
288	++
289	+++
290	+++
291	++
292	+++
293	++
294	++
295	+
296	+
297	+++
298	+++
299	+++
300	++
301	++
302	+++
303	++
304	+
305	+
306	+
307	+++
308	+++
309	++
310	++
311	+++
312	+++
313	++
314	+++

Compound No.	EC_{50} (nM)
315	+++
316	+++
318	+
319	++
320	+++
321	++
322	++
323	++
324	++
325	+++
326	+
327	++
328	+++
329	++
330	++
331	++
332	+
333	+
334	++
335	+
336	+
337	+++
338	+++
339	++
340	+++
341	+
342	+++
343	+++
344	++
345	+++
346	+++
347	+++
348	+++
349	++

Compound No.	EC_{50} (nM)
350	+++
351	+++
352	+
353	++
354	+++
355	+++
356	+++
357	+++
358	++
359	++
360	+++
361	+++
362	+++
363	++
364	+
365	++
366	+++
367	+++
368	+++
369	++
370	+
371	+++
372	+++
373	++
374	++
375	++
386	++
387	+++
388	+++
389	+++
390	+++
391	+
392	+
393	+

Compound No.	EC_{50} (nM)
395	++
396	++
397	++
398	+++
399	+++
400	++
401	+++
402	+
403	+
404	++
405	+++
406	+++
407	++
408	+++
409	+++
410	++
411	++
412	++
413	+++
414	+
415	+++
416	+++
417	+++
418	++
419	+++
420	+++
421	+++

Radioligand Binding (RLB) assay with cell membrane extracts from human GPR43 recombinant cell line

[0206] Human GPR43 radioligand binding assay is performed by adding successively in the wells of a 96 well plate (Master Block, Greiner, 786201), 50 µl of compound of the invention at increasing concentrations (diluted in assay buffer: 50 mM Tris pH 7.4), 25 µl radiolabeled

antagonist (ie. compound n°227 described in WO 2011/092284) diluted in assay buffer and 25 µl cell membrane extracts (10 µg protein/well). The final concentration of radiolabeled antagonist in the assay is 10 nM. The plate is incubated 60 min at 25°C in a water bath and then filtered over GF/B filters (Perkin Elmer, 6005177, presoaked in 0.05% Brij for 2h at room temperature) with a Filtration unit (Perkin Elmer). The filters are washed 3 times with 0.5 ml of ice-cold wash buffer (50 mM Tris pH 7.4). 50 µl of Microscint 20 (Packard), is added and the plate is incubated 15 min on an orbital shaker and then counted with a TopCount™ for 1 min/well.

[0207] In Table 4 biological results obtained using the RLB assay as described above with compounds of the invention are set out in tabulated form. In this table, the constant of inhibition of radioligand binding carried out by the compound of the invention (Ki) is given. The Ki values (nM) obtained is represented as follows: "+++" means Ki < 1µM; "++" means 1µM ≤ Ki ≤ 2µM; "+" means 2µM < Ki.

Table 4: Compounds Ki values in RLB assay.

Compound n°	Ki (nM)
376	+++
377	+
378	++
379	+
380	++
381	++
382	+
383	+
384	+
385	+++
394	+

Cytokines release from Peripheral Blood Mononuclear Cell assay

[0208] Peripheral blood mononuclear cells (PBMC) are purified from heparinised fresh blood sample on a Lymphoprep gradient. PBMC are plated in 96-well assay plate ($2x10^5$ cells/well) and stimulated with or without LPS (100 ng/ml) and increasing concentration of compounds of the invention for 3 hours at 37°C. Cell supernatants are recovered after centrifugation and human soluble TNFα, IL-6 or other cytokines, are quantified using ELISA assay (R&D system) according manufacturer's recommendation.

[0209] When tested in the cytokines release from PBMC assay described above and by way of illustration the compounds 1 and 236 dose dependently inhibit the TNFα, secretion from PBMC

(Figure 1). Additional results with compounds of the invention are set out in tabulated form (Table 5). In Figure 1 and Table 5 the results of the tested compounds are reported as the concentration of the compound required to reach 50% of inhibition (IC_{50}) of LPS induced TNFα, level by these compounds.

Table 5: Compounds IC_{50} values in PBMC assay.

Compound No.	IC_{50}(μM)
161	11.8
325	6.0
345	0.99
361	5.19
390	5.52
421	2.93

[0210] When tested in the cytokines release from PBMC assay described above and by way of illustration the compound 1 dose dependently inhibits the IL-6 secretion from PBMC (Figure 2). The result of the tested compound is reported as the concentration of the compound required to reach 50% of inhibition (IC_{50}) of LPS induced IL-6 level by this compound.

[0211] When tested in the cytokines release from PBMC assay described above and by way of illustration the compounds 1 and 345 of the present invention surprisingly display a greater inhibition of TNFα secretion from LPS-stimulated PBMC than the compounds 39 and 43 disclosed in WO2011/151436A2 (Figure 8).

Septic Shock mouse model

[0212] Mouse male C57 Black 6 (C57BL6), 8 weeks of age, are acclimatized for 7 days. During acclimation and following dosing, animals are housed within a limited access rodent facility and kept in groups of maximum 10 mice, in polypropylene cages, fitted with solid bottoms and filled with wood shavings as bedding material. Animals are provided ad libitum a commercial rodent diet and free access to drinking water, supplied to each cage via polyethylene bottles with stainless steel sipper tubes. The day of the experiments, animals are randomized and experimental groups (n=8) are distributed across cages. A t0 on day 0, the compounds of the invention or controls are administered via oral gavage. At time t 0.5h on day 0, mice are subjected to an intraperitoneal injection of 100 µg of lipopolysachharide (LPS). On day 0 at time t 2h, all mice are tailed bled and serum prepared.

[0213] TNFα, or other markers, is measured in each serum using ELISA assay, according to manufacturer's recommendations.

[0214] When tested in the septic shock mouse model described above and by way of illustration the compound 1 inhibits the TNFα, plasmatic level (Figure 3A) and the compound 345 significantly inhibits the TNFα, plasmatic level (Figure 3B).

Colitis mouse model

[0215] Dextran Sodium Sulfate (DSS) induces a robust colitis used as well-known model of inflammatory bowel diseases including ulcerative colitis and Crohn's disease. Male C57BL6 mice, 25-30 g, receive DSS in drinking water at the concentration of 5 % for 7 days. The tested compound or vehicle control is pre-dosed, via oral route, beginning two days prior to DSS treatment and continuing throughout the 7-day exposure to DSS. The disease activity index (DAI) is measured daily as well as water consumption. At the end of the 7 days of treatment, mice are euthanized and tissues are collected for colonic length and permeability studies.

[0216] Disease Activity Index (DAI): Each parameter is on a 0-4 scale, and the daily DAI score is the average of the scores for each parameter. Weight loss: 0-4; Stool consistency: 0, 2, 4. Rectal Bleeding: 0, 2, 4.**Colonic Length:** Colonic length is recorded ex-vivo in all mice. **Colonic Permeability:** To assess the tissue integrity, colonic permeability is measured in vitro. Specifically, colonic tissues are mounted in modified Ussing chambers and maintained at 37 °C in oxygenated Krebs buffer. Basal potential difference ("PD") and flux of horseradish peroxidase is monitored over 90 min.

[0217] When tested in the colitis mouse model described above and by way of illustration the compound 1 significantly decreases the DAI (Figure 4), significantly increases the colon length (Figure 5). Further, in the colitis mouse model described above and by way of illustration the compound n° 1 significantly improves the conductance of colonic tissues (Figure 6).

Arthritis *K/BxN* mouse *model*

[0218] To induce K/BxN arthritis, sera are pooled from arthritic adult K/BxN mice. Recipient C/57black 6 mice are injected intraperitoneally with 150 µl on days 0 and 2 and disease progression is monitored as described as follows. Development of arthritis is assessed in a blinded manner using a semiquantitative clinical scoring system for each paw: 0 = normal, 1 = mild to moderate swelling of the ankle/wrist joint or erythema and swelling limited to individual digits, 2 = swollen ankle or swelling in two or more digits, and 3 = severe swelling along all aspects of paw or all five digits swollen. Compounds of the invention are given by oral gavage (o.g.) 2 days before arthritis induction, as well as during disease monitoring, twice daily. Control mice received NaCl 0.9% alone.

[0219] When tested in the K/BxN mouse model described above and by way of illustration the compound 1 decreases the clinical score severity (Figure 7).

[0220] While embodiments of the invention have been illustrated and described, it is not intended that these embodiments illustrate and describe all possible forms of the invention. Rather, the words used in the specification are words of description rather than limitation.

REFERENCES CITED IN THE DESCRIPTION

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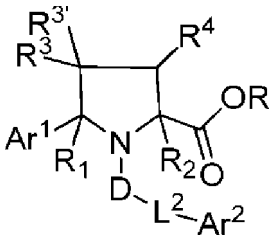
Patentkrav

1. Forbindelse med formlen Ia-Ib':



eller et farmaceutisk acceptabelt salt eller solvat deraf, hvor

R^1 og **R^2** er H,

D er C=O;

L^2 er en enkelt binding;

R er H eller lineær eller forgrenet alkyl, aryl, acyloxyalkyl, dioxolen;

Ar^1 er en 5- til 6-leddet aryl- eller heteroarylgruppe, 3- til 6-leddet cycloalkylgruppe, eller en lineær eller forgrenet C_3-C_6-alkylgruppe, der hver eventuelt er substitueret med én eller to grupper udvalgt fra halo, cyano, alkyl, haloalkyl, cycloalkyl, aryl, heteroaryl, hydroxyl, alkoxy, haloalkoxy, amino, alkylamino, carboxy, alkoxycarbonyl, alkylcarbonyloxy, alkylcarbonylamino, haloalkylcarbonylamino, carbamoyl, hydroxycarbamoyl, alkylcarbamoyl, carbamoylamino, alkylcarbamoylamino, alkylsulfonyl, haloalkylsulfonyl, sulfamoyl, alkylsulfamoyl, alkylsulfonylamino, haloalkylsulfonylamino, eller to substituenter danner en alkylendioxygruppe eller en haloalkylendioxygruppe, hvor hver af aryl- eller heteroarylsubstituenterne eventuelt er substitueret med én eller flere yderligere substituenter, der er udvalgt fra halo, cyano, alkyl, haloalkyl, hydroxyl, alkoxy, haloalkoxy;

Ar^2 er en aryl eller heteroaryl, cycloalkyl, monocyklisk heterocyclyl eller C_2-C_6-alkylgruppe, der hver eventuelt er substitueret med én eller to grupper udvalgt fra halo, cyano, nitro, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, heteroalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, benzoxazol-2-yl, heteroarylalkyl, hydroxyl, hydroxyalkyl, alkoxy, haloalkoxy, alkoxyalkoxy, cycloalkyloxy, cycloalkylalkyloxy, heterocyclyloxy, aryloxy, heteroaryloxy, alkoxyalkyl, haloalkoxyalkyl, arylalkyloxy, heteroarylalkyloxy, aryloxyalkyl, heteroaryloxyalkyl, amino, alkylamino, arylcarbonyl, carboxy, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, alkylcarbonyloxy, arylcarbonyloxy, heteroarylcarbonyloxy, alkylcarbonylamino, carbamoyl, hydroxycarbamoyl, alkylcarbamoyl, arylcarbamoyl, heteroarylcarbamoyl, carbamoylamino, alkylcarbamoylamino, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, heteroarylsulfamoyl, alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, oxo,

eller to substituenter danner en alkylendioxygruppe eller en haloalkylendioxygruppe, eller kondenseret til aryl-, heteroaryl- eller cycloalkylgruppen kan være én eller flere aryl- eller heteroaryldele, hvor hver af substituenterne eventuelt er substitueret med én eller flere yderligere substituenter, der er udvalgt fra halo, cyano, nitro, alkyl, hydroxyalkyl, haloalkyl, cyanomethyl, cycloalkyl, heterocyclyl, aryl eventuelt substitueret med en chlor- eller methylgruppe, heteroaryl, heteroalkyl, hydroxyl, alkoxy, alkoxyalkyl, alkoxyalkoxy, haloalkoxy, cycloalkyloxy, cycloalkylalkyloxy, aryloxy, aralkyloxy eventuelt substitueret med en fluorgruppe, carboxy, alkoxycarbonyl, alkylcarbonyloxy, amino, alkylamino, alkylcarbonylamino, haloalkylcarbonylamino, carbamoyl, hydroxycarbamoyl, alkylcarbamoyl, carbamoylalkyloxy, carbamoylamino, alkylcarbamoylamino, carbamimidoyl, hydroxycarbamimidoyl, alkylsulfonyl, haloalkylsulfonyl, cycloalkylsulfonyl, heterocyclylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, alkylsulfonylamino, haloalkylsulfonylamino, oxo og haloalkoxyalkyl;

$\mathbf{R^3}$ er H, cyano, alkyl, hydroxyalkyl, aralkyl, alkoxyalkyl, acetyl, arylsulfonyl;

$\mathbf{R^{3'}}$ er H eller C_1-C_4-alkyl;

$\mathbf{R^4}$ er H, cyano, C_1-C_4-alkyl;

hvor, medmindre andet er anført:

alkylgruppe, selv eller som en del af en anden substituent, omfatter 1 til 6 carbonatomer,

arylgruppen har 1 eller 2 ringe og indeholder 5 til 12 atomer i ringen,

heterocyclylgruppe, selv eller som en del af en anden substituent, har 1 eller 2 ringe og indeholder 3 til 10 atomer i ringen omfattende 1 til 4 heteroatomer udvalgt fra N-, O- og/eller S-atomer,

heteroaryl, selv eller som en del af en anden substituent, har 1 eller 2 rings og indeholder 5 til 6 atomer i ringen omfattende én eller flere heteroatomer udvalgt fra N-, O- og/eller S-atomer,

cycloalkylgruppen har 1 eller 2 cykliske strukturer og indeholder fra 3 til 10 carbonatomer i ringen;

forudsat forbindelsen med formlen (Ia-1b') ikke er

(2S)-methyl 1-benzoyl-5-mesitylpyrrolidin-2-carboxylat,

(2S)-methyl 1-benzoyl-5-(2,4,6-triethylphenyl)pyrrolidin-2-carboxylat,

(2S,5S)-1-benzoyl-5-mesitylpyrrolidin-2-carboxylsyre,

(2S)-methyl 1-benzoyl-5-propylpyrrolidin-2-carboxylat,

(2S,5S)-methyl 1-benzoyl-5-propylpyrrolidin-2-carboxylat,

(2S,5R)-methyl 1-benzoyl-5-propylpyrrolidin-2-carboxylat,

(2S,5R)-5-(*tert*-butyl)-1-(4-phenylbutanoyl)pyrrolidin-2-carboxylsyre,

(2S,5R)-methyl 5-(tert-butyl)-1-(4-phenylbutanoyl)pyrrolidin-2-carboxylat,

(2R,5R)-1-(4-bromthiophen-2-carbonyl)-5-phenylpyrrolidin-2-carboxylsyre,

(2R,5S)-1-(3-brom-2,6-dimethoxybenzoyl)-5-phenylpyrrolidin-2-carboxylsyre,

1-[7-(4-tert-butyl-phenoxy)-1-cyclopentylmethyl-isoquinolin-3-carbonyl]-(5R)-phenyl-pyrrolidin-(2S)-carboxylsyre,

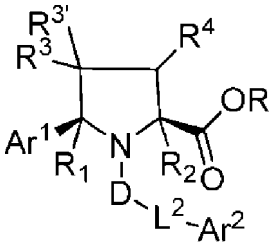
forudsat:

Ar^2 ikke er phthalazin-6-yl, pyrido[2,3-d]pyridazin-2-yl, pyrido[2,3-d]pyridazin-3-yl, eller pyrazino[2,3-d]pyridazin-2-yl;

og/eller **R^3** ikke er en monosubstitueret hydroxymethyl;

til anvendelse i behandling og/eller forebyggelse af inflammation.

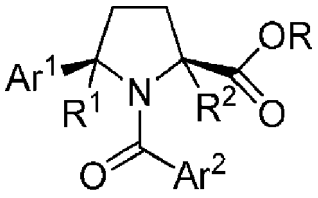
2. Forbindelse til anvendelse ifølge krav **1** med formlen Ib-1b':



Ib-1b'

eller et farmaceutisk acceptabelt salt eller solvat deraf, hvor **D**, **L^2**, **Ar^1**, **Ar^2**, **R**, **R^1**, **R^2**, **R^3**, **R$^{3'}$** og **R^4** er som defineret i krav **1**.

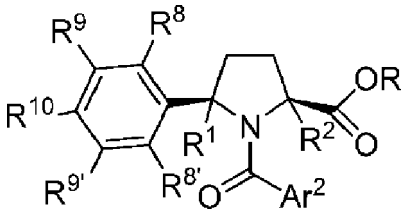
3. Forbindelse til anvendelse ifølge krav **2** med formlen Ib-1d:



Ib-1d

eller et farmaceutisk acceptabelt salt eller solvat deraf, hvor **Ar^1**, **Ar^2**, **R^1**, **R^2** og **R** er som defineret i krav **1**.

4. Forbindelse til anvendelse ifølge krav **3** med formlen Ib-1e:



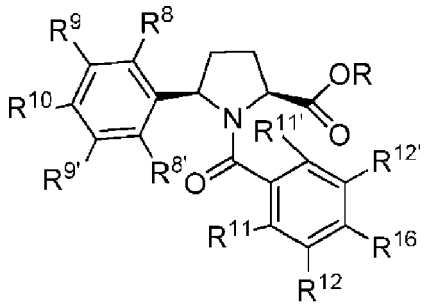
Ib-1e

eller et farmaceutisk acceptabelt salt eller solvat deraf, hvor

Ar^2, **R^1**, **R^2** og **R** er som defineret i krav **1**;

og **R^8**, **$R^{8'}$**, **R^9**, **$R^{9'}$** og **R^{10}** er uafhængigt udvalgt fra H, halo, cyano, alkyl, haloalkyl, cycloalkyl, aryl, heteroaryl, hydroxyl, haloalkoxy, alkylamino, alkoxycarbonyl, alkylcarbonyloxy, alkylcarbonylamino, haloalkylcarbonylamino, carbamoyl, hydroxycarbamoyl, alkylcarbamoyl, carbamoylamino, alkylcarbamoylamino, alkylsulfonyl, haloalkylsulfonyl, sulfamoyl, alkylsulfamoyl, alkylsulfonylamino, eller én eller flere af **R^8** og **R^9**, eller **R^9** og **R^{10}**, eller **R^{10}** og **$R^{9'}$**, eller **$R^{9'}$** og **$R^{8'}$** danner en alkylendioxygruppe eller en haloalkylendioxygruppe sammen med den phenylgruppe, de er bundet til, hvor hver af substituenterne eventuelt er substitueret med én eller flere yderligere substituenter, der er udvalgt fra halo, cyano, alkyl, haloalkyl, hydroxyl, alkoxy, haloalkoxy.

5. Forbindelse til anvendelse ifølge krav **4** med formlen Ib-1g:



Ib-1g

eller et farmaceutisk acceptabelt salt eller solvat deraf, hvor

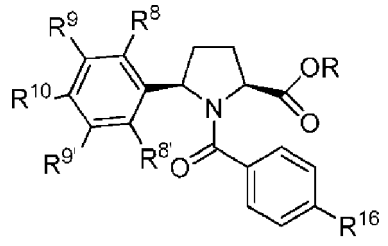
R er som defineret i krav **1**;

R^8, **$R^{8'}$**, **R^9**, **$R^{9'}$** og **R^{10}** er som defineret i krav **4**;

og **R^{11}**, **$R^{11'}$**, **R^{12}**, **$R^{12'}$** og **R^{16}** er uafhængigt udvalgt fra H, halo, cyano, nitro, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, heteroalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, hydroxyl, hydroxyalkyl, alkoxy, haloalkoxy, alkoxyalkoxy, cycloalkyloxy, heterocyclyloxy, aryloxy, heteroaryloxy, alkoxyalkyl, haloalkoxyalkyl, cycloalkylalkyloxy, arylalkyloxy, heteroarylalkyloxy, aryloxyalkyl, heteroaryloxyalkyl, arylcarbonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, alkylcarbonyloxy,

arylcarbonyloxy, heteroarylcarbonyloxy, alkylcarbonylamino, carbamoyl, hydroxycarbamoyl, alkylcarbamoyl, arylcarbamoyl, heteroarylcarbamoyl, carbamoylamino, alkylcarbamoylamino, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, heteroarylsulfamoyl, alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, eller én eller flere af $\mathbf{R^{11}}$ og $\mathbf{R^{12}}$, eller $\mathbf{R^{12}}$ og $\mathbf{R^{16}}$, eller $\mathbf{R^{16}}$ og $\mathbf{R^{12'}}$, eller $\mathbf{R^{12'}}$ og $\mathbf{R^{11'}}$ danner en alkylendioxygruppe eller en haloalkylendioxygruppe sammen med den phenylgruppe, de er bundet til, eller én eller flere af $\mathbf{R^{11}}$ og $\mathbf{R^{12}}$ eller $\mathbf{R^{12}}$ og $\mathbf{R^{16}}$, eller $\mathbf{R^{16}}$ og $\mathbf{R^{12'}}$, eller $\mathbf{R^{12'}}$ og $\mathbf{R^{11'}}$ danner sammen en aryl- eller heteroaryldel kondenseret til den phenylgruppe, de er bundet til, hvor hver af substituenterne eventuelt er substitueret med én eller flere yderligere substituenter, der er udvalgt fra halo, cyano, alkyl, hydroxyalkyl, alkoxyalkyl, haloalkyl, cyanomethyl, cycloalkyl, heterocyclyl, aryl eventuelt substitueret med én chlor- eller methylgruppe, heteroaryl, heteroalkyl, hydroxyl, alkoxy, alkoxyalkoxy, haloalkoxy, cycloalkyloxy, cycloalkylalkyloxy, aryloxy, aralkyloxy eventuelt substitueret med én fluor, amino, alkylamino, carboxy, alkoxycarbonyl, alkylcarbonyloxy, alkylcarbonylamino, haloalkylcarbonylamino, carbamoyl, hydroxycarbamoyl, alkylcarbamoyl, carbamoylalkyloxy, carbamoylamino, alkylcarbamoylamino, carbamimidoyl, hydroxycarbamimidoyl, alkylsulfonyl, haloalkylsulfonyl, cycloalkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, alkylsulfonylamino, haloalkylsulfonylamino og oxo.

6. Forbindelse til anvendelse ifølge krav **5** med formlen Ib-1g1:



Ib-1g1

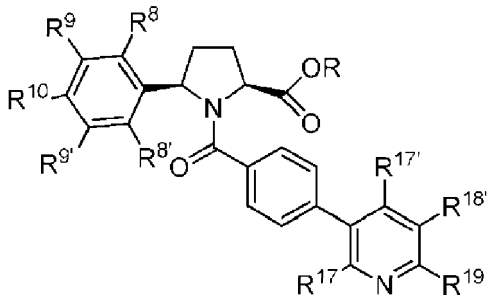
eller et farmaceutisk acceptabelt salt eller solvat deraf, hvor

R er som defineret i krav **1;**

$\mathbf{R^8}$, $\mathbf{R^{8'}}$, $\mathbf{R^9}$, $\mathbf{R^{9'}}$ og $\mathbf{R^{10}}$ er som defineret i krav **4**; og

$\mathbf{R^{16}}$ er som defineret i krav **5**.

7. Forbindelse til anvendelse ifølge krav **6** med formlen Ib-1g1a:



Ib-1g1a

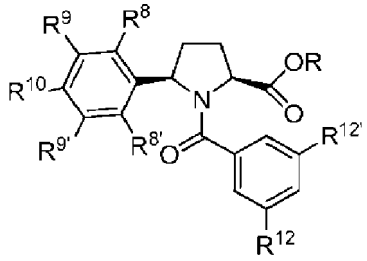
eller et farmaceutisk acceptabelt salt eller solvat deraf, hvor

R er som defineret i krav **1;**

$\mathbf{R^8}$, $\mathbf{R^{8'}}$, $\mathbf{R^9}$, $\mathbf{R^{9'}}$ og $\mathbf{R^{10}}$ er som defineret i krav **4**; og

$\mathbf{R^{17}}$, $\mathbf{R^{17'}}$, $\mathbf{R^{18'}}$ og $\mathbf{R^{19}}$ er uafhængigt udvalgt fra H, halo, cyano, alkyl, haloalkyl, cycloalkyl, heteroalkyl, heterocyclyl, aryl, heteroaryl, hydroxyl, alkoxy, haloalkoxy, alkoxyalkoxy, cycloalkyloxy, alkoxyalkyl, cycloalkylalkyloxy, aryloxy, aralkyloxy, alkylamino, alkylsulfonyl, alkylcarbonylamino, haloalkylcarbonylamino, carbamoyl, hydroxycarbamoyl, alkylcarbamoyl, carbamoylamino, alkylcarbamoylamino, haloalkylsulfonyl, cycloalkylsulfonyl, sulfamoyl, alkylsulfamoyl, alkylsulfonylamino, haloalkylsulfonylamino.

8. Forbindelse til anvendelse ifølge krav **5** med formlen Ib-1g2:



Ib-1g2

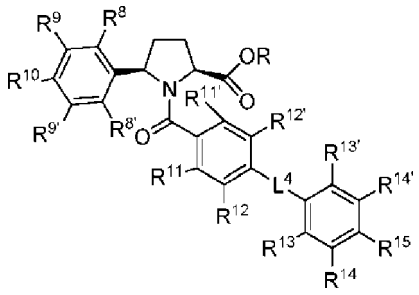
eller et farmaceutisk acceptabelt salt eller solvat deraf, hvor

R er som defineret i krav **1**;

$\mathbf{R^8}$, $\mathbf{R^{8'}}$, $\mathbf{R^9}$, $\mathbf{R^{9'}}$ og $\mathbf{R^{10}}$ er som defineret i krav **4**; og

$\mathbf{R^{12}}$ og $\mathbf{R^{12'}}$ er som defineret i krav **5**.

9. Forbindelse til anvendelse ifølge krav **5** med formlen Ib-1h:



Ib-1h

eller et farmaceutisk acceptabelt salt eller solvat deraf, hvor

R er som defineret i krav **1**;

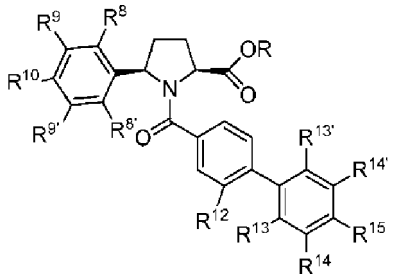
$\mathbf{R^8}$, $\mathbf{R^{8'}}$, $\mathbf{R^9}$, $\mathbf{R^{9'}}$ og $\mathbf{R^{10}}$ er som defineret i krav **4**;

$\mathbf{L^4}$ er en enkeltbinding, -C(O)-, -O-, -O-C_1-C_3-alkylen eller -C_1-C_3-alkylen-O-eventuelt substitueret med én eller flere grupper udvalgt fra fluor eller methyl;

$\mathbf{R^{11}}$, $\mathbf{R^{11'}}$, $\mathbf{R^{12}}$ og $\mathbf{R^{12'}}$ er som defineret i krav **5**; og

$\mathbf{R^{13}}$, $\mathbf{R^{13'}}$, $\mathbf{R^{14}}$, $\mathbf{R^{14'}}$ og $\mathbf{R^{15}}$ er uafhængigt udvalgt fra H, halo cyano, alkyl, haloalkyl, cyanomethyl, cycloalkyl, heteroalkyl, heterocyclyl, aryl, heteroaryl, hydroxyl, hydroxyalkyl, alkoxy, haloalkoxy, alkoxyalkoxy, cycloalkyloxy, alkoxyalkyl, cycloalkylalkyloxy, aralkyloxy eventuelt substitueret med én fluor, amino, alkylamino, alkylcarbonylamino, haloalkylcarbonylamino, carbamoyl, hydroxycarbamoyl, alkylcarbamoyl, carbamoylalkyloxy, alkylcarbamoylamino, carbamimidoyl, hydroxycarbamimidoyl, alkylsulfonyl, haloalkylsulfonyl, cycloalkylsulfonyl, sulfamoyl, alkylsulfamoyl, alkylsulfonylamino, haloalkylsulfonylamino.

10. Forbindelse til anvendelse ifølge krav **9** med formlen Ib-1h1:



Ib-1h1

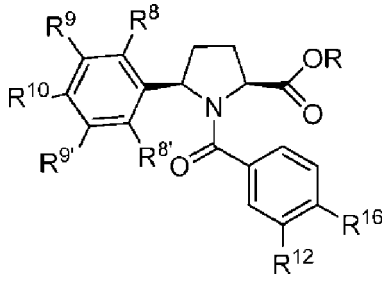
eller et farmaceutisk acceptabelt salt eller solvat deraf, hvor

R er som defineret i krav **1**;

$\mathbf{R^8}$, $\mathbf{R^{8'}}$, $\mathbf{R^9}$, $\mathbf{R^{9'}}$ og $\mathbf{R^{10}}$ er som defineret i krav **4**; og

$\mathbf{R^{12}}$ $\mathbf{R^{13}}$, $\mathbf{R^{13'}}$, $\mathbf{R^{14}}$, $\mathbf{R^{14'}}$ og $\mathbf{R^{15}}$ er som defineret i krav **9**.

11. Forbindelse til anvendelse ifølge krav **5** med formlen Ib-1h':



Ib-1h'

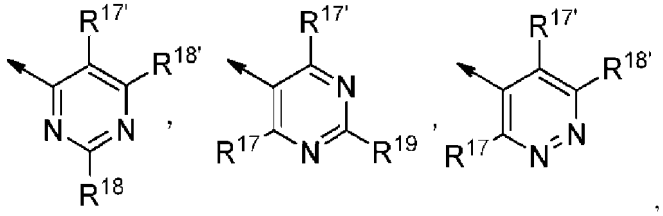
eller et farmaceutisk acceptabelt salt eller solvat deraf, hvor

R er som defineret i krav **1**;

R^8, **$R^{8'}$**, **R^9**, **$R^{9'}$** og **R^{10}** er som defineret i krav **4**;

R^{12} er som defineret i krav **5**; og

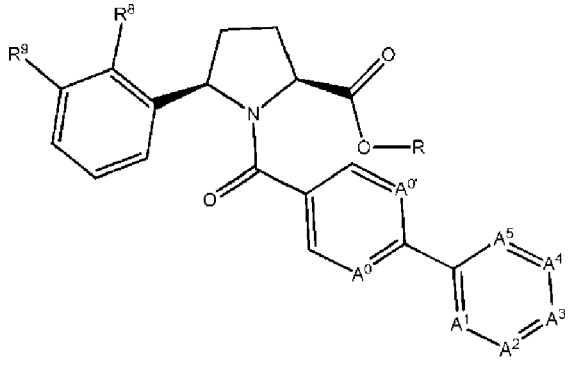
R^{16} er udvalgt fra gruppen af heteroaryldele bestående af:



hvor pilen markerer bindingspunktet til phenylringen; og

R^{17}, **$R^{17'}$**, **R^{18}**, **$R^{18'}$** og **R^{19}** er uafhængigt udvalgt fra H, halo, cyano, alkyl, haloalkyl, hydroxyl, hydroxyalkyl, alkoxy, haloalkoxy, alkoxyalkoxy, cycloalkyloxy, alkoxyalkyl, cycloalkylalkyloxy, aralkyloxy, amino, alkylamino, alkylcarbonylamino, haloalkylcarbonylamino, carbamoyl, hydroxycarbamoyl, alkylcarbamoyl, carbamoylamino, alkylcarbamoylamino, carbamimidoyl, hydroxycarbamimidoyl, alkylsulfonyl, haloalkylsulfonyl, sulfamoyl, alkylsulfamoyl, alkylsulfonylamino, haloalkylsulfonylamino.

12. Forbindelse til anvendelse ifølge krav **5** med formlen Ib-1h":



Ib-1h"

eller et farmaceutisk acceptabelt salt eller solvat deraf, hvor

$\mathbf{R^8}$ er F eller Cl og $\mathbf{R^9}$ er H, eller både $\mathbf{R^8}$ og $\mathbf{R^9}$ er F;

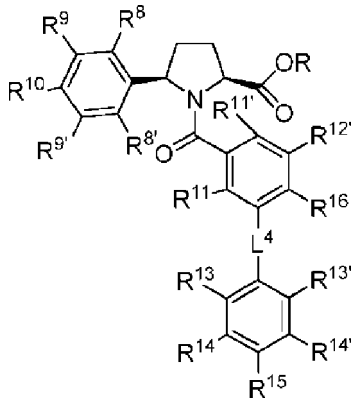
R er H, methyl, ethyl eller *tert*-butyl;

og $\mathbf{A^0}$, $\mathbf{A^{0'}}$, $\mathbf{A^1}$, $\mathbf{A^2}$, $\mathbf{A^3}$, $\mathbf{A^4}$ og $\mathbf{A^5}$ er udvalgt fra kombinationerne ***1*** til ***24***:

Kombination nr.	$\mathbf{A^0}$	$\mathbf{A^{0'}}$	$\mathbf{A^1}$	$\mathbf{A^2}$	$\mathbf{A^3}$	$\mathbf{A^4}$	$\mathbf{A^5}$
1	CH	CH	C-OCH_3	CH	C-$NHSO_2CH_3$	CH	CH
2	CH	CH	C-CH_3	C-$NHSO_2CH_3$	CH	CH	CH
3	CH	CH	C-OCH_3	N	CH	CH	CH
4	CH	CH	C-OCH_3	N	C-OCH_3	N	CH
5	C-OCH_3	CH	CH	N	C-OCH_3	N	CH
6	CH	CH	C-OCH_3	N	N	C-OCH_3	CH
7	CH	CH	C-OCH_3	CH	CH	C-CN	CH
8	CH	CH	C-CH_3	CH	CH	C-CN	CH
9	C-F	CH	C-OCH_3	N	N	C-OCH_3	CH
10	CH	CH	CH	N	CH	CH	C-OCH_3
11	CH	CH	CH	CH	C-$NHSO_2CH_3$	CH	CH
12	CH	CH	CH	C-$NHSO_2CH_3$	CH	CH	CH
13	CH	CH	CH	N	C-OCH_3	N	C-OCH_3
15	CH	CH	C-OCH_3	N	CH	N	CH
16	CH	C-OCH_3	C-OCH_3	CH	CH	CH	CH
17	C-OCH_3	CH	CH	N	CH	CH	C-OCH_3
18	C-OCH_3	CH	C-	N	C-OCH_3	N	CH

			OCH_3				
19	CH	CH	C-OCH_3	CH	C-$NHCOCH_3$	CH	CH
20	CH	CH	C-CN	CH	C-OCH_3	C-OCH_3	CH
21	CH	CH	C-OCH_3	CH	C-$N(CH_3)SO_2CH_3$	CH	CH
23	CH	CH	C-OCH_3	N	CH	N	C-OCH_3
24	CH	CH	C-OCH_3	CH	N	CH	CH

13. Forbindelse til anvendelse ifølge krav **5** med formlen Ib-1i:



Ib-1i

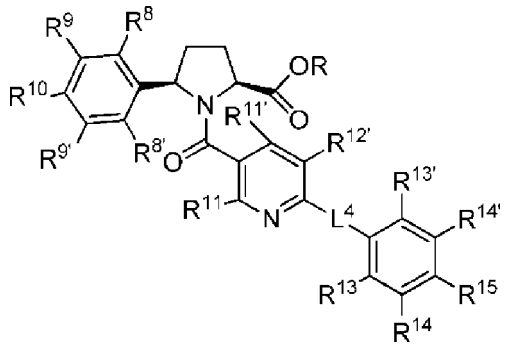
eller et farmaceutisk acceptabelt salt eller solvat deraf, hvor **R** er som defineret i krav 1;

R^8, **$R^{8'}$**, **R^9**, **$R^{9'}$** og **R^{10}** er som defineret i krav **4**;

L^4, **R^{11}**, **$R^{11'}$**, **$R^{12'}$** **R^{13}**, **$R^{13'}$**, **R^{14}**, **$R^{14'}$** og **R^{15}** er som defineret i krav **9**; og

R^{16} er som defineret ovenfor i krav **5**.

14. Forbindelse til anvendelse ifølge krav **4** med formlen Ib-1j:



Ib-1j

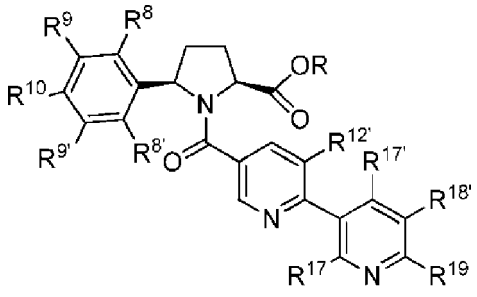
eller et farmaceutisk acceptabelt salt eller solvat deraf, hvor

R er som defineret i krav **1**;

R^8, **$R^{8'}$**, **R^9**, **$R^{9'}$** og **R^{10}** er som defineret i krav **5**; og

L^4, **R^{11}**, **$R^{11'}$**, **$R^{12'}$**, **R^{13}**, **$R^{13'}$**, **R^{14}**, **$R^{14'}$** og **R^{15}** er som defineret ovenfor i krav **9**.

15. Forbindelse til anvendelse ifølge krav **4** med formlen Ib-1k:



Ib-1k

eller et farmaceutisk acceptabelt salt eller solvat deraf, hvor

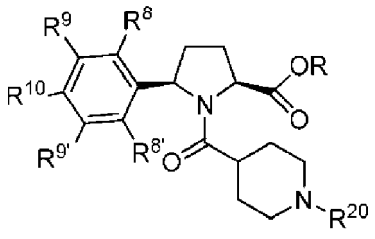
R er som defineret i krav **1;**

R^8, **$R^{8'}$**, **R^9**, **$R^{9'}$** og **R^{10}** er som defineret i krav **4**;

$R^{12'}$ er H, fluor, chlor, CF_3, methyl eller methoxy; og

R^{17}, **$R^{17'}$**, **$R^{18'}$** og **R^{19}** er uafhængigt udvalgt fra H, halo, cyano, nitro, alkyl, haloalkyl, alkoxyalkyl, alkoxy, cycloalkylalkyloxy, haloalkoxy, alkoxyalkoxy, amino, alkylcarbonylamino, alkylsulfonyl, alkylsulfonylamino.

16. Forbindelse til anvendelse ifølge krav **4** med formlen Ib-1l:



Ib-1l

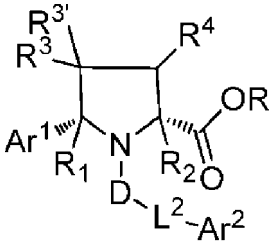
eller et farmaceutisk acceptabelt salt eller solvat deraf, hvor

R er som defineret i krav **1;**

$\mathbf{R^8}$, $\mathbf{R^{8'}}$, $\mathbf{R^9}$, $\mathbf{R^{9'}}$ og $\mathbf{R^{10}}$ er som defineret i krav **4**; og

$\mathbf{R^{20}}$ er en aryl eller heteroaryl, hvor hver aryl eller heteroaryl eventuelt er substitueret med én eller flere substituent(er), der er udvalgt fra halo, alkyl, haloalkyl, cyano, nitro, phenyl eventuelt substitueret med én chlor, alkoxy, heterocyclylsulfonyl, alkylsulfamoyl eller alkylsulfonylamino.

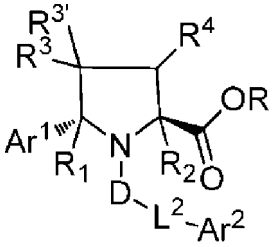
17. Forbindelse til anvendelse ifølge krav **1** med formlen Ic-1b':



Ic-1b'

eller et farmaceutisk acceptabelt salt eller solvat deraf, hvor **D**, $\mathbf{L^2}$, $\mathbf{Ar^1}$, $\mathbf{Ar^2}$, **R**, $\mathbf{R^1}$, $\mathbf{R^2}$, $\mathbf{R^3}$, $\mathbf{R^{3'}}$ og $\mathbf{R^4}$ er som defineret i krav **1**.

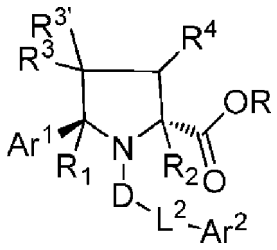
18. Forbindelse til anvendelse ifølge krav **1** med formlen Id-1b':



Id-1b'

eller et farmaceutisk acceptabelt salt eller solvat deraf, hvor **D**, $\mathbf{L^2}$, $\mathbf{Ar^1}$, $\mathbf{Ar^2}$, **R**, $\mathbf{R^1}$, $\mathbf{R^2}$, $\mathbf{R^3}$, $\mathbf{R^{3'}}$ og $\mathbf{R^4}$ er som defineret i krav **1**.

19. Forbindelse til anvendelse ifølge krav **1** med formlen Ie-1b':



Ie-1b'

eller et farmaceutisk acceptabelt salt eller solvat deraf, hvor **D**, **L^2**, **Ar^1**, **Ar^2**, **R**, **R^1**, **R^2**, **R^3**, **$R^{3'}$** og **R^4** er som defineret i krav **1**.

20. Forbindelse til anvendelse ifølge krav **1** udvalgt fra gruppen bestående af:

1 (2S,5R)-5-(2-chlorphenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

2 (2S,5R)-5-(2-chlorphenyl)-1-(2'-methyl-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

3 (2S,5R)-1-(3-((4-chlorbenzyl)oxy)-5-methoxybenzoyl)-5-(2-chlorphenyl)pyrrolidin-2-carboxylsyre

4 (2S,5R)-5-(2-chlorphenyl)-1-(2'-fluor-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

5 (2S,5R)-5-(2-chlorphenyl)-1-(4'-methyl-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

6 (2S,5R)-5-(2-chlorphenyl)-1-(3-methoxy-5-phenethoxybenzoyl)pyrrolidin-2-carboxylsyre

8 (2S,5R)-1-([1,1'-biphenyl]-4-carbonyl)-5-(2-chlorphenyl)pyrrolidin-2-carboxylsyre

9 (2S,5R)-5-(2-chlorphenyl)-1-(3-(3,3-diphenylpropoxy)-5-methoxybenzoyl)pyrrolidin-2-carboxylsyre

10 (2S,5R)-5-(2-chlorphenyl)-1-(3'-fluor-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

11 (2S,5R)-5-(2-chlorphenyl)-1-(3'-methyl-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

12 (2S,5R)-5-(2-chlorphenyl)-1-(3-methoxy-5-((4-(methylsulfonyl)benzyl)oxy)benzoyl)pyrrolidin-2-carboxylsyre

13 (2S,5R)-5-(2-chlorphenyl)-1-(3'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-

2-carboxylsyre

14 (2S,5R)-5-(2-chlorphenyl)-1-(3,5-dimethoxybenzoyl)pyrrolidin-2-carboxylsyre

15 (2S,5R)-5-(2-chlorphenyl)-1-(4-(phenoxymethyl)benzoyl)pyrrolidin-2-carboxylsyre

16 (2S,5R)-5-(2-chlorphenyl)-1-(4-((2-fluorbenzyl)oxy)benzoyl)pyrrolidin-2-carboxylsyre

17 (2S,5R)-1-(3-chlor-5-methoxybenzoyl)-5-(2-chlorphenyl)pyrrolidin-2-carboxylsyre

18 (2S,5R)-5-(2-chlorphenyl)-1-(4'-fluor-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

19 (2S,5R)-5-(2-chlorphenyl)-1-(4-phenethoxybenzoyl)pyrrolidin-2-carboxylsyre

21 (2S,5R)-5-(2-chlorphenyl)-1-(3,5-diethoxybenzoyl)pyrrolidin-2-carboxylsyre

23 (2S,5R)-5-(2-chlorphenyl)-1-(3-phenethoxybenzoyl)pyrrolidin-2-carboxylsyre

24 (2S)-1-([1,1'-biphenyl]-4-carbonyl)-4-benzyl-5-phenylpyrrolidin-2-carboxylsyre

25 (2S,5R)-5-(2-chlorphenyl)-1-(1,2,3,4-tetrahydronaphthalen-2-carbonyl)pyrrolidin-2-carboxylsyre

26 (2S,5R)-5-(2-chlorphenyl)-1-(4-isobutylbenzoyl)pyrrolidin-2-carboxylsyre

27 (2S,5R)-5-(2-chlorphenyl)-1-(2,2-difluorbenzo[d][1,3]dioxole-6-carbonyl)pyrrolidin-2-carboxylsyre

28 (2S,5R)-1-([1,1'-biphenyl]-4-carbonyl)-5-phenylpyrrolidin-2-carboxylsyre

29 (2S,5R)-5-(2-chlorphenyl)-1-(3-fluor-5-methoxybenzoyl)pyrrolidin-2-carboxylsyre

30 (2S,5R)-5-(2-chlorphenyl)-1-(6-phenylnicotinoyl)pyrrolidin-2-carboxylsyre

31 (2S,5R)-5-(2-chlorphenyl)-1-(3-methoxy-5-(2-methoxyethoxy)benzoyl)pyrrolidin-2-carboxylsyre

32 (2S,5R)-5-(2-chlorphenyl)-1-(3'-methoxy-[1,1'-biphenyl]-3-carbonyl)pyrrolidin-2-carboxylsyre

33 (2S,5R)-5-(2-chlorphenyl)-1-(3-methoxy-5-(trifluormethyl)benzoyl)pyrrolidin-2-carboxylsyre

34 (2S,5R)-5-(2-chlorphenyl)-1-(1-(4-methoxyphenyl)-5-phenyl-1H-pyrazol-3-carbonyl)pyrrolidin-2-carboxylsyre

35 (2S,5R)-5-(2-chlorphenyl)-1-(4-isopropoxybenzoyl)pyrrolidin-2-carboxylsyre

36 (2S,5R)-5-(2-chlorphenyl)-1-(3-((3,5-dimethylisoxazol-4-yl)methoxy)-5-methoxybenzoyl)pyrrolidin-2-carboxylsyre

37 (2S,5R)-5-(2-chlorphenyl)-1-(2,3-dihydro-1H-inden-2-carbonyl)pyrrolidin-2-carboxylsyre

38 (2S,5R)-5-(2-chlorphenyl)-1-(3-methyl-5-(trifluormethoxy)benzoyl)pyrrolidin-2-carboxylsyre

39 (2S,5R)-1-(3-(benzyloxy)benzoyl)-5-(2-chlorphenyl)pyrrolidin-2-carboxylsyre

40 (2S,5R)-5-(2-chlorphenyl)-1-(3-methoxybenzoyl)pyrrolidin-2-carboxylsyre

41 (2S,5R)-5-(2-chlorphenyl)-1-(2-phenylpyrimidin-5-carbonyl)pyrrolidin-2-carboxylsyre

42 (2S,5R)-5-(2-chlorphenyl)-1-(4-(trifluormethoxy)benzoyl)pyrrolidin-2-carboxylsyre

43 (2S,5R)-5-(2-chlorphenyl)-1-(4-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)benzoyl)pyrrolidin-2-carboxylsyre

44 4-((2S,5R)-2-carboxy-5-(2-chlorphenyl)pyrrolidin-1-carbonyl)-2,6-dimethoxypyrimidin-1-iumformiat

45 (2S,5R)-5-(2-chlorphenyl)-1-(4-phenylbutanoyl)pyrrolidin-2-carboxylsyre

46 (2S,5R)-5-(2-chlorphenyl)-1-(3-methyl-5-(trifluormethyl)benzoyl)pyrrolidin-2-carboxylsyre

47 (2S,5R)-1-([1,1'-biphenyl]-4-carbonyl)-5-(3-chlorpyridin-2-yl)pyrrolidin-2-carboxylsyre

48 (2S,5R)-5-(2-chlorphenyl)-1-(3-hydroxy-5-(trifluormethyl)benzoyl)pyrrolidin-2-carboxylsyre

49 (2S,5S)-5-(2-chlorphenyl)-1-(3-methoxybenzoyl)pyrrolidin-2-carboxylsyre

50 (2S,5R)-1-(3,5-dimethoxybenzoyl)-5-phenylpyrrolidin-2-carboxylsyre

51 (S)-5-([1,1'-biphenyl]-3-yl)-1-(3-methoxybenzoyl)pyrrolidin-2-carboxylsyre

52 (2S,5R)-5-(2-chlorphenyl)-1-(3-phenylpropanoyl)pyrrolidin-2-carboxylsyre

53 (2S,5S)-5-(2-chlorphenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

54 (2S,5R)-1-([1,1'-biphenyl]-4-carbonyl)-5-(pyridin-2-yl)pyrrolidin-2-carboxylsyre

55 (2S,5R)-5-(2-chlorphenyl)-1-(5-phenylpicolinoyl)pyrrolidin-2-carboxylsyre

57 (2S,5R)-5-(2-fluorphenyl)-1-(3-methoxybenzoyl)pyrrolidin-2-carboxylsyre

59 (2R,5S)-1-([1,1'-biphenyl]-4-carbonyl)-5-phenylpyrrolidin-2-carboxylsyre

62 (2S,5R)-1-(3-methoxybenzoyl)-5-(2-methoxyphenyl)pyrrolidin-2-carboxylsyre

63 (2R,5S)-5-(2-chlorphenyl)-1-(3-methoxybenzoyl)pyrrolidin-2-carboxylsyre

65 (2S)-5-(4-chlorphenyl)-1-(3-methoxybenzoyl)pyrrolidin-2-carboxylsyre

66 (2S)-5-([1,1'-biphenyl]-4-yl)-1-(3-methoxybenzoyl)pyrrolidin-2-carboxylsyre

67 (2S,5R)-methyl-5-(2-chlorphenyl)-1-(3-methoxybenzoyl)pyrrolidin-2-carboxylat

69 (2S)-5-cyclohexyl-1-(3-methoxybenzoyl)pyrrolidin-2-carboxylsyre

71 (2S,5S)-5-(2-chlorphenyl)-1-(3,5-dimethoxybenzoyl)pyrrolidin-2-carboxylsyre

72 (2S,5R)-5-([1,1'-biphenyl]-2-yl)-1-(3-methoxybenzoyl)pyrrolidin-2-carboxylsyre

75 (2S,5R)-5-(2-chlorphenyl)-1-(6-phenylpyrimidin-4-carbonyl)pyrrolidin-2-carboxylsyre

76 (2S,5R)-5-(2-chlorphenyl)-1-(6-(2-fluorphenyl)nicotinoyl)pyrrolidin-2-carboxylsyre

77 (2S,5R)-5-(2-chlorphenyl)-1-(6-(2-chlorphenyl)nicotinoyl)pyrrolidin-2-carboxylsyre

78 (2S,5R)-5-(2-chlorphenyl)-1-(6-(2-methoxyphenyl)nicotinoyl)pyrrolidin-2-carboxylsyre

79 (2S,5R)-5-(2-chlorphenyl)-1-(6-(3-fluorphenyl)nicotinoyl)pyrrolidin-2-carboxylsyre

80 (2S,5R)-5-(2-chlorphenyl)-1-(6-(3-methoxyphenyl)nicotinoyl)pyrrolidin-2-carboxylsyre

81 (2S,5R)-5-(2-chlorphenyl)-1-(6-(4-methoxyphenyl)nicotinoyl)pyrrolidin-2-carboxylsyre

82 (2S,5R)-5-(2-chlorphenyl)-1-(6-(4-fluorphenyl)nicotinoyl)pyrrolidin-2-carboxylsyre

83 (2S,5R)-5-(2-chlorphenyl)-1-(2-(2-chlorphenyl)pyrimidin-5-carbonyl)pyrrolidin-2-carboxylsyre

84 (2S,5R)-5-(2-chlorphenyl)-1-(2-methyl-6-phenylnicotinoyl)pyrrolidin-2-carboxylsyre

85 (2S,5R)-1-(4-chlor-2-(pyridin-3-yl)pyrimidin-5-carbonyl)-5-(2-chlorphenyl)pyrrolidin-2-carboxylsyre

86 (2S,5R)-1-(4-chlor-2-(pyridin-2-yl)pyrimidin-5-carbonyl)-5-(2-chlorphenyl)pyrrolidin-2-carboxylsyre

87 (2S,5R)-1-(4-chlor-2-(pyridin-4-yl)pyrimidin-5-carbonyl)-5-(2-chlorphenyl)pyrrolidin-2-carboxylsyre

88 (2S,5R)-5-(2-chlorphenyl)-1-(4-(pyridin-2-yl)benzoyl)pyrrolidin-2-carboxylsyre

89 (2S,5R)-1-(4-((4-chlorphenoxy)methyl)benzoyl)-5-(2-chlorphenyl)pyrrolidin-2-carboxylsyre

90 (2S,5R)-5-(2-chlorphenyl)-1-(4-((4-fluorphenoxy)methyl)benzoyl)pyrrolidin-2-carboxylsyre

91 (2S,5R)-5-(2-chlorphenyl)-1-(4-((4-methoxyphenoxy)methyl)benzoyl)pyrrolidin-2-carboxylsyre

92 (2S,5R)-1-(4-((2-chlorphenoxy)methyl)benzoyl)-5-(2-chlorphenyl)pyrrolidin-2-carboxylsyre

93 (2S,5R)-5-(2-chlorphenyl)-1-(4-((2-methoxyphenoxy)methyl)benzoyl)pyrrolidin-2-carboxylsyre

94 (2S,5R)-5-(2-chlorphenyl)-1-(4-((3-methoxyphenoxy)methyl)benzoyl)pyrrolidin-2-carboxylsyre

95 (2S,5R)-1-(4-((3-chlorphenoxy)methyl)benzoyl)-5-(2-chlorphenyl)pyrrolidin-2-carboxylsyre

96 (2S,5R)-5-(2-chlorphenyl)-1-(4-((p-tolyloxy)methyl)benzoyl)pyrrolidin-2-carboxylsyre

97 (2S,5R)-5-(2-chlorphenyl)-1-(4-((3-methoxybenzyl)oxy)benzoyl)pyrrolidin-2-carboxylsyre

98 (2S,5R)-1-(4-((3-chlorbenzyl)oxy)benzoyl)-5-(2-chlorphenyl)pyrrolidin-2-carboxylsyre

99 (2S,5R)-5-(2-chlorphenyl)-1-(4-((3,5-dimethylisoxazol-4-yl)methoxy)benzoyl)pyrrolidin-2-carboxylsyre

100 (2S,5R)-5-(2-chlorphenyl)-1-(4-((3,5-dimethyl-1H-pyrazol-1-yl)methoxy)benzoyl)pyrrolidin-2-carboxylsyre

101 (2S,5R)-5-(2-chlorphenyl)-1-(4-(pyridin-2-ylmethoxy)benzoyl)pyrrolidin-2-carboxylsyre

102 (2S,5R)-5-(2-chlorphenyl)-1-(4-(pyridin-4-ylmethoxy)benzoyl)pyrrolidin-2-carboxylsyre

103 (2S,5R)-5-(2-chlorphenyl)-1-(4-(pyridin-3-ylmethoxy)benzoyl)pyrrolidin-2-carboxylsyre

104 (2S,5R)-5-(2-chlorphenyl)-1-(4-(5-methyl-1H-pyrazol-1-yl)benzoyl)pyrrolidin-2-carboxylsyre

105 (2S,5R)-5-(2-chlorphenyl)-1-(4-(isoxazol-5-yl)benzoyl)pyrrolidin-2-

carboxylsyre

106 (2S,5R)-1-(4-(4H-1,2,4-triazol-4-yl)benzoyl)-5-(2-chlorphenyl)pyrrolidin-2-carboxylsyre

107 (2S,5R)-5-(2-chlorphenyl)-1-(4-(5-(p-tolyl)-1H-1,2,3-triazol-1-yl)benzoyl)pyrrolidin-2-carboxylsyre

108 (2S,5R)-5-(2-chlorphenyl)-1-(4-(5-oxo-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl)benzoyl)pyrrolidin-2-carboxylsyre

109 (2S,5R)-5-(2-chlorphenyl)-1-(4-(5-methyl-3-(trifluormethyl)-1H-pyrazol-1-yl)benzoyl)pyrrolidin-2-carboxylsyre

110 (2S,5R)-1-(4-(1H-pyrazol-1-yl)benzoyl)-5-(2-chlorphenyl)pyrrolidin-2-carboxylsyre

111 (2S,5R)-5-(2-chlorphenyl)-1-(4-(oxazol-5-yl)benzoyl)pyrrolidin-2-carboxylsyre

112 (2S,5R)-5-(2-chlorphenyl)-1-(4-(3,5-dimethyl-1H-pyrazol-1-yl)benzoyl)pyrrolidin-2-carboxylsyre

113 (2S,5R)-5-(2-chlorphenyl)-1-(2',5'-dichlor-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

114 (2S,5R)-5-(2-chlorphenyl)-1-(4-(pyrimidin-5-yl)benzoyl)pyrrolidin-2-carboxylsyre

115 (2S,5R)-5-(2-chlorphenyl)-1-(4-(furan-3-yl)benzoyl)pyrrolidin-2-carboxylsyre

116 (2S,5R)-5-(2-chlorphenyl)-1-(4-(6-methoxypyridin-3-yl)benzoyl)pyrrolidin-2-carboxylsyre

117 (2S,5R)-5-(2-chlorphenyl)-1-(4-(3-fluorpyridin-4-yl)benzoyl)pyrrolidin-2-carboxylsyre

118 (2S,5R)-5-(2-chlorphenyl)-1-(4-(pyridin-3-yl)benzoyl)pyrrolidin-2-carboxylsyre

119 (2S,5R)-5-(2-chlorphenyl)-1-(4-(6-(dimethylamino)pyridin-3-yl)benzoyl)pyrrolidin-2-carboxylsyre

120 (2S,5R)-5-(2-chlorphenyl)-1-(4-(pyridin-4-yl)benzoyl)pyrrolidin-2-carboxylsyre

121 (2S,5R)-5-(2-chlorphenyl)-1-(4-(6-methylpyridin-3-yl)benzoyl)pyrrolidin-2-carboxylsyre

122 (2S,5R)-5-(2-chlorphenyl)-1-(4-(2-methoxypyridin-3-yl)benzoyl)pyrrolidin-2-carboxylsyre

123 (2S,5R)-5-(2-chlorphenyl)-1-(4'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

124 (2S,5R)-5-(2-chlorphenyl)-1-(4'-cyano-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-

carboxylsyre

125 (2S,5R)-5-(2-chlorphenyl)-1-(4-(4-methoxypyridin-3-yl)benzoyl)pyrrolidin-2-carboxylsyre

126 (2S,5R)-1-(4'-chlor-[1,1'-biphenyl]-4-carbonyl)-5-(2-chlorphenyl)pyrrolidin-2-carboxylsyre

127 (2S,5R)-1-(3'-chlor-[1,1'-biphenyl]-4-carbonyl)-5-(2-chlorphenyl)pyrrolidin-2-carboxylsyre

128 (2S,5R)-1-(2'-chlor-[1,1'-biphenyl]-4-carbonyl)-5-(2-chlorphenyl)pyrrolidin-2-carboxylsyre

129 (2S,5R)-5-(2-chlorphenyl)-1-(4'-(methylsulfonamido)-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

130 (2S,5R)-5-(2-chlorphenyl)-1-(3'-(methylsulfonamido)-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

131 (2S,5R)-5-(2-chlorphenyl)-1-(2'-(methylsulfonamido)-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

132 (2S,5R)-5-(2-chlorphenyl)-1-(4-(naphthalen-2-yl)benzoyl)pyrrolidin-2-carboxylsyre

133 (2S,5R)-5-(2-chlorphenyl)-1-(3',5'-difluor-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

134 (2S,5R)-5-(2-chlorphenyl)-1-(2'-hydroxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

135 (2S,5R)-5-(2-chlorphenyl)-1-(2'-(trifluormethoxy)-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

136 (2S,5R)-1-(2'-(benzyloxy)-[1,1'-biphenyl]-4-carbonyl)-5-(2-chlorphenyl)pyrrolidin-2-carboxylsyre

137 (2S,5R)-5-(2-chlorphenyl)-1-(2'-phenoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

138 (2S,5R)-5-(2-chlorphenyl)-1-(2'-isopropoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

139 (2S,5R)-5-(2-chlorphenyl)-1-(2'-isobutoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

140 (2S,5R)-5-(2-chlorphenyl)-1-(2'-(cyclopropylmethoxy)-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

141 (2S,5R)-5-(2-chlorphenyl)-1-(2'-((4-fluorbenzyl)oxy)-[1,1'-biphenyl]-4-

carbonyl)pyrrolidin-2-carboxylsyre

142 (2S,5R)-5-(2-chlorphenyl)-1-(4-(6-chlorpyridin-3-yl)benzoyl)pyrrolidin-2-carboxylsyre

143 (2S,5R)-5-(2-chlorphenyl)-1-(4-(6-fluorpyridin-3-yl)benzoyl)pyrrolidin-2-carboxylsyre

144 (2S,5R)-5-(2-chlorphenyl)-1-(4-(2-chlorpyridin-4-yl)benzoyl)pyrrolidin-2-carboxylsyre

145 (2S,5R)-1-(4-(2-chlor-3-fluorpyridin-4-yl)benzoyl)-5-(2-chlorphenyl)pyrrolidin-2-carboxylsyre

146 (2S,5R)-5-(2-chlorphenyl)-1-(4-(2-chlorpyridin-3-yl)benzoyl)pyrrolidin-2-carboxylsyre

147 (2S,5R)-1-(4-(6-(benzyloxy)pyridin-3-yl)benzoyl)-5-(2-chlorphenyl)pyrrolidin-2-carboxylsyre

148 (2S,5R)-1-(4-(1H-pyrazol-4-yl)benzoyl)-5-(2-chlorphenyl)pyrrolidin-2-carboxylsyre

149 (2S,5R)-5-(2-chlorphenyl)-1-(4-(thiophen-3-yl)benzoyl)pyrrolidin-2-carboxylsyre

150 (2S,5R)-5-(2-chlorphenyl)-1-(4-cyclohexylbenzoyl)pyrrolidin-2-carboxylsyre

151 (2S,5R)-5-(2-chlorphenyl)-1-(4'-(methylsulfonyl)-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

153 (2S,5R)-5-(2-chlorphenyl)-1-(2'-(methylsulfonyl)-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

154 (2S,5R)-5-(2-chlorphenyl)-1-(4-(tetrahydro-2H-pyran-4-yl)benzoyl)pyrrolidin-2-carboxylsyre

156 (2S,5R)-5-(2-chlorphenyl)-1-(4-phenoxybenzoyl)pyrrolidin-2-carboxylsyre

157 (2S,5R)-1-(4-benzylbenzoyl)-5-(2-chlorphenyl)pyrrolidin-2-carboxylsyre

158 (2S,5R)-1-(4-benzoylbenzoyl)-5-(2-chlorphenyl)pyrrolidin-2-carboxylsyre

159 (2S,5R)-5-(2-chlorphenyl)-1-(4-(pyrimidin-2-yl)benzoyl)pyrrolidin-2-carboxylsyre

160 (2S,5R)-5-(2-chlorphenyl)-1-(4-(4,6-dimethoxypyrimidin-2-yl)benzoyl)pyrrolidin-2-carboxylsyre

161 (2S,5R)-5-(2-chlorphenyl)-1-(4-(2,4-dimethoxypyrimidin-5-yl)benzoyl)pyrrolidin-2-carboxylsyre

162 (2S,5R)-5-(2-chlorphenyl)-1-(4-(2-methoxypyrimidin-5-yl)benzoyl)pyrrolidin-

2-carboxylsyre

163 (2S,5R)-5-(2-chlorphenyl)-1-(4-(2-(dimethylamino)pyrimidin-5-yl)benzoyl)pyrrolidin-2-carboxylsyre

164 (2S,5R)-5-(2-chlorphenyl)-1-(4-(2-morpholinopyrimidin-5-yl)benzoyl)pyrrolidin-2-carboxylsyre

165 (2S,5R)-5-(2-chlorphenyl)-1-(4-(2-(piperidin-1-yl)pyrimidin-5-yl)benzoyl)pyrrolidin-2-carboxylsyre

168 (2S,5R)-5-(2-chlorphenyl)-1-(cyclohexancarbonyl)pyrrolidin-2-carboxylsyre

169 (2S,5R)-5-(2-chlorphenyl)-1-(4-methylpentanoyl)pyrrolidin-2-carboxylsyre

172 (2S,5R)-5-(2-chlorphenyl)-1-(4-(4-methylpiperidin-1-yl)-3-nitrobenzoyl)pyrrolidin-2-carboxylsyre

173 (2S,5R)-5-(2-chlorphenyl)-1-(4-(2-oxopiperidin-1-yl)benzoyl)pyrrolidin-2-carboxylsyre

174 (2S,5R)-5-(2-chlorphenyl)-1-(3-methyl-4-morpholinbenzoyl)pyrrolidin-2-carboxylsyre

175 (2S,5R)-5-(2-chlorphenyl)-1-(4-(piperidin-1-yl)benzoyl)pyrrolidin-2-carboxylsyre

176 (2S,5R)-5-(2-chlorphenyl)-1-(4-morpholinbenzoyl)pyrrolidin-2-carboxylsyre

177 (2S,5R)-5-(2-chlorphenyl)-1-(1-(2-cyanophenyl)piperidin-4-carbonyl)pyrrolidin-2-carboxylsyre

178 (2S,5R)-5-(2-chlorphenyl)-1-(4-(4-chlorphenyl)cyclohexancarbonyl)pyrrolidin-2-carboxylsyre

179 (2S,5R)-5-(2-chlorphenyl)-1-(4-phenylcyclohexancarbonyl)pyrrolidin-2-carboxylsyre

184 (2R,5S)-5-(2-chlorphenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

189 (2S,5R)-5-(2-chlorphenyl)-1-(6-(2-fluorphenyl)nicotinoyl)pyrrolidin-2-carboxylsyre

191 (2S,5R)-5-(2-chlorphenyl)-1-(5-methoxy-6-phenylnicotinoyl)pyrrolidin-2-carboxylsyre

192 (2S,5R)-5-(2-chlorphenyl)-1-(4-(2-methoxyphenoxy)benzoyl)pyrrolidin-2-carboxylsyre

193 (2S,5R)-5-(2-chlorphenyl)-1-(4-(3-methoxypyridin-4-yl)benzoyl)pyrrolidin-2-carboxylsyre

194 (2S)-5-(2-chlorphenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)-4,4-dimethylpyrrolidin-2-carboxylsyre

195 (2S)-5-(2-chlorphenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)-4-methylpyrrolidin-2-carboxylsyre

196 (2S,5R)-5-(2-chlorphenyl)-1-(2-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

197 (2S,5R)-5-(2-chlorphenyl)-1-(2'-cyano-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

198 (2S,5R)-5-(2-chlorphenyl)-1-(2',6'-dimethoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

199 (2S,5R)-5-(2-chlorphenyl)-1-(2',4'-dichlor-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

200 (2S,5R)-5-(2-chlorphenyl)-1-(2'-(trifluormethyl)-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

201 (2S,5R)-5-(2-chlorphenyl)-1-(2,2'-dimethoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

202 (2S,5R)-1-(4'-chlor-2'-methoxy-[1,1'-biphenyl]-4-carbonyl)-5-(2-chlorphenyl)pyrrolidin-2-carboxylsyre

203 (2S,5R)-5-(2-chlorphenyl)-1-(4-(4-methoxypyrimidin-5-yl)benzoyl)pyrrolidin-2-carboxylsyre

204 (2S,5R)-5-(2-chlorphenyl)-1-(2',4'-dimethoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

205 (2S,5R)-1-([1,1'-biphenyl]-4-carbonyl)-5-(pyridin-3-yl)pyrrolidin-2-carboxylsyre

206 (2R,5R)-5-(2-chlorphenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

207 (2S,5R)-5-(2-chlorphenyl)-1-(1-phenyl-1H-benzo[d]imidazol-5-carbonyl)pyrrolidin-2-carboxylsyre

208 (2S,5R)-methyl-5-(2-chlorphenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylat

211 (2S,4S,5R)-5-(2-chlorphenyl)-4-(hydroxymethyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

217 (2S,4S,5S)-5-(2-chlorphenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)-4-(phenylsulfonyl)pyrrolidin-2-carboxylsyre

220 (2S,5R)-5-(2-chlorphenyl)-4-cyano-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

221 (2S,3R,5R)-5-(2-chlorphenyl)-3-cyano-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

224 (2S,5R)-1-(2-chlor-[1,1'-biphenyl]-4-carbonyl)-5-(2-chlorphenyl)pyrrolidin-2-carboxylsyre

225 (2S,5R)-1-(2'-chlor-2-methoxy-[1,1'-biphenyl]-4-carbonyl)-5-(2-chlorphenyl)pyrrolidin-2-carboxylsyre

226 (2S,5R)-5-(2-chlorphenyl)-1-(2'-(2-methoxyethoxy)-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

227 (2S,5R)-5-(2-chlorphenyl)-1-(4-(2-methylthiophen-3-yl)benzoyl)pyrrolidin-2-carboxylsyre

228 (2S,5R)-5-(2-chlorphenyl)-1-(2',6'-dichlor-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

229 (2S,5R)-1-(2'-chlor-4'-methoxy-[1,1'-biphenyl]-4-carbonyl)-5-(2-chlorphenyl)pyrrolidin-2-carboxylsyre

230 (2S,5R)-5-(2-chlorphenyl)-1-(3-methoxy-4-(pyrimidin-5-yl)benzoyl)pyrrolidin-2-carboxylsyre

231 (2S,5R)-1-(2'-carbamimidoyl-[1,1'-biphenyl]-4-carbonyl)-5-(2-chlorphenyl)pyrrolidin-2-carboxylsyre

232 (2S,5R)-5-(2-fluorphenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

233 (2S,5R)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)-5-(o-tolyl)pyrrolidin-2-carboxylsyre

234 (2S,5R)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)-5-(2-methoxyphenyl)pyrrolidin-2-carboxylsyre

235 (2S,5R)-5-(2-chlorphenyl)-1-(2'-(methoxymethyl)-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

236 (2S,5R)-5-(2-chlorphenyl)-1-(4-(2,6-dimethoxypyridin-3-yl)benzoyl)pyrrolidin-2-carboxylsyre

237 (2S,5R)-5-(2-chlorphenyl)-1-(3-methoxy-4-(2-methoxypyrimidin-5-yl)benzoyl)pyrrolidin-2-carboxylsyre

238 (2S,5R)-5-(2-chlorphenyl)-1-(4-(5-methoxypyrazin-2-yl)benzoyl)pyrrolidin-2-carboxylsyre

239 (2S,5R)-5-(2-chlorphenyl)-1-(4-(2-(2-methoxyethoxy)pyridin-3-yl)benzoyl)pyrrolidin-2-carboxylsyre

240 (2S,5R)-5-(2-chlorphenyl)-1-(4-(3-methoxypyrazin-2-yl)benzoyl)pyrrolidin-2-carboxylsyre

241 (2S,5R)-1-(4-(2-chlor-4-(dimethylamino)pyrimidin-5-yl)benzoyl)-5-(2-chlorphenyl)pyrrolidin-2-carboxylsyre

242 (2S,5R)-5-(2-chlorphenyl)-1-(4-(2,6-dimethoxypyrimidin-4-yl)benzoyl)pyrrolidin-2-carboxylsyre

243 (2S,5R)-5-(2-chlorphenyl)-1-(2'-(dimethylamino)-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

244 (2S,5R)-5-(2-chlorphenyl)-1-(4-(2-methoxypyrimidin-4-yl)benzoyl)pyrrolidin-2-carboxylsyre

245 (2S,5R)-5-(2-chlorphenyl)-1-(3-methoxy-4-(2-methoxypyrimidin-4-yl)benzoyl)pyrrolidin-2-carboxylsyre

246 (2S,5R)-5-(2-fluorphenyl)-1-(4-(2-methoxypyridin-3-yl)benzoyl)pyrrolidin-2-carboxylsyre

247 (2S,5R)-1-(4-(2,4-dimethoxypyrimidin-5-yl)benzoyl)-5-(2-fluorphenyl)pyrrolidin-2-carboxylsyre

248 (2S,5R)-5-(2-chlorphenyl)-1-(2-methyl-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

249 (2S,5R)-5-(2-chlorphenyl)-1-(3-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

251 (2S,5R)-5-(2-chlorphenyl)-1-(5-phenylpyrazin-2-carbonyl)pyrrolidin-2-carboxylsyre

252 (2S,5R)-5-(2-chlorphenyl)-1-(5-methoxy-6-(2-methoxyphenyl)nicotinoyl)pyrrolidin-2-carboxylsyre

253 (2S,5R)-5-(2-chlorphenyl)-1-(4-(5-methoxypyrimidin-4-yl)benzoyl)pyrrolidin-2-carboxylsyre

254 (2S,5R)-5-(2-chlorphenyl)-1-(4-(pyridazin-4-yl)benzoyl)pyrrolidin-2-carboxylsyre

255 (2S,5R)-1-(4-(1H-1,2,3-triazol-1-yl)benzoyl)-5-(2-chlorphenyl)pyrrolidin-2-carboxylsyre

256 (2S,5R)-5-(2-chlorphenyl)-1-(4-(4-(p-tolyl)-1H-1,2,3-triazol-1-yl)benzoyl)pyrrolidin-2-carboxylsyre

257 (2S,5R)-5-(2-chlorphenyl)-1-(1-(2-methoxyphenyl)piperidin-4-carbonyl)pyrrolidin-2-carboxylsyre

258 (2S,5R)-5-(2-chlorphenyl)-1-(4-(2-methoxyphenyl)piperazin-1-carbonyl)pyrrolidin-2-carboxylsyre

259 (2S,5R)-5-(2-chlorphenyl)-1-(1-(4-methoxypyrimidin-5-yl)piperidin-4-carbonyl)pyrrolidin-2-carboxylsyre

260 (2S,5R)-5-(2-chlorphenyl)-1-(4-(4-methoxypyrimidin-5-yl)piperazin-1-carbonyl)pyrrolidin-2-carboxylsyre

261 (2S,5R)-5-(2-chlorphenyl)-1-(3-methoxy-4-(4-methylpiperidin-1-yl)benzoyl)pyrrolidin-2-carboxylsyre

262 (2S,5R)-5-(2-chlorphenyl)-1-(3-methoxy-4-(1-methylpiperidin-4-yl)benzoyl)pyrrolidin-2-carboxylsyre

263 (2S,5R)-5-(2-chlorphenyl)-1-(2-cyano-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

264 (2S,5R)-5-(2-chlorphenyl)-1-(2-isobutoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

265 (2S,5R)-5-(2-chlorphenyl)-1-(4-(2,4-dichlorpyrimidin-5-yl)benzoyl)pyrrolidin-2-carboxylsyre

266 (2S,5R)-5-(2-chlorphenyl)-1-(4-(2,4-dimethoxypyrimidin-5-yl)-3-methoxybenzoyl)pyrrolidin-2-carboxylsyre

267 (2S,5R)-1-(4-(2-chlor-4-methoxypyrimidin-5-yl)benzoyl)-5-(2-chlorphenyl)pyrrolidin-2-carboxylsyre

268 (2S,3S,5S)-5-(2-chlorphenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)-3-methylpyrrolidin-2-carboxylsyre

269 (2S,5R)-1-(4-(2,6-dimethoxypyridin-3-yl)benzoyl)-5-(2-fluorphenyl)pyrrolidin-2-carboxylsyre

270 (2S,5R)-1-(2'-(2-amino-2-oxoethoxy)-[1,1'-biphenyl]-4-carbonyl)-5-(2-chlorphenyl)pyrrolidin-2-carboxylsyre

271 (2S,5R)-5-(2-chlorphenyl)-1-(2-(cyclopropylmethoxy)-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

272 (2S,5R)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)-5-phenylpyrrolidin-2-carboxylsyre

273 (2S,5R)-5-(3-chlorphenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

274 (2S,5R)-5-(4-chlorphenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

275 (2S,5R)-5-(3-fluorphenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

276 (2S,5R)-5-(4-fluorphenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

278 (2S,5R)-4-acetyl-5-(2-chlorphenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

279 (2S,4S,5R)-5-(2-chlorphenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)-4-(methoxymethyl)pyrrolidin-2-carboxylsyre

280 (2S,5R)-5-(2-chlorphenyl)-1-(4-(2-methoxypyrimidin-4-yl)benzoyl)pyrrolidin-2-carboxylsyre

281 (2S,5R)-5-cyclohexyl-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

283 (2S,5R)-1-(4-(2-chlor-4-methoxypyrimidin-5-yl)benzoyl)-5-(2-chlorphenyl)pyrrolidin-2-carboxylsyre

284 (2S,5R)-5-(2-chlorphenyl)-1-(4-(3-methoxypyridin-2-yl)benzoyl)pyrrolidin-2-carboxylsyre

285 (2R,5R)-5-(2-fluorphenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

286 (2S,5S)-5-(2-fluorphenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

287 (2R,5S)-5-(2-fluorphenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

288 (2S,5R)-5-(2-chlorphenyl)-1-(2-(trifluormethyl)-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

289 (2S,5R)-5-(2-chlorphenyl)-1-(2',4'-difluor-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

290 (2S,5R)-5-(2-chlorphenyl)-1-(2-methyl-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

291 (2S,5R)-5-(2,6-difluorphenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

292 (2S,5R)-5-(2,4-difluorphenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

293 (2S,5R)-5-(2,4-dichlorphenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

294 (2S,5R)-5-isobutyl-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

295 (2S,5R)-5-isopropyl-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

296 (2S,5R)-1-(3-chlor-4-(pyrimidin-4-yl)benzoyl)-5-(2-chlorphenyl)pyrrolidin-2-carboxylsyre

297 (2S,5R)-5-(2-chlorphenyl)-1-(2-fluor-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

298 (2S,5R)-5-(2-chlorphenyl)-1-(2'-fluor-4'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

299 (2S,5R)-5-(2-chlorphenyl)-1-(4'-fluor-2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

300 (2S,5R)-5-(2-chlorphenyl)-1-(4-(6-ethoxypyridin-3-yl)benzoyl)pyrrolidin-2-carboxylsyre

301 (2S,5R)-5-(2-chlorphenyl)-1-(4-(6-isopropoxypyridin-3-yl)benzoyl)pyrrolidin-2-carboxylsyre

302 (2S,5R)-5-(2-chlorphenyl)-1-(4-(6-methoxy-2-methylpyridin-3-yl)benzoyl)pyrrolidin-2-carboxylsyre

303 (2S,5R)-1-(3-chlor-4-(2-methoxypyrimidin-4-yl)benzoyl)-5-(2-chlorphenyl)pyrrolidin-2-carboxylsyre

304 (2S,5R)-1-(3-chlor-4-(pyrimidin-5-yl)benzoyl)-5-(2-chlorphenyl)pyrrolidin-2-carboxylsyre

305 (2S,5R)-5-(2-chlorphenyl)-4-cyano-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)-3-methylpyrrolidin-2-carboxylsyre

306 (2S,4S,5R)-5-(2-chlorphenyl)-4-cyano-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)-4-methylpyrrolidin-2-carboxylsyre

307 (2S,5R)-5-(2-chlorphenyl)-1-(2',3'-dimethoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

308 (2S,5R)-5-(2-chlorphenyl)-1-(3',4'-dimethoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

309 (2S,5R)-5-(2-chlorphenyl)-1-(2',3',4'-trimethoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

310 (2S,5R)-5-(2-chlorphenyl)-1-(2',3',6'-trimethoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

311 (2S,5R)-5-(2-chlorphenyl)-1-(3',5'-dimethoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

312 (2S,5R)-5-(2-chlorphenyl)-1-(2',5'-dimethoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

313 (2S,5R)-5-(2-chlorphenyl)-1-(2'-isopropyl-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

314 (2S,5R)-1-(2,2'-dimethoxy-[1,1'-biphenyl]-4-carbonyl)-5-(2-fluorphenyl)pyrrolidin-2-carboxylsyre

315 (2S,5R)-1-(2-fluor-2'-methoxy-[1,1'-biphenyl]-4-carbonyl)-5-(2-fluorphenyl)pyrrolidin-2-carboxylsyre

316 (2S,5R)-5-(2-chlorphenyl)-1-(2-fluor-2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

318 (2S,5R)-5-cyclopentyl-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

319 (2S,5R)-5-(2-chlorphenyl)-1-(2'-ethyl-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

320 (2S,5R)-5-(2-chlorphenyl)-1-(4-(2,6-dimethylpyridin-3-yl)benzoyl)pyrrolidin-2-carboxylsyre

321 (2S,5R)-1-(4-(2,4-bis(benzyloxy)pyrimidin-5-yl)benzoyl)-5-(2-chlorphenyl)pyrrolidin-2-carboxylsyre

322 (2S,5R)-1-([1,1':4',1"-terphenyl]-4-carbonyl)-5-(2-chlorphenyl)pyrrolidin-2-carboxylsyre

323 (2S,5R)-5-(2-chlorphenyl)-1-(4'-propyl-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

324 (2S,5R)-1-(4'-(tert-butyl)-[1,1'-biphenyl]-4-carbonyl)-5-(2-chlorphenyl)pyrrolidin-2-carboxylsyre

325 (2S,5R)-1-(3-chlor-4-(2,4-dimethoxypyrimidin-5-yl)benzoyl)-5-(2-chlorphenyl)pyrrolidin-2-carboxylsyre

326 (2S,5R)-5-(2-chlorphenyl)-1-(5-(2-methoxyphenyl)pyrazin-2-carbonyl)pyrrolidin-2-carboxylsyre

327 (2S,5R)-5-(2-chlorphenyl)-1-(3-methoxy-4-(4-methoxypyridin-3-yl)benzoyl)pyrrolidin-2-carboxylsyre

328 (2S,5R)-5-(2-chlorphenyl)-1-(3-methoxy-4-(6-methoxypyridin-3-yl)benzoyl)pyrrolidin-2-carboxylsyre

329 (2S,5R)-1-(3-chlor-4-(2-methoxypyrimidin-5-yl)benzoyl)-5-(2-chlorphenyl)pyrrolidin-2-carboxylsyre

330 (2S,5R)-1-(3-chlor-4-(6-methoxypyridin-3-yl)benzoyl)-5-(2-chlorphenyl)pyrrolidin-2-carboxylsyre

331 (2S,5R)-5-(2-chlorphenyl)-1-(1-(4-(4-chlorphenyl)thiazol-2-yl)piperidin-4-carbonyl)pyrrolidin-2-carboxylsyre

332 (2S,5R)-5-(2-fluorphenyl)-1-(5-methoxy-6-(2-methoxyphenyl)nicotinoyl)pyrrolidin-2-carboxylsyre

333 (2S,5R)-1-(1-(benzo[d]oxazol-2-yl)piperidin-4-carbonyl)-5-(2-chlorphenyl)pyrrolidin-2-carboxylsyre

334 (2S,5R)-5-(2-chlorphenyl)-1-(3-methoxy-4-(pyrrolidin-1-yl)benzoyl)pyrrolidin-2-carboxylsyre

335 (2S,5R)-5-(2-chlorphenyl)-1-(5-methoxy-6-(2-methoxyphenyl)nicotinoyl)pyrrolidin-2-carboxylsyre

336 (2S,5R)-5-(2-chlorphenyl)-1-(1-(2-methoxyphenyl)piperidin-4-carbonyl)pyrrolidin-2-carboxylsyre

337 (2S,5R)-5-(2-chlorphenyl)-1-(4-(2,4-dimethoxypyrimidin-5-yl)-3-methoxybenzoyl)pyrrolidin-2-carboxylsyre

338 (2S,5R)-5-(2-bromphenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

339 (2S,5R)-5-(2-chlorphenyl)-1-(3'-cyano-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

340 (2S,5R)-5-(2-chlorphenyl)-1-(3'-cyano-2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

341 (2S,5R)-5-(2-chlorphenyl)-1-(3'-cyano-2',4'-bis(2,2,2-trifluorethoxy)-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

342 (2S,5R)-1-(3'-amino-2'-methyl-[1,1'-biphenyl]-4-carbonyl)-5-(2-chlorphenyl)pyrrolidin-2-carboxylsyre

343 (2S,5R)-5-(2-chlorphenyl)-1-(2'-methyl-3'-(methylsulfonamido)-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

344 (2S,5R)-1-(3'-acetamido-2'-methyl-[1,1'-biphenyl]-4-carbonyl)-5-(2-chlorphenyl)pyrrolidin-2-carboxylsyre

345 (2S,5R)-5-(2-chlorphenyl)-1-(5'-cyano-2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

346 (2S,5R)-5-(2-chlorphenyl)-1-(5'-cyano-2'-methyl-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

347 (2S,5R)-5-(2-chlorphenyl)-1-(4-(4,6-dimethoxypyridin-3-yl)benzoyl)pyrrolidin-2-carboxylsyre

348 (2S,5R)-5-(2-chlorphenyl)-1-(4-(3,6-dimethoxypyridazin-4-yl)benzoyl)pyrrolidin-2-carboxylsyre

349 (2S,5S)-5-isopentyl-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

350 (2S,5R)-5-(2-chlorphenyl)-1-(2'-methoxy-4'-(methylsulfonamido)-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

351 (2S,5R)-1-(4'-acetamido-2'-methoxy-[1,1'-biphenyl]-4-carbonyl)-5-(2-chlorphenyl)pyrrolidin-2-carboxylsyre

352 (2S,5R)-1-(3'-carbamimidoyl-[1,1'-biphenyl]-4-carbonyl)-5-(2-chlorphenyl)pyrrolidin-2-carboxylsyre

353 (2S,5R)-5-(2-chlorphenyl)-1-(3'-((E)-N'-hydroxycarbamimidoyl)-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

354 (2S,5R)-5-(2-fluorphenyl)-1-(2'-methoxy-4'-(methylsulfonamido)-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

355 (2S,5R)-5-(2,4-difluorphenyl)-1-(4-(2,6-dimethoxypyridin-3-yl)benzoyl)pyrrolidin-2-carboxylsyre

356 (2S,5R)-5-(2-chlorphenyl)-1-(3-methoxy-4-(5-methoxypyridin-3-yl)benzoyl)pyrrolidin-2-carboxylsyre

357 (2S,5R)-1-(4'-amino-2'-methoxy-[1,1'-biphenyl]-4-carbonyl)-5-(2-chlorphenyl)pyrrolidin-2-carboxylsyre

358 (2S,5R)-5-(2-chlorphenyl)-1-(2',3,6'-trimethoxy-[2,3'-bipyridin]-5-carbonyl)pyrrolidin-2-carboxylsyre

359 (2S,5R)-1-(3'-carbamoyl-[1,1'-biphenyl]-4-carbonyl)-5-(2-chlorphenyl)pyrrolidin-2-carboxylsyre

360 (2S,5R)-5-(2-chlorphenyl)-1-(5'-cyano-2',3'-dimethoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

361 (2S,5R)-5-(2-chlorphenyl)-1-(2'-cyano-4',5'-dimethoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

362 (2S,5R)-5-(2-chlorphenyl)-1-(3',4',5'-trimethoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

363 (2S,5R)-5-(2-chlorphenyl)-1-(2'-(cyanomethyl)-4',5'-dimethoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

364 (2S,5R)-5-(2-chlorphenyl)-1-(3',4'-dicyano-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

365 (2S,5R)-5-(2-chlorphenyl)-1-(5'-cyano-2'-fluor-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

366 (2S,5R)-5-(2-chlorphenyl)-1-(2-fluor-3',4'-dimethoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

367 (2S,5R)-5-(2-chlorphenyl)-1-(4-(2,6-dimethoxypyridin-3-yl)-3-fluorbenzoyl)pyrrolidin-2-carboxylsyre

368 (2S,5R)-5-(2-chlorphenyl)-1-(3-fluor-4-(6-methoxypyridin-3-yl)benzoyl)pyrrolidin-2-carboxylsyre

369 (2S,5R)-5-(2-chlorphenyl)-1-(1-(2-cyano-4-(trifluormethyl)phenyl)piperidin-4-carbonyl)pyrrolidin-2-carboxylsyre

370 (2S,5R)-1-(1-(2-chlor-4-(trifluormethyl)phenyl)piperidin-4-carbonyl)-5-(2-chlorphenyl)pyrrolidin-2-carboxylsyre

371 (2S,5R)-1-(5'-cyano-2'-methoxy-[1,1'-biphenyl]-4-carbonyl)-5-(2-fluorphenyl)pyrrolidin-2-carboxylsyre

372 (2S,5R)-1-(4-(2,6-dimethoxypyridin-3-yl)-3-fluorbenzoyl)-5-(2-fluorphenyl)pyrrolidin-2-carboxylsyre

373 (2S,5R)-1-(3-fluor-4-(6-methoxypyridin-3-yl)benzoyl)-5-(2-fluorphenyl)pyrrolidin-2-carboxylsyre

374 (2S,5R)-1-(4-(3,6-dimethoxypyridazin-4-yl)benzoyl)-5-(2-fluorphenyl)pyrrolidin-2-carboxylsyre

375 (2S,5R)-1-(3'-carbamoyl-4'-cyano-[1,1'-biphenyl]-4-carbonyl)-5-(2-chlorphenyl)pyrrolidin-2-carboxylsyre

376 (2S,5R)-5-(2-chlorphenyl)-1-(1-(2-nitro-4-(trifluormethyl)phenyl)piperidin-4-carbonyl)pyrrolidin-2-carboxylsyre

377 (2S,5R)-5-(2-chlorphenyl)-1-(1-(4-(morpholinosulfonyl)-2-nitrophenyl)piperidin-4-carbonyl)pyrrolidin-2-carboxylsyre

378 (2S,5R)-5-(2-chlorphenyl)-1-(1-(2-nitro-4-(piperidin-1-ylsulfonyl)phenyl)piperidin-4-carbonyl)pyrrolidin-2-carboxylsyre

379 (2S,5R)-5-(2-chlorphenyl)-1-(1-(4-(N,N-diethylsulfamoyl)-2-nitrophenyl)piperidin-4-carbonyl)pyrrolidin-2-carboxylsyre

380 (2S,5R)-5-(2-chlorphenyl)-1-(1-(4-methyl-2-nitrophenyl)piperidin-4-carbonyl)pyrrolidin-2-carboxylsyre

381 (2S,5R)-5-(2-chlorphenyl)-1-(1-(2-cyano-4-nitrophenyl)piperidin-4-carbonyl)pyrrolidin-2-carboxylsyre

382 (2S,5R)-5-(2-chlorphenyl)-1-(1-(4-nitrophenyl)piperidin-4-carbonyl)pyrrolidin-2-carboxylsyre

383 (2S,5R)-5-(2-chlorphenyl)-1-(1-(2-fluor-4-nitrophenyl)piperidin-4-carbonyl)pyrrolidin-2-carboxylsyre

384 (2S,5R)-5-(2-chlorphenyl)-1-(1-(3-methoxy-4-nitrophenyl)piperidin-4-carbonyl)pyrrolidin-2-carboxylsyre

385 (2S,5R)-1-(1-(5-chlor-2-nitrophenyl)piperidin-4-carbonyl)-5-(2-chlorphenyl)pyrrolidin-2-carboxylsyre

386 (2S,5R)-5-(2-cyanophenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

387 (2S,5R)-5-(2-chlorphenyl)-1-(2'-cyano-4'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

388 (2S,5R)-5-(2-chlorphenyl)-1-(2-fluor-4'-(methylsulfonamido)-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

389 (2S,5R)-5-(2-chlorphenyl)-1-(2-fluor-3'-(methylsulfonamido)-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

390 (2S,5R)-5-(2-chlorphenyl)-1-(2'-cyano-2-fluor-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

391 (2S,5R)-5-(2-chlorphenyl)-1-(1-(2-cyano-4-(methylsulfonamido)phenyl)piperidin-4-carbonyl)pyrrolidin-2-carboxylsyre

392 (2S,5R)-5-(2-chlorphenyl)-1-(1-(2-cyano-4-methoxyphenyl)piperidin-4-carbonyl)pyrrolidin-2-carboxylsyre

393 (2S,5R)-5-(2-chlorphenyl)-1-(1-(2-(methylsulfonamido)-4-(trifluormethyl)phenyl)piperidin-4-carbonyl)pyrrolidin-2-carboxylsyre

394 (2S,5R)-5-(2-chlorphenyl)-1-(1-(2-nitrophenyl)piperidin-4-carbonyl)pyrrolidin-2-carboxylsyre

395 (2S,5R)-5-(2-chlorphenyl)-1-(1-(4-cyanophenyl)piperidin-4-carbonyl)pyrrolidin-2-carboxylsyre

396 (2S,5R)-5-(3,5-difluorphenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

397 (2S,5R)-5-(3,4-difluorphenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

398 (2S,5R)-5-(2,3-difluorphenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

399 (2S,5R)-5-(2,5-difluorphenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

400 (2S,5R)-5-([1,1'-biphenyl]-2-yl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

401 (2S,5R)-1-(2'-cyano-4'-methoxy-[1,1'-biphenyl]-4-carbonyl)-5-(2-fluorphenyl)pyrrolidin-2-carboxylsyre

402 (2S,5R)-5-(4-cyanophenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

403 (2S,5R)-5-(2-chlorphenyl)-1-(4-(5-methyl-4-(phenylsulfonyl)-1H-1,2,3-triazol-1-yl)benzoyl)pyrrolidin-2-carboxylsyre

404 (2S,5R)-5-(2-chlorphenyl)-1-(3'-cyano-4'-fluor-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

405 (2S,5R)-1-(2'-chlor-5'-cyano-[1,1'-biphenyl]-4-carbonyl)-5-(2-chlorphenyl)pyrrolidin-2-carboxylsyre

406 (2S,5R)-5-(2-chlorphenyl)-1-(2'-cyano-4'-(trifluormethyl)-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

407 (2S,5R)-5-(2-chlorphenyl)-1-(1-(2-methoxy-4-(trifluormethyl)phenyl)piperidin-4-carbonyl)pyrrolidin-2-carboxylsyre

408 (2S,5R)-5-(2-chlorphenyl)-1-(2'-methyl-3'-(N-methylmethylsulfonamido)-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

409 (2S,5R)-5-(2-chlorphenyl)-1-(2'-methoxy-4'-(N-methylmethylsulfonamido)-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

410 (2S,5R)-5-(2-chlorphenyl)-1-(6-(5-cyano-2-methoxyphenyl)-5-methoxynicotinoyl)pyrrolidin-2-carboxylsyre

411 (2S,5R)-5-(2-chlorphenyl)-1-(6-(2,4-dimethoxyphenyl)-5-methoxynicotinoyl)pyrrolidin-2-carboxylsyre

412 (2S,5R)-5-(2-chlorphenyl)-1-(6-(2,4-dimethoxyphenyl)nicotinoyl)pyrrolidin-2-carboxylsyre

413 (2S,5R)-1-(2'-cyano-4'-(trifluormethyl)-[1,1'-biphenyl]-4-carbonyl)-5-(2-fluorphenyl)pyrrolidin-2-carboxylsyre

414 (2S,5R)-1-(3'-cyano-4'-fluor-[1,1'-biphenyl]-4-carbonyl)-5-(2-fluorphenyl)pyrrolidin-2-carboxylsyre

415 (2S,5R)-1-(2'-chlor-5'-cyano-[1,1'-biphenyl]-4-carbonyl)-5-(2-fluorphenyl)pyrrolidin-2-carboxylsyre

416 (2S,5R)-5-(2-chlorphenyl)-1-(4-(3,6-dimethoxypyridazin-4-yl)-3-fluorbenzoyl)pyrrolidin-2-carboxylsyre

417 (2S,5R)-5-(2-fluorphenyl)-1-(2'-methyl-3'-(N-methylmethylsulfonamido)-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

418 (2S,5R)-5-(2-fluorphenyl)-1-(2'-methoxy-4'-(N-methylmethylsulfonamido)-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

419 (2S,5R)-5-(2-chlorphenyl)-1-(4-(4,6-dimethoxypyrimidin-5-yl)benzoyl)pyrrolidin-2-carboxylsyre

420 (2S,5R)-5-(2,3-difluorphenyl)-1-(4-(2,4-dimethoxypyrimidin-5-yl)benzoyl)pyrrolidin-2-carboxylsyre

421 (2S,5R)-1-(5'-cyano-2'-methyl-[1,1'-biphenyl]-4-carbonyl)-5-(2,3-difluorphenyl)pyrrolidin-2-carboxylsyre

422 (2S,5R)-5-(2,3-difluorphenyl)-1-(2'-methoxy-4'-(methylsulfonamido)-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

423 (2S,5R)-5-(2,3-difluorphenyl)-1-(2'-methyl-3'-(methylsulfonamido)-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

424 (2S,5R)-5-(2-fluorphenyl)-1-(2'-methyl-3'-(methylsulfonamido)-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre

425 (2S,5R)-5-(2,3-difluorphenyl)-1-(4-(2-methoxypyridin-3-yl)benzoyl)pyrrolidin-2-carboxylsyre

426 (2S,5R)-5-(2,3-difluorphenyl)-1-(3-methoxy-4-(2-methoxypyrimidin-5-yl)benzoyl)pyrrolidin-2-carboxylsyre

427 (2S,5R)-5-(2-fluorphenyl)-1-(3-methoxy-4-(2-methoxypyrimidin-5-yl)benzoyl)pyrrolidin-2-carboxylsyre

428 (2S,5R)-5-(2,3-difluorphenyl)-1-(4-(3,6-dimethoxypyridazin-4-yl)benzoyl)pyrrolidin-2-carboxylsyre

429 (2S,5R)-1-(5'-cyano-2'-methoxy-[1,1'-biphenyl]-4-carbonyl)-5-(2,3-difluorphenyl)pyrrolidin-2-carboxylsyre

430 (2S,5R)-1-(5'-cyano-2'-methyl-[1,1'-biphenyl]-4-carbonyl)-5-(2-fluorphenyl)pyrrolidin-2-carboxylsyre

431 (2S,5R)-5-(2,3-difluorphenyl)-1-(4-(3,6-dimethoxypyridazin-4-yl)-3-fluorbenzoyl)pyrrolidin-2-carboxylsyre

432 (2S,5R)-1-(4-(3,6-dimethoxypyridazin-4-yl)-3-fluorbenzoyl)-5-(2-fluorphenyl)pyrrolidin-2-carboxylsyre

og farmaceutisk acceptable salte og solvater deraf.

21. Forbindelse til anvendelse ifølge et hvilket som helst af krav 1 til **20** til udsættelse af udbrud af en inflammatorisk sygdom hos en patient.

22. Forbindelse til anvendelse ifølge et hvilket som helst af krav 1 til **20** til behandling og/eller forebyggelse af sygdomme udvalgt fra gruppen bestående af rheumatoid arthritis; inflammatorisk tarmsygdom (IBD) indbefattende, men ikke begrænset til, Crohns sygdom, ulcerøs colitis og colitis; Pagets sygdom; osteoporose; multipelt myelom; uveitis; akut og kronisk myelogen leukæmi; pankreatisk β-celledestruktion; rheumatoid spondylitis; osteoarthritis; gigtagtig arthritis og andre arthritistilstande; gigt; adult respiratorisk distress-syndrom (ARDS); kronisk pulmonale inflammatoriske sygdomme; silikose; pulmonal sarkoidose; psoriasis; rhinitis; anafylaksi; kontaktdermatitis; pancreatitis; astma; muskeldegeneration; kakeksi, såsom kakeksi sekundær til infektion eller ondartethed, kakeksi sekundær til erhvervet immundefektsyndrom; Reiters syndrom; type I diabetes; knogleresorptionssygdom; graft vs. værtreaktion; iskæmisk reperfusionslæsion; hjernetraume; multipel sklerose; cerebral malaria; sepsis; septisk shock; toksisk shocksyndrom; endotoksisk shock; gram negativ sepsis; feber og myalgi på grund af infektion, såsom influenza; halsbrand.

23. Forbindelse til anvendelse ifølge et hvilket som helst af krav **1** til **22,** hvor forbindelsen er (2S,5R)-5-(2-chlorphenyl)-1-(2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre eller et farmaceutisk acceptabelt salt eller solvat deraf.

24. Forbindelse til anvendelse ifølge et hvilket som helst af krav **1** til **22,** hvor forbindelsen er (2S,5R)-5-(2-chlorphenyl)-1-(2'-methyl-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre eller et farmaceutisk acceptabelt salt eller solvat deraf.

25. Forbindelse til anvendelse ifølge et hvilket som helst af krav **1** til **22,** hvor forbindelsen

er (2S,5R)-1-(3-((4-chlorbenzyl)oxy)-5-methoxybenzoyl)-5-(2-chlorphenyl)pyrrolidin-2-carboxylsyre eller et farmaceutisk acceptabelt salt eller solvat deraf.

26. Forbindelse til anvendelse ifølge et hvilket som helst af krav **1** til **22,** hvor forbindelsen er (2S,5R)-5-(2-chlorphenyl)-1-(2'-(trifluormethoxy)-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre eller et farmaceutisk acceptabelt salt eller solvat deraf.

27. Forbindelse til anvendelse ifølge et hvilket som helst af krav **1** til **22,** hvor forbindelsen er (2S,5R)-5-(2-chlorphenyl)-1-(2'-(cyclopropylmethoxy)-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre eller et farmaceutisk acceptabelt salt eller solvat deraf.

28. Forbindelse til anvendelse ifølge et hvilket som helst af krav **1** til **22,** hvor forbindelsen er (2S,5R)-5-(2-chlorphenyl)-1-(4-(2,6-dimethoxypyridin-3-yl)benzoyl)pyrrolidin-2-carboxylsyre eller et farmaceutisk acceptabelt salt eller solvat deraf.

29. Forbindelse til anvendelse ifølge et hvilket som helst af krav **1** til **22,** hvor forbindelsen er (2S,5R)-1-(4-(2,6-dimethoxypyridin-3-yl)benzoyl)-5-(2-fluorphenyl)pyrrolidin-2-carboxylsyre eller et farmaceutisk acceptabelt salt eller solvat deraf.

30. Forbindelse til anvendelse ifølge et hvilket som helst af krav **1** til **22,** hvor forbindelsen er (2S,5R)-5-(2-chlorphenyl)-1-(2',5'-dimethoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre eller et farmaceutisk acceptabelt salt eller solvat deraf.

31. Forbindelse til anvendelse ifølge et hvilket som helst af krav **1** til **22,** hvor forbindelsen er (2S,5R)-5-(2-chlorphenyl)-1-(5'-cyano-2'-methoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre eller et farmaceutisk acceptabelt salt eller solvat deraf.

32. Forbindelse til anvendelse ifølge et hvilket som helst af krav **1** til **22,** hvor forbindelsen er (2S,5R)-5-(2-chlorphenyl)-1-(5'-cyano-2'-methyl-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre eller et farmaceutisk acceptabelt salt eller solvat deraf.

33. Forbindelse til anvendelse ifølge et hvilket som helst af krav **1** til **22,** hvor forbindelsen er (2S,5R)-5-(2-chlorphenyl)-1-(2-fluor-3',4'-dimethoxy-[1,1'-biphenyl]-4-carbonyl)pyrrolidin-2-carboxylsyre eller et farmaceutisk acceptabelt salt eller solvat deraf.

34. Forbindelse til anvendelse ifølge et hvilket som helst af krav **1** til **22,** hvor forbindelsen er (2S,5R)-5-(2-chlorphenyl)-1-(4-(2,6-dimethoxypyridin-3-yl)-3-fluorbenzoyl)pyrrolidin-2-carboxylsyre eller et farmaceutisk acceptabelt salt eller solvat deraf.

35. Forbindelse til anvendelse ifølge et hvilket som helst af krav **1** til **22,** hvor forbindelsen er (2S,5R)-1-(4-(2,6-dimethoxypyridin-3-yl)-3-fluorbenzoyl)-5-(2-fluorphenyl)pyrrolidin-2-carboxylsyre eller et farmaceutisk acceptabelt salt eller solvat deraf.

36. Forbindelse til anvendelse ifølge et hvilket som helst af krav **1** til **22,** hvor forbindelsen er (2S,5R)-1-(5'-cyano-2'-methyl-[1,1'-biphenyl]-4-carbonyl)-5-(2,3-difluorphenyl)pyrrolidin-2-carboxylsyre eller et farmaceutisk acceptabelt salt eller solvat deraf.

DRAWINGS

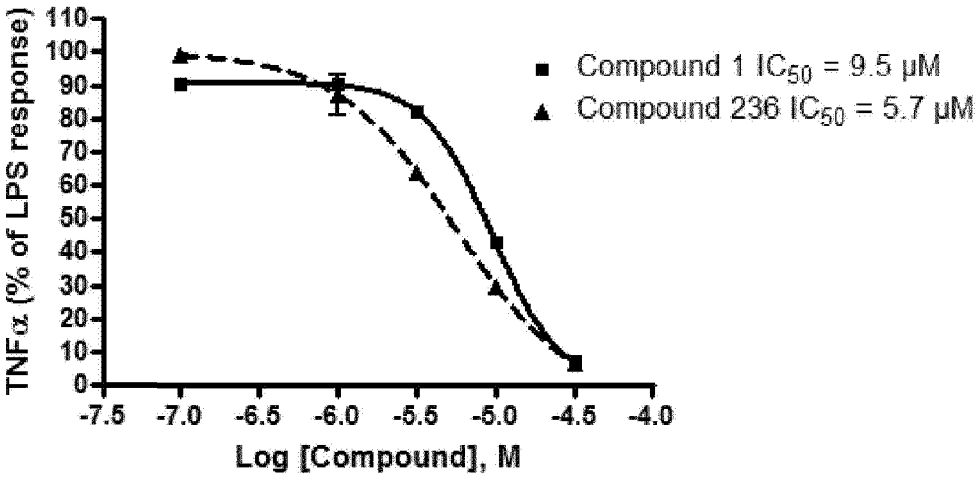


FIG. 1

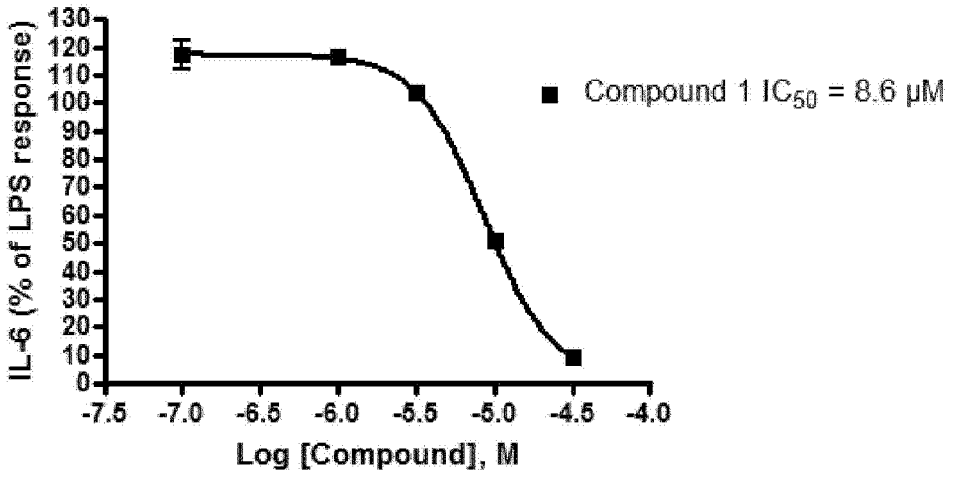


FIG. 2

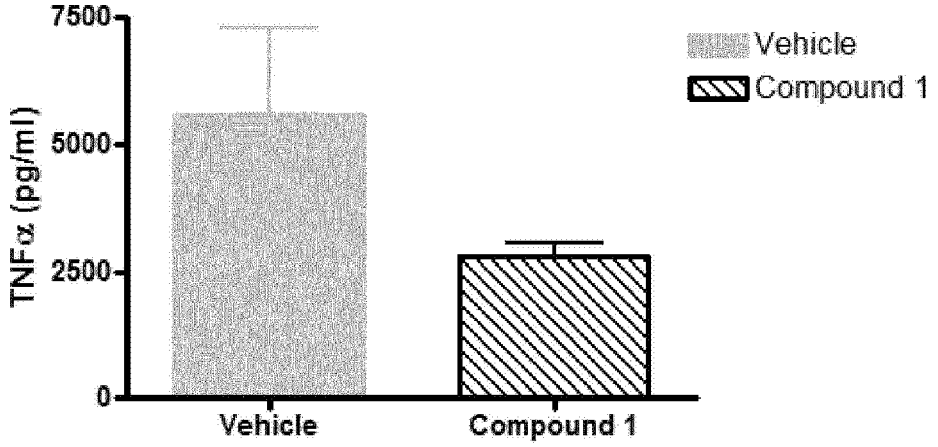
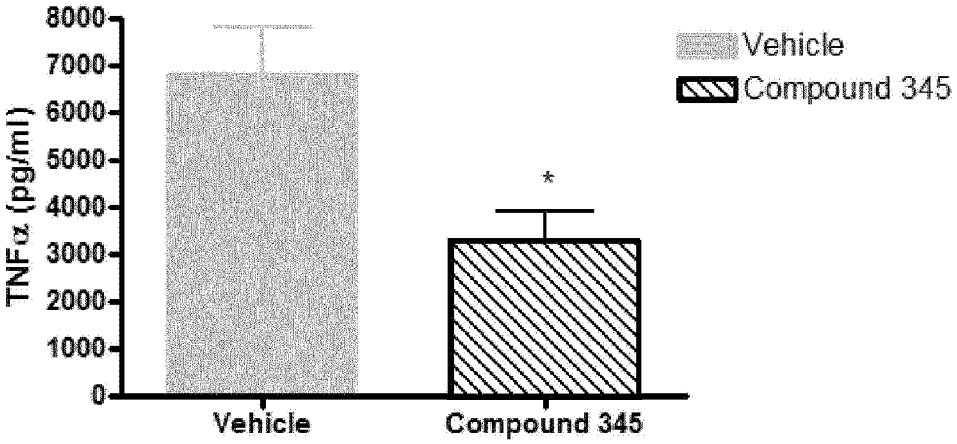
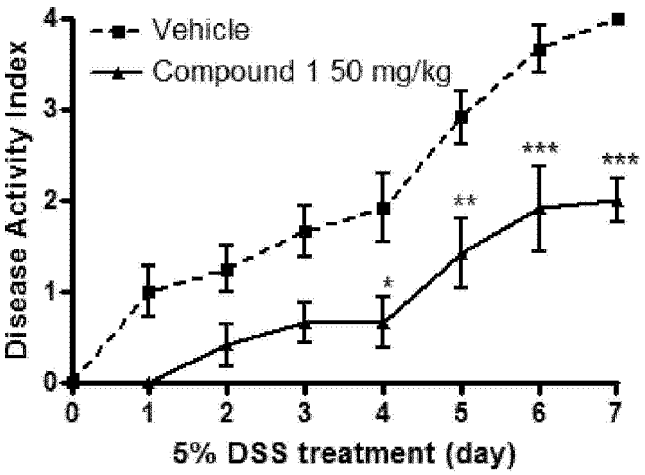


FIG. 3A



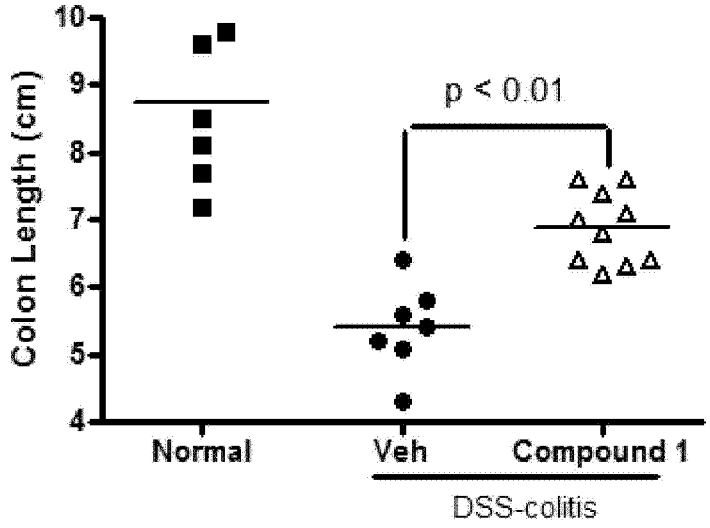
*p<0.05; student's t test. Vehicle vs compound 345

FIG. 3B



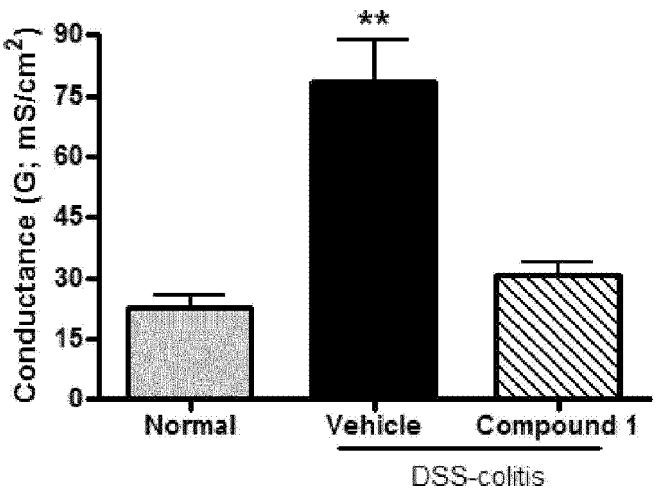
Statistics: two-way ANOVA and Bonferroni post-hoc
**p<0.05; **p<0.01; ***p<0.001 vehicle vs treatment (n=6 ± sem)*

FIG. 4



One-way ANOVA followed by Bonferroni post-hoc test

FIG. 5



***p<0.01; one-way ANOVA followed by Bonferroni post-hoc test. Vehicle vs compound 1 and normal.*

FIG. 6

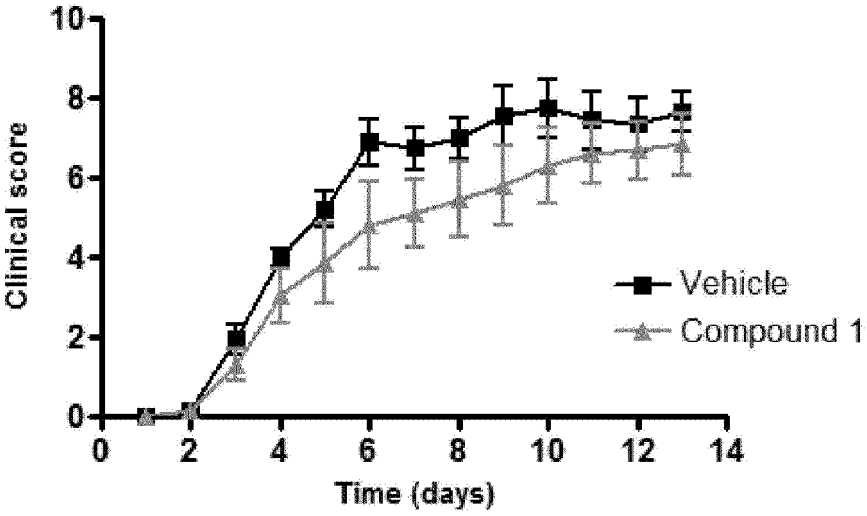


FIG. 7

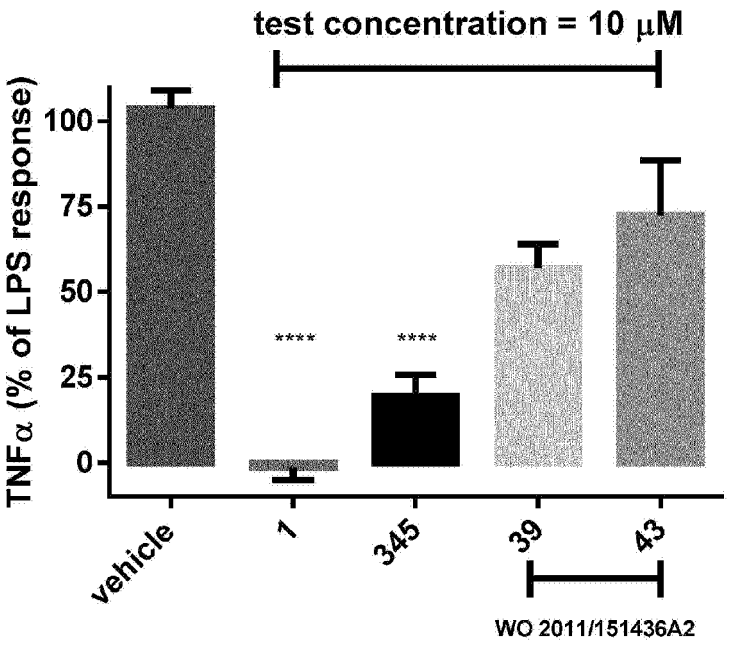

test concentration = 10 μM
TNFα (% of LPS response)
100
75
50
25
0
****
****
vehicle
1
345
39
43
WO 2011/151436A2

FIG. 8